UNDERSTANDING THE NATURE, EXTENT, AND BRAIN DYNAMICS OF DEFICIENT PATTERN SEPARATION

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Abstract

Recent research suggests that the specificity and precision in long-term declarative memory depend on pattern separation. Subfields within the mammalian hippocampus have been shown to mediate this neurobiological process, particularly the dentate gyrus (DG). This subfield interacts with other parts of the medial temporal lobe and neocortex to differentiate highly similar details belonging to separate, yet overlapping, events into discrete episodes at encoding. In humans, the brain-behavior correlates of pattern separation have been explored in modified associative memory tests, which tax the mnemonic discrimination of previously learned images of everyday objects from visually similar lures. Older individuals with reduced hippocampal volumes and patients with hippocampal lesions are impaired relative to controls on these tests. Based on this evidence, researchers have concluded that visual mnemonic discrimination tests are functionally sensitive to the process of hippocampal pattern separation. This assertion may be premature. Despite the preponderance of studies of visual pattern separation over the past 15 years, little is known about whether hippocampal pattern separation works 1) in other modalities or cognitive domains; 2) through interacting with prior knowledge or pre-experimentally novel information, and 3) in concert with activities of perceptual categorization. The present research addresses these issues. In Study 1, I examine whether presumed deficits in pattern separation apply to perception as they do to memory and are evident, even within vision, for stimuli such as faces, which presumably do not crucially depend on the hippocampus. In Study 2, I pursue whether pattern separation extends to modalities other than vision, notably audition. In Study 3, I aim to quantify the impact of prior knowledge on pattern separation and whether discrimination of abstract inputs can be measured at encoding and retrieval. Three groups of participants were tested throughout these studies: young adults, middle-older adults, and older adults. In addition, a rare individual with focal hippocampal lesions to his DG helped to contextualize hippocampal

involvement in Studies 1 and 2. The research I conducted on memory and perception combines novel behavioral paradigms and electrophysiological (EEG) techniques sensitive to the temporal dynamics involved in oddity detection to understand better the nature, extent, and brain dynamics of deficient pattern separation. The data analyzed allowed me to make inferences about the nature, scope, and brain dynamics of pattern separation in younger, middle-older, and older adults and in a hippocampal patient. The research addresses unanswered questions about pattern separation and the role of the hippocampus in learning and memory across other processing domains, modalities and involving different types of stimuli. As our population ages, so will the number of individuals who will suffer age-related cognitive impairment. One of the most common among them is a decline or loss of episodic memory, characterized by an inability to recall past personal experiences in detail, specificity, and precision. Similar losses of detail, specificity, and accuracy are observed in perception. Knowledge gained from this research helps to inform the development of tools for clinical assessment and intervention.

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Chapter 1

1 General Introduction

1.1 The mnemonic function of pattern separation

The past 65 years have witnessed the accumulation of an impressive body of evidence that the hippocampus supports memory for experiences that are unique to time and place (Eichenbaum, 2004; Moscovitch, 1992; Rosenbaum et al., 2008; Scoville & Milner, 1957; Vargha-Khadem et al., 1997). This reexperiencing is known as episodic memory, or declarative memory for personally experienced events defined by their spatiotemporal context and recollection processes (Tulving, 2002a, 1983). It is an impressive ability, considering humans' potential to experience and maintain representations of thousands of unique items daily, even in response to a single exposure (Brady et al., 2008; Sherry & Schacter, 1987; Standing, 1973). Essential to the ability to encode so many events is the brain's capacity to distinguish the minutiae that particularize highly similar memories. This function is thought to rely on pattern separation.

Pattern separation is a neurobiological process through which the hippocampus, a structure within the human medial temporal lobe (MTL), differentiates elements belonging to separate, yet potentially overlapping, events into discrete neural codes (Marr, 1971; Norman & O'Reilly, 2003; O'Reilly & McClelland, 1994; Treves & Rolls, 1994). Classical theories of the neural connectivity responsible for pattern separation have focused on four areas of the human hippocampal formation: 1) the entorhinal cortex; 2) the dentate gyrus (DG); 3) the CA3 subfield; and the CA1 subfield. See Figure 1-1 (Duvernoy, 2005) for an illustration of the hippocampus proper (the cornu ammonis) — or the CA1, CA2, CA3, and CA4 subfields — the DG and the subiculum. The interconnectivity among and between the entorhinal cortex and the DG, CA3, and CA1, also known as the trisynaptic circuit or loop (Blumenfeld, 2010), is key to our understanding of pattern separation (Hainmueller & Bartos, 2020). Pattern completion, sometimes thought of as the flip side to pattern separation, is the reinstatement of memories from partial cues facilitated by the recurrent collaterals or neurons synapsing upon neurons within the CA3 (Treves & Rolls, 1994).

The rise of the classical concepts of pattern separation paralleled advancements in the neuroanatomical knowledge of the MTL. Schematic diagrams of the rodent and monkey MTL (e.g., Amaral, 1993; Amaral et al., 1990; Amaral & Witter, 1989; Suzuki & Amaral, 1990; Witter & Amaral, 1991) influenced models of human hippocampal function and information processing. As the abstract to one paper began: "Anatomists involved with studies of the hippocampal formation are being prodded by computational modelers and physiologists who demand detailed and quantitative information concerning hippocampal neurons and circuits" (Amaral et al., 1990). Among the neurons and circuits of most interest were those which flowed from the entorhinal cortex (EC) via the perforant pathway through the subiculum to the DG and from the DG via the mossy pathway to the CA3 (Amaral, 1993; Lynch et al., 1976). Lesser-studied projections also travel from the EC to the CA1 and CA3 (Blumenfeld, 2010; Rolls, 2016; Witter & Amaral, 1991). Furthermore, and essential to our understanding of pattern separation, the pyramidal cells of the CA3 receive inputs from the DG via the unmyelinated axons of the mossy fiber pathway (O'Reilly & McClelland, 1994). CA3 neurons project onto the CA1, and from there feedforward to the EC; CA3 neurons synapse onto other CA3 cell bodies through recurrent collaterals. This "EC → DG → CA3 [↔ CA3] → CA1 → EC" network is what is known as the trisynaptic circuit or loop (Blumenfeld, 2010).

The EC's projections onto the rat hippocampus had been detailed in anatomical papers for several decades (Blackstad, 1958; Hjorth-Simonsen, 1972; Steward, 1976; Witter et al., 1988), by the time computational modelers of pattern separation had begun to publish their work. See Figure 1-2. However, the entorhinal cortex had not yet achieved its status as it is today of being the primary gateway from the neocortex to the human hippocampus in the service of memory (Norman et al., 2008). Neuroanatomical data was emerging, however, that some sort of processing and segregation was happening to information as it flowed from the entorhinal cortex throughout the hippocampal regions (Amaral, 1993; Amaral & Witter, 1989).

Cognitive scientists who reviewed these and other papers and prodded their authors were becoming aware of the evidence that integrative, higher-order association areas of the brain (e.g., frontal, temporal, and lobes) channeled information to the EC in humans and from there to the hippocampus (e.g., Squire et al., 1989). That left them to work in the tradition of the "Hebb-Marr" model (e.g., McNaughton & Morris, 1987) with the goal to "provide a framework for

associating functional properties of memory with the mechanisms of pattern separation, learning (synaptic modification), and pattern completion" (O'Reilly & McClelland, 1994).

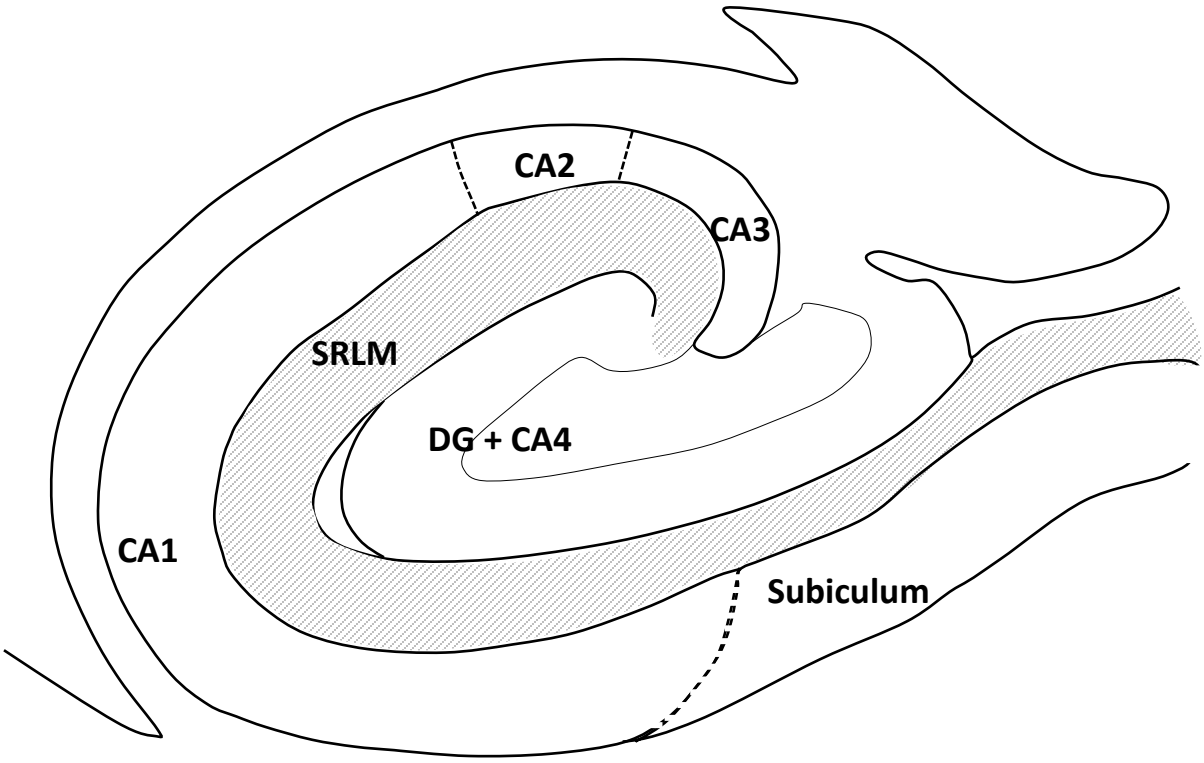


Figure 1-1. The human hippocampal formation

Adapted from *The Human Hippocampus (3rd ed.),* H. Duvernoy, et al., p. 20.

Consensus was reached that as sensory information flowed throughout the DG, it became more widely distributed across a broader field of neurons. From there, it was projected onto the CA3, where through this subfield's recurrent collateral activity, sparsely encoded memories could be reinstated by a single component part of their representation. Others noted how CA3 neurons project onto the CA1 and feedforward to the EC and back to the higher-order association cortices of the brain. The result was that sensory information in higher-order areas of the brain that arrived at the EC and flowed through the hippocampus was changed. Experiences became more complex and mnemonically sparse. Thus, the classical model on pattern separation was born, without one human experiment on the theory being conducted. See Figure 1-3.

Pattern separation fit well with the evolution of ideas about episodic memory, particularly the concept that humans rely on the hippocampus to bind together details about specific experiences. These make an episode unique and aid in its recollection (Kirwan & Stark, 2007; Kumaran et al.,

2016; Tulving, 2002b). Pattern separation is what helps us make these learned episodes more distinguishable or more orthogonal in representation. Pattern completion allows us to auto-associate an experience from one element of its input pattern.

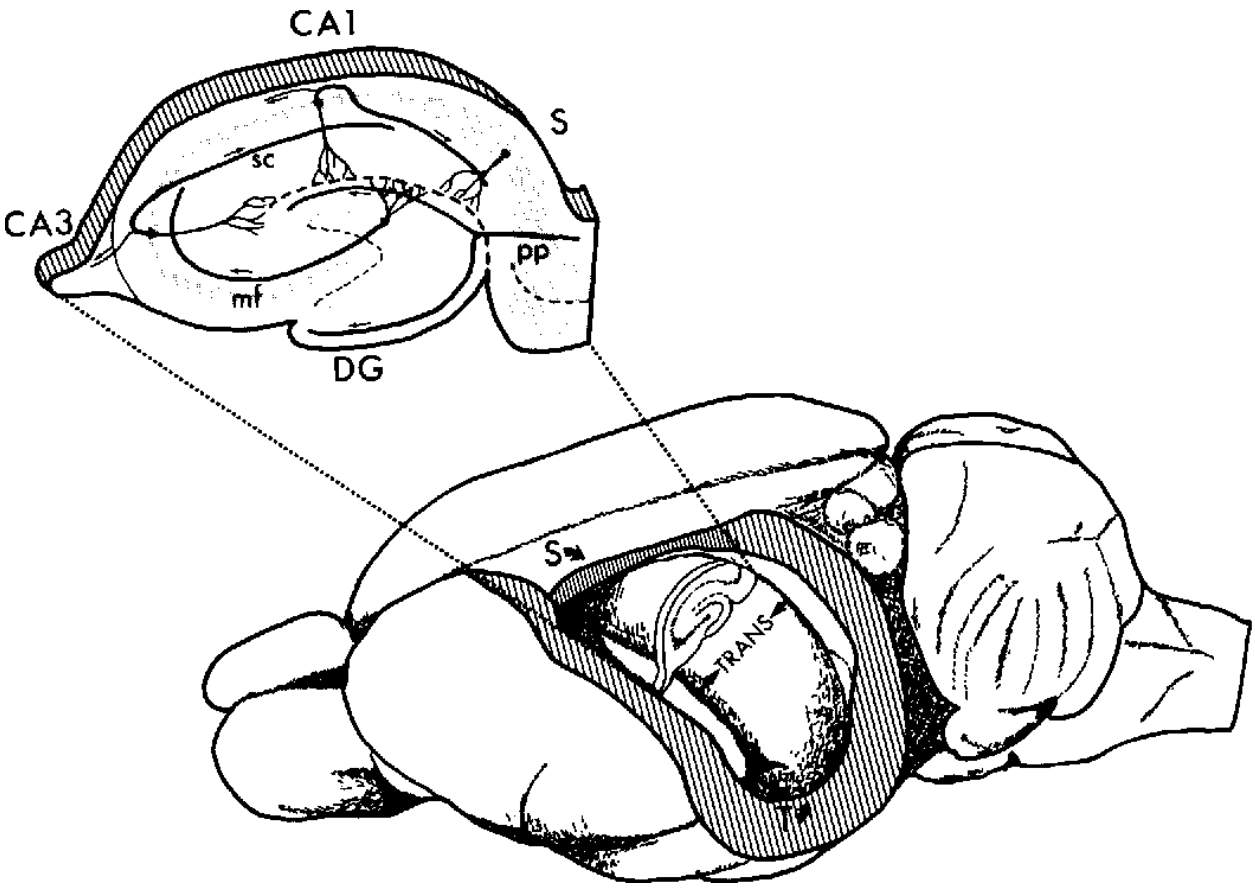


Figure 1-2. The rat hippocampal formation

Reprinted from Amaral and Witter (1989), with permission from Elsevier. Abbreviations: DG (dentate gyrus); mf (mossy fibers); pp (perforant path); SC (Schaffer collaterals).

A typical example used to illustrate pattern separation, dating back to at least the early 1990s (e.g., O'Reilly & McClelland, 1994), is that pattern separation helps us distinguish where we parked our car from one day to the next (e.g., Schapiro et al., 2017). I will instead use an example from Penny Lanes, not parking lots. Earlier this month, I overheard a radio host talking about an English musician whose illustrious career was overshadowed by playing the piccolo trumpet solo in Penny Lane. That got me wondering whether anyone has recently covered the Beatles song and how they would recreate that signature solo. I then discovered a marvelous performance of Elvis Costello performing in the East Room of the White House in 2010. The

guest of honour was Paul McCartney, who was being celebrated for receiving the Library of Congress Gershwin Prize for Popular Song. A stellar crowd, including President Barack Obama and Paul McCartney, were poised in the front row. The trumpet solo (*piccolo* trumpet solo) was played by a stalwart master sergeant from "The President's Own" United States Marine Band (as Elvis Costello elatedly announced to much applause). Having started on this journey, I searched for more Penny Lanes and found James Corden's Carpool Karaoke with the famous Beatle riding shotgun. They drove through Liverpool lanes, all the while carpool karaoke-ing Fab Four hits. Paul got out of the van and signed his name to the famous sign at the top of Penny Lane. They visited the barbershop where the barber (a woman now) still shows photographs on the wall.

Suppose anyone mentions Penny Lane, piccolo trumpets, Carpool Karaoke or Elvis Costello, or barbers showing photographs. In that case, I have a dozen or so ways to complete my memories of that 30 minutes, or so I went down a Penny Lane roundabout. That recollection might be about my episodic memory of the White House performance or the carpool singalong with Sir Paul. These memories are intertwined, but through pattern separation, their elements are distinctive. So, I don't remember James Corden sitting in the audience between Michelle Obama and Paul McCartney. Nor do I place a member of the marine guard marching along a Liverpool street while Elvis Costello barks about a fireman's clean machine. Pattern separation and pattern completion make all my Penny Lanes — in my ears and in my eyes — shiny and wet beneath my own blue suburban sky.

1.2 Evidence hippocampus is specialized for pattern separation

Despite pattern separation fitting nicely into broader theories of episodic memory and the hippocampus, it is a relatively new arrival to the field of memory research. Twenty-five years ago, one would not have a found typical and atypical pattern separation being the subject of a Ph.D. dissertation. If deficiencies were found with the brain's ability to keep memories unique, they likely would have been attributed to more general aspects of faulty memory, such as confabulation (Kopelman, 1987). Alternately, an inability to pattern separate might be considered a side effect of neurodegenerative processes that affect the delayed recall of memory more broadly, such as a symptom of Alzheimer's disease (Locascio et al., 1995). Then, it is not surprising that the turn of the century authoritative *Oxford Handbook of Memory* (Tulving &

Craik, 2000) makes no mention of pattern separation (never mind its typicality or atypicality) anywhere within the 700 pages between its covers.

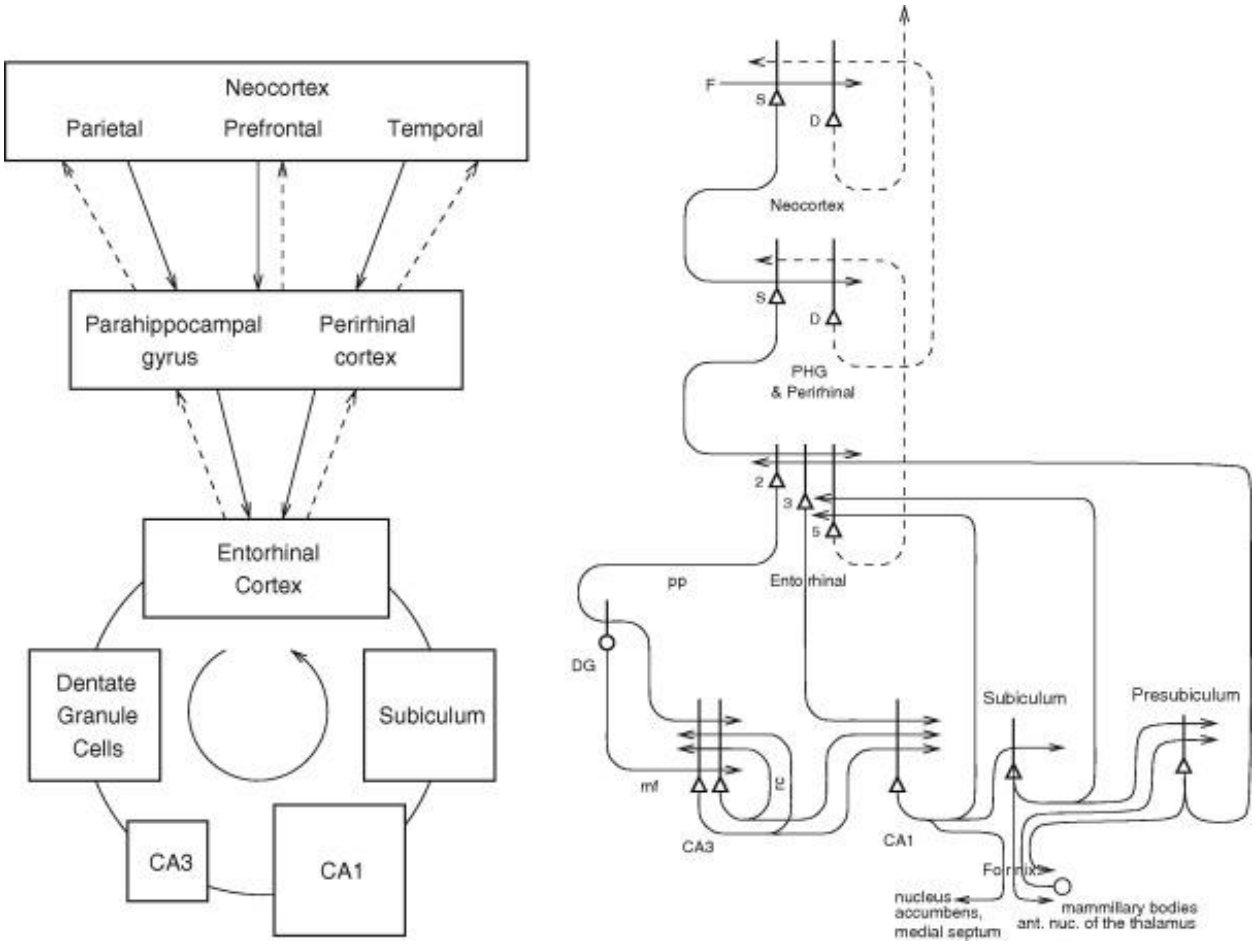


Figure 1-3. The neural architecture of pattern separation and pattern completion

Left: forward and back projections in the entorhinal cortex and hippocampal formation. **Right**: Detailed representation of excitatory neurons within the trisynaptic circuit. Figure reprinted from *Neurobiology of Learning and Memory*, 129, Edmund T. Rolls, Pattern separation, completion, and categorisation in the hippocampus and neocortex, 4–28, Copyright (2016), with permission from Elsevier. Figure Abbreviations. "D: Deep pyramidal cells. DG: Dentate Granule cells. F: Forward inputs to areas of the association cortex from preceding cortical areas in the hierarchy. mf: mossy fibers. PHG: parahippocampal gyrus and perirhinal cortex. pp: perforant path. rc: recurrent collateral of the CA3 hippocampal pyramidal cells. S: Superficial pyramidal cells. 2: pyramidal cells in layer 2 of the entorhinal cortex. 3: pyramidal cells in layer 3 of the entorhinal cortex. The thick lines above the cell bodies represent the dendrites." (Rolls, 2016, p. 6).

1.2.1 Animal studies

The first experimental evidence supporting computational models of pattern separation was found not in humans but in animal studies (Hunsaker & Kesner, 2013; J. Leutgeb et al., 2005, 2007; S. Leutgeb et al., 2004). A common approach involved investigators training rodents on particular environments and then probing the rats' ability to discriminate between modified versions of previously learned spatial/temporal events. Using this paradigm, Leutgeb et al. (2007) found that subtle changes to a rat's environment alter place-modulated cells in the DG. When the scene was made even more different, the CA3 subfield, but not the DG, became active (J. Leutgeb et al., 2007). Other studies used rodents with lesions to regions-of-interest. Ahn & Lee (2014) found that rats with damage to their hippocampal formation could reach performance similar to controls on a visual pattern-scene learning task. However, when the patterns in the scenes were made ambiguous — for example, a striped pattern changing direction — the lesioned rats were significantly impaired at identifying the lures. As theorized from computational models, the conclusion here was that the DG is critical in discriminating between similar past events, even when using nonspatial stimuli (Ahn & Lee, 2014).

1.2.2 Human behavioral testing

The initial human study of "behavioral pattern separation" arrived in 2007 (Kirwan & Stark, 2007). This study operationalized pattern separation as the ability to detect highly similar pictures in a continuous recognition memory paradigm. In the first of two experiments, young adults underwent fMRI testing while being presented with nameable visual objects (e.g., a rubber duck, a wheelbarrow). In the second experiment, faces were used as the test stimuli. Participants in both experiments were taxed on their ability to discriminate previously seen items (targets) from highly similar items (lures) or different items (foils). The investigators predicted the ability to identify the lures both as new and as similar depended on "adequate representation of differences between the stimuli, which is the definition of computational pattern separation" (Kirwan & Stark, 2007, p. 626). They found that participants were accurate at identifying visual object targets and foils as new and old. However, participants were relatively weak at identifying the pictures as similar (54.49% accurate), incorrectly calling them old 33.61% of the time (Kirwan & Stark, 2007). Neuroimaging results were unable to pinpoint activity in hippocampal subregions (e.g., DG/CA3). However, the authors observed signals in the hippocampus that they speculated corresponded with lure discrimination (Kirwan & Stark, 2007).

The Kirwan and Stark study set the template for most behavioral testing of pattern separation from 2007 to the present. The visual object-based paradigm they used was further developed and refined, eventually being reintroduced as the Behavioral Pattern Separation Task — Object Version (BPS-O; Stark et al., 2013), later renamed the Mnemonic Similarity Task (MST; Stark et al., 2015). The MST is available as a free, downloadable Windows-based program. The use of the MST in hundreds of studies has informed much of what we know about human behavioral pattern separation over the past decade. In addition, the MST's value as a computerized cognitive screening tool for neurodegenerative pathologies such as Alzheimer's disease is a promising area of study (Papp et al., 2021; Stark et al., 2019).

One of the key ways the MST has helped broaden our knowledge of the relationship between the hippocampus and pattern separation is through pitting young versus old/patients versus control in tests of mnemonic discrimination. For example, older individuals with reduced hippocampal volumes, as well as patients with hippocampal lesions, are impaired relative to younger adults (or age-matched controls) on the MST (Baker et al., 2016; Bakker et al., 2008b; Bennett et al., 2019; Doxey & Kirwan, 2015; Nauer et al., 2020; Riphagen et al., 2020). Based on this evidence, researchers have concluded that the MST and other visual lure discrimination (or mnemonic discrimination) tests are functionally sensitive to hippocampal pattern separation (Kirwan & Stark, 2007; Stark et al., 2013, 2019; Stark & Stark, 2017).

1.2.3 Human neuroimaging

Exposing participants to visual lures during high-resolution functional magnetic resonance imaging (fMRI) has helped localize the neural correlations of pattern separation. Bakker et al. (2008) and Lacy et al. (2011) used 3 Tesla (T) fMRI to scan young adults. Bakker et al. found that the participants' DG/CA3 was more active than other subregions of the hippocampus when presented with lure items. Lacy et al. (2011) reported that the DG/CA3 responds to incoming signals in a stepwise manner, where small changes in the input result in a marked shift in representation. In contrast, the CA1 subfield activity varied in a seemingly more graded increase in intensity depending on the relative similarity of the item presented and whether it was a first or second presentation (Lacy et al., 2011). Doxey and Kirwan (2015) discovered that precision in pattern separation in older and younger participants correlated with brain volumes in the left DG and CA3, more than it did in other areas of the MTL (Doxey & Kirwan, 2015). More recently,

ultra-high-resolution 7 T MRI and multivariate pattern analysis (Berron et al., 2016; Molitor et al., 2021) have provided a way to distinguish between brain signals localized to DG or CA3 subfields. In a paradigm using a spatial scene-similarity task, it was found that the DG, more so than the neighbouring CA3, pattern separates representations of similar scenes (Berron et al., 2016).

Furthermore, broader, whole-brain neuroimaging has expanded our knowledge of neocortical areas, which may pattern separate in conjunction with hippocampal subregions (Nash et al., 2021; Stevenson et al., 2020). Nash et al. found a concentration of hippocampal activity (localized to the subiculum) in an MST-based functional neuroimaging study of young adults. The exploratory analysis also revealed widespread brain activity, although no regions were found to indicate a pattern separation profile similar to that found in the hippocampus (Nash et al., 2021). However, a connectivity analysis revealed significant pattern separation activation patterns between the left hippocampus and the dorsal medial prefrontal cortex (Nash et al., 2021).

1.2.4 Patient testing

Detailed observations and descriptions of single cases of individuals with focal damage to specific hippocampal subfields are rare. That is likely because patients with memory impairments following hippocampal damage typically have lesions that cannot be localized to the DG/CA3. Indeed, their brain damage often extends beyond the MTL. Such widespread deficits make it difficult to localize pattern separation impairments to the human DG or CA3. Despite these qualifications, the few patient studies that have been published have provided intriguing results. For example, Kirwan et al. (2012) tested three hippocampal amnesic cases in a modified recognition memory paradigm (using images of objects or faces). As with healthy controls, the amnesiacs could identify targets and foils correctly; but unlike controls, they were impaired at recognizing lures. These findings were interpreted as a deficit in pattern separation due to hippocampal lesions, possibly due to a dysfunctional DG (Kirwan et al., 2012).

Target and foil accuracy within normal limits of controls was also found in MST testing of patient BL (Baker et al., 2016). This patient stands out in the literature as being the only known case of suspected bilateral ischemic lesions thought to be limited to the DG of the hippocampus (Baker et al., 2016). BL’s accuracy for lure discrimination was severely impaired relative to

controls, supporting computational theories, animal studies and human neuroimaging. As BL is the focus of two studies described in this dissertation, I will expand more upon the presumed etiology of his behavioral pattern separation deficits in proceeding sections.

1.3 Missing empirical evidence for pattern separation

Based upon the evidence summarized above, researchers have concluded that visual mnemonic discrimination tests are functionally sensitive to the neurobiological process of hippocampal pattern separation (Baker et al., 2016; Kirwan & Stark, 2007; Stark et al., 2013, 2019). This assertion may be premature. Despite the preponderance of studies of pattern separation over the past 15 years, little is known about whether hippocampal pattern separation works 1) in other modalities or cognitive domains; 2) through interacting with prior knowledge or pre-experimentally novel information; and, 3) in concert with nonmnemonic perceptual activities. My research systematically examines these gaps in our understanding of pattern separation as a hippocampally dependent episodic memory process.

1.3.1 Pattern separation in non-visual domains

In theory, pattern separation "expansion recoding" (Knierim & Neunuebel, 2016) can be performed across any sensory/perceptual domain (Hunsaker & Kesner, 2012; Kent et al., 2016). Despite the reliability and ubiquity of studies on behavioral discrimination of visual stimuli, investigators lack evidence to confirm whether pattern separation generalizes to other modalities (Liu et al., 2015). Our understanding of behavioral discrimination in humans also lags our broader knowledge of episodic recognition memory. For example, modality-specific differences are apparent when contrasting auditory and visual objects in recognition memory experiments (M. Cohen et al., 2009; Gloede et al., 2017), including those using naturalistic sounds (Bigelow & Poremba, 2014). Even within the visual modality, it is unclear if the hippocampus and its subfields have a bias towards discriminating specific perceptual inputs, particularly those which assist in spatial mapping (Gilbert et al., 2001; O'Reilly & Rudy, 2001) or respond to oddball visual stimuli (Barense et al., 2007, 2010).

The dearth of evidence from outside the visual domain is particularly problematic for pattern separation theorists operating within the camp of complementary learning systems (CLS; McClelland et al., 1995; Norman & O'Reilly, 2003). They conceive the hippocampus as agnostic

to the modality of information processed when encoding similar memories (Huffman & Stark, 2014; Larocque et al., 2013). With each representation in the hippocampus encoded distinctly, pattern separation and pattern completion would facilitate learning and memory across multiple perceptual domains (Huffman & Stark, 2014; Hunsaker & Kesner, 2013; O'Reilly & McClelland, 1994).

1.3.2 Pattern separation of non-semantically familiar stimuli

Just as we know relatively little about behavioral pattern separation outside of the visual domain, we also have a limited understanding of how pattern separation operates upon stimuli with no pre-experimental familiarity. The use of visual stimuli with pre-experimental associations — for example, stimuli that can be semantically identified (e.g., a tricycle) — could point to other confounds: that is, whether the conceptual knowledge of the item leads participants to produce a linguistic semantic association when mentally processing the object (e.g., "tricycle"), or an episodic autobiographical association (e.g., "that looks like the trike I received for my fourth birthday"). This conscious elaboration facilitated by these semantic or episodic conceptual "tags" may influence pattern separation/pattern completion and compromise the experimental paradigm (Hunsaker & Kesner, 2013; Liu et al., 2015). Alternately, some stimuli may evoke domain-specific semantic processing in the neocortex or other areas upstream of the hippocampus (Hunsaker & Kesner, 2013; Kent et al., 2016).

1.3.3 Extra-hippocampal perceptual and cognitive relationships

Kent and colleagues (2016) described five "surprising hypotheses" of how pattern separation is incorporated with other brain activities. Number one on their list was the hypothesis that pattern separation may not be limited to the DG and that it is "fundamental to many aspects of cognition, including perception; it is not just for memory" (Kent et al., 2016, p. 2). Tentative support for this speculation on the perceptual side comes from recent findings that older adults' performance on the MST is significantly and positively correlated with their visual acuity (Davidson et al., 2019). Early support for Kent et al.'s assertion on the cognitive side is evidence that MST accuracy correlates with general cognitive abilities, not necessarily with long-term memory (Foster & Giovanello, 2020; Pishdadian et al., 2020). Furthermore, a high-resolution whole-brain investigation of young adults completing the MST showed that the task involves areas of the

hippocampus and a network of brain regions outside of the MTL, including the dorsal medial prefrontal cortex (Nash et al., 2021).

1.4 Rationale for present studies

We must investigate the gaps in our understanding of how pattern separation works in domains other than visual object perception and in concert with perceptual activities. These insights will help clinicians better construct and administer pattern separation tests as neuropsychological indicators of hippocampal integrity (Stark et al., 2019). Filling these gaps will also help us better understand the extent of hippocampal processing of highly similar inputs to building a unifying theory of hippocampal-neocortical interactions (Kent et al., 2016). Furthermore, given the critical role ascribed to pattern separation for episodic memory, it is crucial to determine whether pattern separation effects can be detected through visual lure discrimination in memory and other tests requiring fine mnemonic and perceptual discrimination. A key question here is whether these effects are related to performance on other tests of episodic memory that decline with age and in hippocampal patients whose deficits resemble age-related disorders.

Pursuing answers to these questions is at the heart of this dissertation. The proposed research on memory and perception will combine novel behavioral paradigms and electrophysiological (EEG) techniques sensitive to the temporal dynamics involved in oddity detection to better understand the nature, extent, and brain dynamics of deficient pattern separation. Participants will include older and younger adults and a rare individual with lesions to his DG. The research will address unanswered questions about pattern separation and the hippocampus's role in learning and memory across other processing domains, modalities and involving different types of stimuli. I will also investigate the question of whether pattern separation involves non-mnemonic abilities and, if so, whether it interacts with other neural and cognitive processes such as categorical perception, visual perceptual memory, and predictive coding.

1.5 Methodological approach

1.5.1 Objectives and participants

The research described in this work primarily aimed to determine if presumed deficits in pattern separation: a) apply to perception as they do to memory (Aim 1); b) extend to modalities other than vision, notably audition (Aim 2); and, c) interact with prior knowledge or can be detected

using abstract stimuli (Aim 3). In addition, three secondary aims were also intended for this work: whether presumed deficits in pattern separation a) are evident, even within vision, for stimuli such as faces, which presumably do not crucially depend on the hippocampus (Aim 4); b) can be measured at encoding, as well as during retrieval (Aim 5); and, c) are detectable in a patient with a hippocampal lesion (Aim 6). Three groups of participants were recruited: young adults (Experiment 2 and 3; age range: 18-29 years old); middle older adults (Experiment 1 and 2; age range 48–66); older adults (Experiment 2; age range 67–93); and an individual with a hippocampal lesion (patient BL, Experiments 1 and 2). I expected performance related to pattern separation to be worse in both middle older and older adults than young adults and worse in a patient with a hippocampal lesion relative to controls.

To address the aims described above, I ran three experiments. These experiments were comprised of novel and traditional pattern separation tests. The novel tests also assessed perceptual discrimination and categorization. The data I collected and analyzed allowed me to make inferences about the nature, extent, and brain dynamics of pattern separation in younger, middle older, and older adults and in a hippocampal patient.

Healthy older and younger adults were recruited from York University, Baycrest Health Sciences (via an internal research participant database), and the community. Sample sizes were based on power analyses or sample sizes from previous studies. All non-student participants received monetary compensation for their participation. Student participants recruited via the York University Research Participant Pool received course credits. Informed consent was obtained in accordance with the ethics review boards at York University and Baycrest and conformed to the Canadian Tri-Council Research Ethics guidelines.

Included in two of the three studies was patient BL, a male in his late 50s with 13 years of education. In 1985, BL was diagnosed with hypoxic-ischemic brain injury following an electrical injury and cardiac arrest (Kwan et al., 2015). Standard neuropsychological testing with BL has revealed mildly impaired anterograde memory and moderately impaired retrograde episodic memory. High-resolution 3T MRI scans of BL’s hippocampus have indicated that he has selective bilateral ischemic lesions limited to the DG and a portion of CA3, CA3 (See Figure 1-4). Other regions implicated in pattern separation and pattern completion, including entorhinal and perirhinal cortices, appear unaffected. A 2016 study reported that BL has difficulty

distinguishing between studied targets and unstudied lures that are visually similar (Baker et al., 2016). In addition, he displays a heightened tendency to recognize studied scenes from degraded pictures. Findings converge on evidence that volume loss within the DG/CA3 tracks the brain's ability to pattern separate (Bennett et al., 2019; Chadwick et al., 2014; Doxey & Kirwan, 2015; Riphagen et al., 2020).

1.5.2 Statistical analyses

Statistical analyses were done using SPSS Version 28 or the Palamedes toolbox (Prins & Kingdom, 2018) for MATLAB. When necessary, I ran *t*-tests, Pearson correlations, and ANOVAs; multiple comparison corrections were applied using the Bonferroni or Games-Howell procedures (Field, 2018; Sauder & DeMars, 2019). Confidence intervals for correlations and paired-samples *t*-tests have been reported and interpreted according to accepted guidelines (Field, 2018; Howell, 2010), including using the bias-corrected accelerated (BCa) option in SPSS (Field, 2013). To better gauge recognition memory performance, the sensitivity measure *d'* was calculated as the normalized difference between hits and false alarms (Macmillan & Creelman, 2005). Variations on *d'* calculations have been described in specific studies. To ensure the reliability of findings in a single case, we compared BL's performance to healthy controls using Crawford and Howell's modified *t*-test for single cases (Crawford & Garthwaite, 2002).

1.6 Overview of Studies

1.6.1 Experiment 1: Does pattern separation mediate the interplay of memory and perception?

Experiment 1 examines the extent to which lesions to the DG also affect categorizing and discriminating familiar and unfamiliar morphed faces. Recent evidence suggests that the ability to differentiate highly confusable faces could involve pattern separation, mediated by the DG. Hippocampal involvement, however, may depend on existing face memories (Hoover et al., 2010). I tested patient BL and healthy controls in a categorical perception (CP) identification and discrimination experiment using images of famous and nonfamous faces to investigate these possibilities.

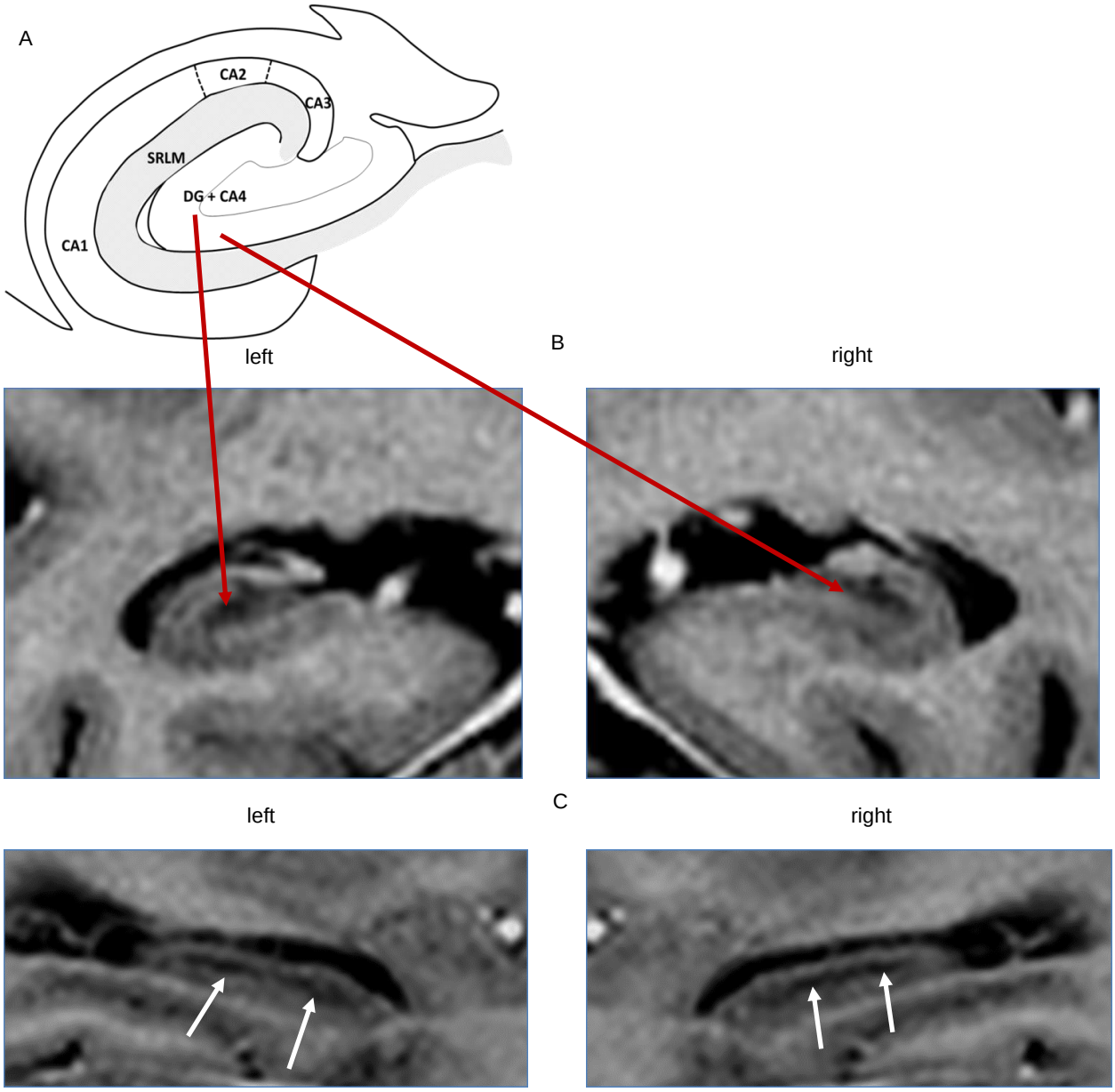


Figure 1-4. MRI scans of BL's hippocampus revealing lesions to the dentate gyrus

Notes. (A) Reference image, adapted from Duvernoy (2005), illustrates normal anatomy of the left hippocampus. The hippocampal strata (SRLM) lie along the interface between the dentate gyrus and CA1-CA3 subfields and subiculum. The SRLM is exposed as a band of hyperintensity on the inverted coronal T2-weighted hippocampal images as seen in B, and is a landmark to define the area of dentate gyrus. (B) The inverted T2 through the middle body of BL's hippocampus shows a hypointense lesion (hyperintense in non-inverted T2) almost exclusively affecting dentate gyrus. (C) T2 of the sagittal view depicts the length of the hippocampal lesion, which extends across almost the entire dentate gyrus in both hemispheres (arrows).

1.6.2 Experiment 2: Are comparable deficits in pattern separation observed across vision and audition in young versus older participants and in patients versus healthy controls?

Experiment 2 sheds light on the relatively unexplored aspect of human behavioral discrimination in the auditory domain. Modality differences in performance would suggest that vision has privileged access to pattern separation mechanisms. Variations in performance across the lifespan — as well as in patient BL — will implicate hippocampal involvement as, within the hippocampus proper, volume loss to the DG/CA3 subfields and connecting pathways are also associated with age-related functional declines (Small et al., 2002; Wu et al., 2008; Yassa, Mattfeld, et al., 2011). Furthermore, volume loss within the DG/CA3 tracks declines in the brain's ability to pattern separate (Bennett et al., 2019; Chadwick et al., 2014; Doxey & Kirwan, 2015; Riphagen et al., 2020).

1.6.3 Experiment 3: Does auditory pattern separation rely on prior knowledge?

In Experiment 3, I combine a behavioral paradigm with the brain's perceptual discrimination index, known as "mismatch negativity" (MMN; Näätänen et al., 1978), to determine the neural substrates enabling pattern separation. Humans are very good at pattern separating or differentiating highly similar inputs belonging to separate yet overlapping events into discrete episodes at encoding. This process likely depends on our ability to encode similar sensory input into distinct memory representations automatically. MMN experiments with clinical populations provide some suggestions that the MMN response transcends its role as an index of perceptual discrimination and relates to higher-order cognitive processes, such as long-term memory (Alain et al., 1998; Baldeweg & Hirsch, 2015; Näätänen, 2019), although this has never been directly tested. In humans, behavioral pattern separation is classically illustrated by assessing participants' ability to differentiate pre-experimentally known visual objects that were studied from those that were unstudied, some of which are visually and semantically similar to the studied items (Bakker et al., 2008b; Stark et al., 2015). Unclear is the extent to which mnemonic discrimination applies to the auditory domain or unknown abstract stimuli (Liu et al., 2015).

Chapter 2 , Study 1

2 The human dentate gyrus contributes to categorical face perception

2.1 Preface

For years, I have been intrigued by whether the hippocampus, independent of surrounding MTL areas, plays a role in face perception. The hippocampus has been ascribed a role in processing scenes; the extent to which its role applies to other stimuli, such as faces, is debated. Recent evidence suggests that the ability to differentiate highly confusable faces could involve pattern separation mediated by the hippocampus's DG subfield. Hippocampal involvement, however, may depend on existing face memories, which may or may not be dependent on this area of the MTL.

To answer these questions, I set out to examine the status of categorical face perception in BL, a rare individual with selective lesions to the DG of his hippocampus and an established deficit in pattern separation. CP, which possesses research literature dating back to the 1950s, shares psychophysical properties with pattern separation. For example, both phenomena include the presumption of sparse and invariant coding and all-or-none thresholds that transform linear inputs into nonlinear representations. I was encouraged by the prospect that both pattern separation and CP could be combined in one experiment that could test the relationship between memory and perception. Furthermore, the use of faces, which can be morphed from one identity to another, allowed me to examine whether face perception depends on hippocampal integrity.

At a time when scientific findings are under intense scrutiny and converging evidence vital, this lesion study set out to provide a direct test in humans of a specific role for the hippocampus that extends beyond memory to perception and beyond scenes to faces. This study, which I ran in collaboration with Dr. R. Shayna Rosenbaum, Dr. Morris Moscovitch, Yarden Levy, and Ariana Youm, provides an essential missing link in understanding the perceptual and mnemonic processes involved in face processing by the DG.

2.2 Introduction

A morphed image of Vladimir Putin and Donald Trump on the cover of *Time* magazine (July 30, 2018) appears to have equal parts Trump and Putin (Figure 2-1). By straddling an identification boundary between the two political figures, the illustration, created by artist Nancy Burson, achieves the publication's editorial purpose. The unsettling ambiguity created by the hybrid image's reduced discriminability also highlights a unique property of human perception and memory: our natural bent to a) generalize categorically, and b) differentiate perceptually between items that lie along a physical (sensory) continuum. This process is known as categorical perception (CP; Studdert-Kennedy et al., 1970). CP is clearly illustrated in our treatment of speech sounds, or colors in a rainbow, as discrete from one another, although they lie on uninterrupted continua of sound and light wavelengths, (Goldstone & Hendrickson, 2010). The tendency to categorize and differentiate endures even when a continuum is artificially created, as in the Putin-Trump mash-up (Beale & Keil, 1995). Here, we examine the extent to which lesions to the DG — a subfield of the hippocampus necessary for disambiguating similar input in memory through a process known as pattern separation (Berron et al., 2016) — may also have differential effects on the perception of familiar and unfamiliar morphed faces.

Although researchers have considered the core face network to be implicated in CP of faces (Freeman et al., 2010), none has suggested an essential role for the hippocampus. Recent work, however, indicates that differentiating highly similar faces may also be mediated by the hippocampus (Inhoff et al., 2019; Robin et al., 2019), possibly through pattern separation (Bein, Duncan, et al., 2020; Yaros et al., 2019). Indeed, such mnemonic discrimination of faces in middle-aged and older adults can be predicted by left DG and CA3 volume size (Kern et al., 2021). CP categorization mechanisms potentially also enlist the CA3 or CA1 hippocampal subfields, which receive inputs from the DG (Rolls & Kesner, 2006). These areas are implicated in pattern completion/generalization of visual stimuli (Bakker et al., 2008b; Schapiro et al., 2014) and could play a role in transforming face perceptual codes into memory representations (Quiroga, 2017).

Figure 2-1 "Trump/Putin 2018" (© Nancy Burson 2018)

Complicating whether pattern separation, completion, or generalization are factors in CP of faces is the role of perceptual expertise. For example, memory is cited as a reason why CP effects seem stronger for familiar faces than for faces learned in the lab (Angeli et al., 2008; Y. Lee et al., 2014). On the pattern separation side of the equation, perceptual expertise, represented by a person's pre-existing social categorization of faces (i.e., the "other race" effect), was found by Chang and colleagues (A. Chang et al., 2015) to play a role in the ability of young adults to discriminate morphed faces.

Still, direct evidence of the interaction of CP with memory remains elusive (Damper & Harnad, 2000). We hypothesized that the pattern separation function of the DG and the pattern completion/generalization functions of CA3/CA1, together with personal expertise, influence CP categorization/identification. Specifically, these elements push and pull on the operational markers of CP: the attendant effects of within-category "compression" (i.e., reducing perceived differences of faces within one identity category) and between-category "expansion" (i.e.,

amplifying perceived differences of faces straddling a category boundary (Studdert-Kennedy et al., 1970).

To test this hypothesis, we presented BL, an amnesic person with rare bilateral hippocampal lesions selective to the DG (Baker et al., 2016) and age-matched controls with blended images of famous faces (FF) and nonfamous faces (NF) in a CP identification and discrimination experiment. Baker et al. (2016) established that BL has a deficit in visual object pattern separation (also known as mnemonic discrimination). We predicted that if CP relies on the process of pattern separation, then BL would exhibit atypical behavior in identifying and discriminating NF relative to FF, as the former would show the greatest reliance on the DG in learning new face-identity information. Meanwhile, CP tasks that rely on generalization (i.e., within-category discrimination) would be more dependent on pattern completion or generalization, mediated, respectively, by BL's relatively intact CA3 and CA1 (Baker et al., 2016). The results of our tests provide a critical bridge between perception and memory in general and CP and hippocampally mediated pattern separation in particular.

2.3 Materials and methods

2.3.1 Control participants

We assessed CP in 38 neurotypical adults, matched in age and education to an individual with bilateral DG lesions and impaired pattern separation (BL, described next). Three controls were excluded from final analyses due to a mismatch between identification and discrimination faces (a programming error) and one control was excluded for being unable to discriminate faces at endpoints, resulting in a final test group of 34 middle-older control participants, 50–64 years of age [mean (SD) = 55.82 (4.18), 19 female]. We recruited all controls from the community via advertisements or participant databases at York University and Baycrest Health Sciences. Controls had a Montreal Cognitive Assessment (MoCA) score at or above 26 (out of a 30-point maximum). Participants provided written, informed consent in accordance with the ethics review boards at York University and Baycrest and standards of the Canadian Tri-Council Research Ethics guidelines.

2.3.2 Patient BL

To better understand how the DG region is also involved in learning and representing face categories, we examined CP abilities in BL, a memory-impaired individual with lesions to the DG. BL, who was 57.9 years old at the time of his last testing session, sustained a hypoxic-ischemic brain injury in 1985 following an electrical injury and cardiac arrest (Kwan et al., 2015). In 2015, high-resolution 3T MRI scans of BL's hippocampus revealed bilateral ischemic lesions that appeared to be restricted to the DG and a portion of the CA3 hippocampal subfield (Baker et al., 2016; Kwan et al., 2015). Whole-brain imaging (Baker et al., 2016) revealed that BL has relative volume loss in regions within his left superior-posterior parietal cortex (27% lower in volume than that of 8 controls) and right precuneus (26% lower in volume than that of 8 controls). Neuropsychological testing (Kwan et al., 2015) demonstrated that BL has borderline-low average memory for verbal material and impaired memory for unfamiliar visual material in the context of average intellectual function. We found BL's motor speed and dexterity were also affected. In addition, BL is impaired on a test of mnemonic discrimination (behavioral pattern separation) of visual objects (Baker et al., 2016). As measured by the Benton Facial Recognition Test, BL's face recognition was found to be within normal limits.

For the CP task, BL was tested on three different occasions: Session 1 (S1, September 2017), Session 2 (S2, December 2017), and Session 3 (S3, October 2018). Throughout S1, we found BL to be impaired at categorizing FF and NF, leading to shallow slopes (See Table 2-1), which were more indicative of continuous than categorical perception. His labeling of FF, but not NF, improved in S2. Nevertheless, S2 was characterized by biased FF discrimination at the 10–30% endpoint relative to the 70–90% endpoint (see Table 2-1). This skewed discrimination raised the possibility of learning effects between S1 and S2 and called into question our ability to average across these pairs for within-category FF analysis. After S2, we speculated that a large number of trials (856) and multiple learning sessions across the CP experiment might be placing a significant cognitive load on BL, impairing task performance. To address this concern, an experimenter responded on BL's behalf in S3. This last session took place 315 days after S2 (to mitigate learning effects). It was the only one in which BL's identification of both face types was within the limits of controls and, therefore, the only one in which we could attempt to contrast his performance with that of controls. That the experimenter responded on BL's behalf and not for control participants is similar to studies in which patients are equated with controls by

reaching a specified criterion, even if it takes more trials to reach that criterion relative to controls. Unless otherwise stated, the results of the last session are those reported here.

Table 2-1. BL's identification and discrimination over three sessions

	Identification				Discrimination (Within-Category)			
	Threshold (α)		Slope (κ)		10–30%		70–90%	
Session	FF	NF	FF	NF	FF	NF	FF	NF
S1	.45	.72	0.49	0.05	.30	.20	.40	.20
S2	.58	.85	2.43	0.47	.10	.15	.60	.20
S3	.49	.35	2.08	1.14	.25	.15	.25	.20

Note. FF = famous faces. NF = nonfamous faces. Threshold (α) = category boundary (Face 2 intensity proportion). Slope (κ) = the slope of the logistic curve at the contrast detection threshold (i.e., the first derivative of β, or the slope of logistic curve). Identification scores are reported in terms of proportion reported as Face 2. Discrimination scores are reported in terms of proportion correct.

2.3.3 Experimental design and statistical analyses

2.3.3.1 Face stimuli

Evidence from Beale and Keil (1995) have suggested that categorical perception can occur when using faces as a categorical item and morphing one face to another along an artificial continuum. For the present study, stimulus selection for the morphed pairs was initiated by downloading from the Internet pictures of faces of American and Canadian public figures (e.g., politicians, actors, musicians) who rose to fame within the last 30 years. For NF, pictures of faces of people who were not famous or recognizable were selected from an existing database (Y. Lee et al., 2014). We paired faces within FF and NF according to age, race, and gender (e.g., Ryan Gosling and Benedict Cumberbatch).

We processed all faces/face pairs according to Lee et al. (Y. Lee et al., 2014). Briefly, faces were cropped into ovals. An oval-shaped mask was generated for each image using Adobe Photoshop, consisting of a horizontal and a vertical region. The horizontal region consisted of 0.5 centimeters from the leftmost left eye to 0.5 centimeters to the rightmost right eye, a precise way to remove hair and ears from each face. The vertical region consisted of the length spanning from the forehead to the chin of each image. The resulting facial mask provided a consistent way

to reduce facial position variations across images within the oval and facilitated face morphing. This consistency was maintained by centering each facial mask at 3.0 x 4.7 degrees within the oval.

The resulting images were matched in pairs and morphed using FaceMorpher Lite (Luxand, Inc.), allowing one image to be morphed with another while matching for face feature coordinates. Morphs were created for 9, 10-degree interval transitions and labeled for the percentage of Face 2 in the pair. For example, 90% Benedict contained 10% Ryan and 90% Benedict; 80% Benedict contained 20% Ryan and 80% Benedict; 70% Benedict contained 30% Ryan and 70% Benedict; and, 60% Benedict contained 40% Ryan and 60% Benedict. In addition, a matching morph pair was created (50% Ryan and 50% Benedict). Face stimuli were presented electronically using E-Prime 2.0 software running on a Dell Latitude E5540 computer (Intel Core i7-4600U). The computer's screen size was 15.6 inches with a 1366 x 768 x 60-hertz resolution.

2.3.4 Procedure

Our experiment followed standard operationalization of CP (Liberman et al., 1957; Studdert-Kennedy et al., 1970) and was divided into two phases: an identification (or categorization) phase and a discrimination phase. General procedures mirrored those followed by Lee et al. (Y. Lee et al., 2014).

2.3.4.1 Famous face name recognition

Before testing, participants completed a famous face recognition task, allowing the experimenter to select a group of famous faces well-known to each participant. During this pre-test, the experimenter read a list of names, and the participant was required to note the context in which the celebrity was famous. The participant was also required to describe the celebrity's general appearance. Following these tasks, four pairs of famous faces (two pairs of women and two pairs of men) were selected for the FF category. Four pairs of NFs (two pairs of women and two pairs of men) were preselected to accompany the FF pairs.

2.3.4.2 Identification task

2.3.4.2.1 Training trials

We presented face image pairs in blocks of paired morphs. These blocks were randomized across participants, and trial order was randomized within blocks. In order to ensure that participants could demonstrate a benchmark capacity for successfully labeling FFs and NFs appearing in subsequent trials, each identification block was introduced with a learning task. Participants were presented with the cropped face pairs that would feature in the subsequent identification blocks during these training trials. The faces were shown side-by-side and without morphing (e.g., 100% Ryan and 100% Ben). Below each face, the celebrity's real name, or an invented name for the nonfamous person, was displayed. Participants had two minutes to study the face-name pairs. This training phase was accompanied by a recognition test of single faces at 100% to ensure participants could label each face appropriately (participants had a choice of two names). During the training trials, participants obtained feedback about whether their responses were correct. Training was complete after participants demonstrated on three consecutive trials that they could correctly select the name corresponding to each image presented at 100%.

2.3.4.2.2 Face-name labelling

During the identification blocks, participants categorized images that were morphed along the nine-interval continuum of contrasts described above and that spanned the two prototypes studied at training. Each image trial consisted of one morphed face presented in the middle of the screen, with one name appearing above the face and one name presented below the face. These trials were randomly presented five times per morph pair per interval, leading to 20 faces (5 x 4 pairs) appearing in each morph step per category, with 180 trials in total for each level of face. We instructed controls to respond accurately and quickly to the identification question, *Who is this?,* for each morph by clicking the up or down arrow key in the direction of the perceived identity name (Figure 2-2). Patient BL named the face verbally and the experimenter responded on his behalf. All participants were given up to 4 s to make their choices. If they did not respond within 4 s, the image disappeared. The face names then remained alone on the screen until the participant made a selection.

2.3.4.3 Discrimination task

The images presented during the discrimination phase were identical to those presented during the identification task except that they were presented simultaneously as pairs to assess participants' ability to discriminate between highly similar morphed exemplars of the endpoint prototypes. The discrimination task began with participants studying each of the four famous and four nonfamous face pairs at 100% for two minutes. We did not test participants on their ability to identify the faces at 100%. Instead, the participants were randomly presented with 62 trials per pair at the following intensity levels of Face 2: 10-10%; 10-30%; 20-20%, 20-40%, 30-30%, 30-50%, 40-40%, 40-60%, 50-50%, 50-70%, 60-60%, 60-80%, 70-70%, 70-90%, 80-80%, 90-90%. For each "same" face (e.g., 10-10%), there were three trials per image pair, giving a total of 12 same trials across each same condition for each intensity interval. For each different FF or NF morph step (e.g., 10-30%), there were five trials per image pair, giving of total of 20 different trials across each FF or NF different intensity interval. To reduce the load of memory inherent in ABX or similar tasks (Gerrits & Schouten, 2004), we programmed face pairs to be presented at the same time, side-by-side on the screen (Figure 2-2). We instructed participants to focus on the two images presented in each trial instead of the identity of the faces and respond by way of an arrow press, within four seconds, if the images presented were the same or different.

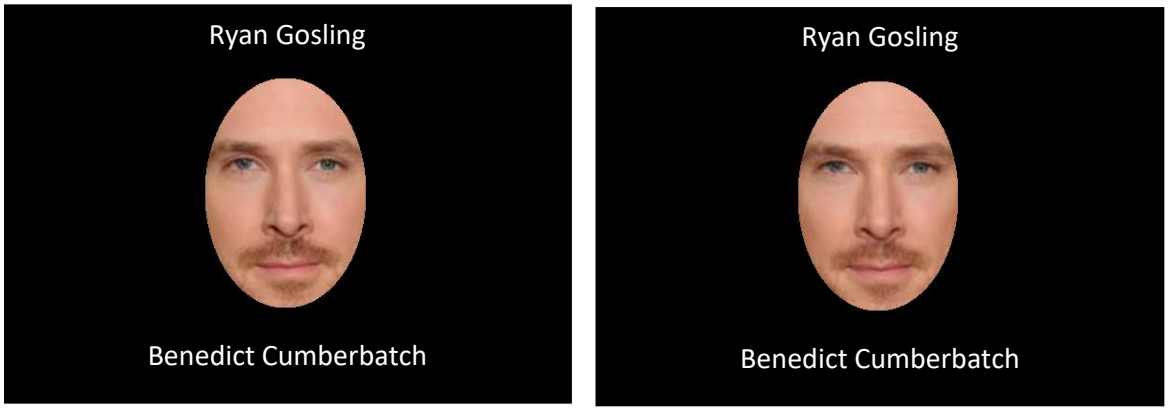
2.3.4.4 Scene classification and discrimination task

At the same time, we administered the experiment with FF and NF, we also ran a pilot identification and discrimination task. It consisted of morphed scene stimuli. It was run on controls and patient BL (during his first two testing sessions). The scene trials were ordered after the face trials (i.e., faces classification, scene classification, faces discrimination, scene discrimination). These data are not reported here because the stimuli we created did not serve their intended purpose.

2.4 Analysis

Although we followed a standard CP identification and discrimination two-phase experimental approach, we expanded on traditional data analyses in several ways. First, we applied a goodness-of-fit test to evaluate the logistic function used to model the measured psychometric function (i.e., participant classification). This function relates the proportion of trials assigned to

(A) Identification Phase: *who is this?*



(B) Discrimination Phase: *same or different?*

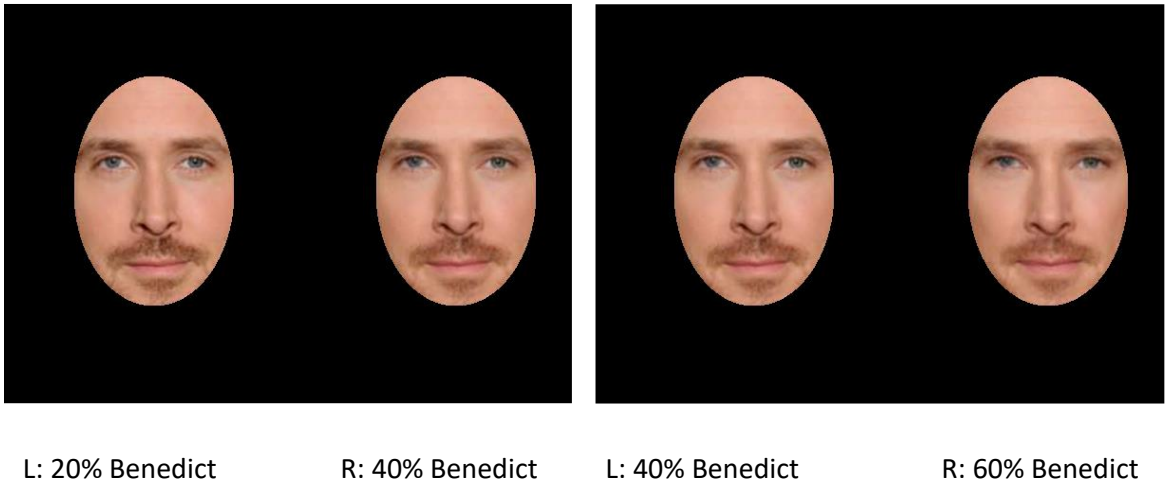


Figure 2-2. CP identification and discrimination phases with sample images

a progressive series of identification steps to the intensity of the stimulus in that continuum. When graphed, the logistic function takes on a sigmoidal or S-shaped curve. We anticipated that we would find distinct labeling combined with a sharp boundary between categories, thus meeting one of four operational criteria traditionally used to demonstrate CP in the domain of speech perception (R. E. Pastore et al., 1984; Studdert-Kennedy et al., 1970). The goodness-of-fit

test is well-suited to describe participants' ability to meet this criterion in other perceptual domains, such as face recognition.

Two additional operational criteria are usually evaluated during the discrimination phase (R. E. Pastore, 1987). Here, participants in CP experiments must display a detectable advantage, or "peaks" (Harnad, 1987b; Studdert-Kennedy et al., 1970) in discriminating stimuli that cross a category boundary (e.g., 40% of Benedict Cumberbatch's face and 60% of Benedict Cumberbatch's face). A closely related third operational criterion is the presence of "troughs" of inferior discrimination (Harnad, 1987b; Studdert-Kennedy et al., 1970) for within-category stimuli (e.g., 70% of Benedict Cumberbatch's face and 90% of Benedict Cumberbatch's face). These "peaks and troughs" criteria are traditionally analyzed by contrasting proportion (or percentage) correct in within-category versus between-category trials. We expanded on such traditional CP data analysis by using signal detection measures (*d'*) to evaluate differential sensitivity in within- and between-category conditions. Signal detection measures are thought to be particularly appropriate for analyzing discrimination when using same-different tasks (Angeli et al., 2008; Macmillan & Creelman, 2005).

A final CP operational criterion — sometimes referred to as a "strong form" of CP (Macmillan & Creelman, 2005) — is thought to occur when there is a close correspondence between the identification phase and the discrimination phase (Liberman et al., 1957; Macmillan, 1987; McKone et al., 2001; Studdert-Kennedy et al., 1970). In this scenario, discrimination performance can be predicted from identification judgments. Researchers often fail to find evidence of such a relationship; discrimination is typically better than that expected from identification labelling ability alone (Macmillan, 1987; R. E. Pastore, 1987). Nonetheless, the strong criterion has historically dominated the other operational criteria, with some considering it CP's defining concept (Liberman et al., 1957; Macmillan et al., 1977; Massaro, 1987a; R. E. Pastore, 1987; Studdert-Kennedy et al., 1970). For our part, we chose to investigate predicted and obtained discrimination accuracy — and the concomitant relationship between discrete identification thought to rely primarily on memory and discrete discrimination thought to rely principally on perception (Y. Lee et al., 2014). We did so by analyzing predicted versus obtained results using mean absolute error (MAE) tests. We also implemented a novel approach for prediction, which predicts *d'* discrimination from identification results.

Analysis of the identification and discrimination data were done using IBM SPSS Statistics 27 or the Palamedes Toolbox (Version 1.10.9; Prins & Kingdom, 2018) for MATLAB. Where appropriate, effect sizes were reported and interpreted according to accepted guidelines (Field, 2013). We conducted post hoc comparisons using the Bonferroni correction. Specific analysis measures using this software for the two phases of the experiment are described below.

2.4.1 Identification analysis

2.4.1.1 Endpoint identification accuracy

Endpoint accuracy, or participants' ability to learn and identify faces at 90% intensity of Face 1 versus Face 2, was evaluated across face type using paired-samples *t*-tests in SPSS. The dependent variable was identification accuracy. We computed this value as the proportion of correct trials averaged across each face-name combination at each endpoint (i.e., 20 trials for 10% of Face 2 and 20 trials for 90% of Face 2). We considered endpoint accuracy as a measure of participants' ability to correctly match faces with names and a way of investigating potential biases in face-name combinations.

2.4.1.2 Identification psychometric function

For each participant, we coded the number of faces at each point along the 9-point continuum of stimuli intensity that participants perceived as Face 2 over Face 1 (i.e., Face 1 = 0 and Face 2 = 1). These identification counts, a function of a single predictor (Face 2 intensity), were used to compute the identification psychometric function (PF). The PF was derived through fitting a binary logistic regression model (Field, 2013; Kingdom & Prins, 2016) to each participant's data using the Palamedes toolbox for MATLAB. The model specifies a nonlinear function for the regression of a dichotomous Y (e.g., Face 1 or Face 2) on a single predictor, X_i (e.g., Face 2 intensity = .10) and can be given as follows (Kingdom & Prins, 2016; Wegrzyn et al., 2015):

Equation 1

$$F_{Logistic}(x;\alpha,\beta) = \frac{1}{1 + e^{(-\beta(x-\alpha))}}$$

in which parameters α and β correspond, respectively, to the threshold and slope of the PF (Kingdom & Prins, 2016) estimated from each participant's identification data. The threshold (α)

is the point at which the proportion of responses of one stimulus relative to another reaches a criterion. This point is usually 50% in CP experiments using morphed faces (Angeli et al., 2008; Beale & Keil, 1995; Y. Lee et al., 2014; Levin & Beale, 2000; McKone et al., 2001; Rotshtein et al., 2005; Wegrzyn et al., 2015). In our experiment, the threshold aligns with the category boundary, or the point of subjective equality, beyond which participants began to identify a morphed face as Face 2 more than Face 1. A plot of the logistic function typically takes on a S-shaped (sigmoid) curve (Kingdom & Prins, 2016; Wegrzyn et al., 2015). The threshold is assumed to be the steepest point of the sigmoidal curve (McKone et al., 2001; Prins & Kingdom, 2018).

We expected that participant identification data would be best characterized nonlinearly, as represented by the logistic function. This sigmoidal or S-shaped change tracks identification from left to right as contrasts of the stimuli moved stepwise from one endpoint prototype (e.g., 90% of Ryan Gosling's face and 10% of Benedict Cumberbatch's face) to another (e.g., 10% of Ryan Gosling's face and 90% of Benedict Cumberbatch's face). The logistic function is thought to express the tendency of neurons to become "saturated" once a firing threshold (e.g., where perception changes qualitatively and confidently from one face to another) is reached (Rolls, 2008). We also expected that the sharpest change (i.e., the steepest slope) in classification would occur at the threshold (or category boundary). This boundary would be at, or near, a predicted point of subjective equality/maximum ambiguity (approximately 50%), where a concomitant change in identification from one face-name category to another typically occurs (Angeli et al., 2008; Beale & Keil, 1995; Y. Lee et al., 2014; Rotshtein et al., 2005).

We fit the logistic function to each participant's data using a maximum likelihood criterion in the Palamedes toolbox (Prins & Kingdom, 2018) for MATLAB. We created a series of vectors to contain the data, including stimulus intensity levels and the proportion of responses of a Face 2 judgment over a Face 1 judgment across morph steps. To attenuate potential bias in the parameter estimates, relatively small guess and lapse rates for the model function were set at .02 (Kingdom & Prins, 2016; Klein, 2001; Stokes et al., 2019). The steepness of the estimated threshold (κ) for each participant was generated by finding the first derivative of the slope at the point of subjective equality.

2.4.1.3 Identification goodness-of-fit

In order to determine how well the identification of faces aligned with the logistic regression model, we ran a goodness-of-fit routine in the Palamedes toolbox for MATLAB (Prins & Kingdom, 2018) on each participant's data. This routine supplied deviance estimates, or a measure of the lack-of-fit of the observed data to the model PF (J. Cohen, 2003). We then analyzed the aggregate deviation scores in each condition using the chi-square cumulative distribution function, chi2cdf(x,v,'upper'), in MATLAB. We followed guidelines that an unacceptable fit corresponds to a probability value of $p < 0.05$ (Kingdom & Prins, 2016).

2.4.2 Discrimination analysis

2.4.2.1 Obtained discrimination: Proportion correct

As we wanted to use signal detection measures (Macmillan & Creelman, 2005) to evaluate the unbiased discrimination sensitivity of participants, we first averaged hits (percentage correct) for endpoint morph steps (.10–.30 and .70–.90). To establish that these within-category faces were strongly correlated and without statistical variation, we assessed their differences using paired-samples *t*-tests. We also calculated hits for between-category faces, using the 40–60% morph step. False alarms were calculated for the respective identical pairs which could be matched with the within- or between-category endpoints (e.g., 10–10%, 60–60%). False alarms were calculated as the ratio of incorrectly responding *different* to these same pair trials.

2.4.2.2 Obtained discrimination: *d'*

The *d'* values for within-category faces and between-category faces were determined using Palamedes MATLAB routines for a one alternative-forced-choice same-different (1AFC Same-Different) task within a differencing model, or one in which stimuli rove along a continuum (Kingdom & Prins, 2016; Macmillan, 1987). The decision strategy assumed by this model is that participants respond *different* only when the perceived dissimilarities in each pair exceeds a criterion (Kingdom & Prins, 2016; Macmillan & Creelman, 2005). This criterion is thought to be conservative in same-different tasks, with observers more likely to answer "same" than different. The *d'* strategy outlined above responds to this bias inherent in same-different tasks (Kingdom & Prins, 2016; Macmillan & Creelman, 2005; Prins & Kingdom, 2018). Subsequent analysis of the discrimination data in SPSS Version 27 took advantage of the experiment's factorial design to

produce a 2x2 repeated-measures ANOVA. The factors were Familiarity (two levels) and Categorical Boundary (two levels), with the dependent variable being discrimination *d'*.

2.4.2.3 Prediction of discrimination from identification

A theoretical constant from the earliest CP experiments with speech sounds (e.g. Liberman et al., 1957) is that discrimination performance can be predicted from identification performance. The supposition is that participants can only discriminate to the extent in which they can categorize (Liberman et al., 1957; Macmillan et al., 1977; R. E. Pastore, 1987; Studdert-Kennedy et al., 1970). Therefore, the expected proportion correct in any discrimination trial, for example, one in which two stimuli (e.g. Face 2 at 10% intensity and Face 2 at 30% intensity) are presented, can be estimated from the proportion correct of Face 2 at 10% intensity and Face 2 at 30% intensity during the identification phase (Macmillan & Creelman, 2005; Massaro, 1975; Pollack & Pisoni, 1971). In other words, the probability of discriminating the two faces in any trial is consistent with the combined probabilities of the two faces measured at classification. We computed predicted discrimination scores for the proportion of correct, "different" responses to different trials using Eq. (2) (Massaro, 1975). We used it to estimate the correct discrimination accuracy (proportion correct) for any combination of two different stimuli as follows:

Equation 2

$$P(different|F_1 \neq F_2) = P(\text{"Face2"}|F_1)P(\text{"Face1"}|F_2) + P(\text{"Face1"}|F_1)P(\text{"Face2"}|F_2),$$

in which "Face2" equals the proportion of Face 2 responses during identification, "Face1" equals the proportion of Face 1 responses during identification (i.e., 1-Face 2); F_1 equals the first face in the image pair and F_2 equals the second face in the image pair.

We also employed a novel discrimination method to predict *d'* scores for identification, which involved computing the probability of correct "same" responses to same trials using Eq. (3) (Massaro, 1975), given as:

Equation 3

$$P(same) = (P\ Face\ 2)^2 + (P\ Face\ 1)^2,$$

in which *P Face 2* and *P Face 1* (i.e., 1-Face 2) correspond to the identification scores, and *P* (same) equals the estimated proportion correct at discrimination.

2.4.3 Patient analysis

To ensure the reliability of findings in single cases, we used Crawford and Howell's modified *t*-test for single cases (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). This test treats a control sample's data as sample statistics rather than population parameters (Crawford & Howell, 1998). In doing so, the Crawford and Howell *t*-test provides a way to control for Type I errors when testing whether a single case's score is significantly below that of a control group with fewer than 50 participants (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). This modified *t*-test can limit the power of statistical inference applied to a data set. Consequently, it can lead to overly conservative conclusions and Type II errors (false negatives). The program used to calculate the modified *t*-test, Singlims_ES (Crawford et al., 2010), reports estimates of the percentage of the normal population falling below a single case's score. Furthermore, it provides details on the confidence interval (CI) of the observed result and the estimated effect size (Crawford et al., 2010). The effect size supplied by Singlims_ES, z_{cc}, is a direct analog to Cohen's *d* (Crawford et al., 2010). Thus, it measures the standardized difference between the single case's score and the control mean. Interpreting these additional statistics (i.e., confidence intervals, effect sizes) provides researchers with more meaningful ways to evaluate a single case's data when typical significance levels (e.g., $p < 0.05$) are not met.

2.5 Results

2.5.1 Identification task

2.5.1.1 Controls competent at identifying the least confusable faces

To establish that participants could learn and correctly label faces, including those with no pre-experimental familiarity, we used paired-samples *t*-tests to contrast the identification accuracy of endpoint faces (10 versus 90% of Face 2). We found that controls showed a strong ability to identify FF at the 10% endpoint ($M = .97$, $SE = .01$) as well as at the 90% endpoint ($M = .96$, $SE = .01$). We failed to find evidence that the difference between the two endpoints, 0.01, which has a bias-corrected and accelerated confidence interval (BCa) 95% CI [–.01, .03], was significant $t(33) = 1.16$, $p = .256$, $d = .20$. Although participants had greater difficulty identifying the NF

endpoints, they could label both the 10% endpoint (*M* = .90, *SE* = .02) as well as at the 90% endpoint (*M* = .94, *SE* = .01) well above chance. We did not find evidence that the difference between the two NF endpoints, –.04%, was significant, BCa 95% CI [–.09, .00], *t*(33) = –1.97, *p* = .057. The difference represented a small-to-medium effect *d* = –.34, 95% CI [–.68, .01], leading us to speculate that — in line with what Lee and colleagues (2014) reported in one of their NF conditions — there might be a moderate bias to identify some NF faces.

2.5.1.2 Does identification follow a comparable logistic function in controls and patient BL?

2.5.1.2.1 Controls have typical midpoint identification thresholds

The underlying sensory, perceptual, and mnemonic mechanisms typifying the psychometric function of face categorization can be revealed by comparing the logistic function parameters of the FF and NF values. We found the thresholds for the logistic function for both FF (*M* = .50, *SE* = 0.01) and NF (*M* = .50, *SE* = 0.01) to be at .50, or the predicted point of subjective equality (). We did not find evidence that the very small divergence between the two thresholds, –0.005, was significantly different, BCa 95% CI [–.02, .01], two-tailed *t*-test, *t*(33) = –.53, *p* = .602, *d* = –.09. These findings illustrate middle-older, healthy controls' ability to categorize familiar and unfamiliar faces in a binary way. Such an ability, however, is a necessary but not a sufficient indicator of CP (McKone et al., 2001; Studdert-Kennedy et al., 1970).

Table 2-2. Logistic function parameters, BL vs. controls

	Control sample (N = 34)		
Logistic Parameter	*Mean*	*SE*	*BL's score*
FF threshold (α)	.50	.01	.49
NF threshold (α)	.50	.01	.35
FF slope (κ)	3.08	.22	2.08
NF slope (κ)	2.57	.20	1.14

Note. FF = famous faces. NF = nonfamous faces. Threshold (α) = category boundary (Face 2 intensity proportion). Slope (κ) = the slope of the logistic curve at the contrast detection threshold (i.e., the first derivative of β, or the slope of the tangent line to the curve at the threshold). Values for controls are averaged across participants in the group.

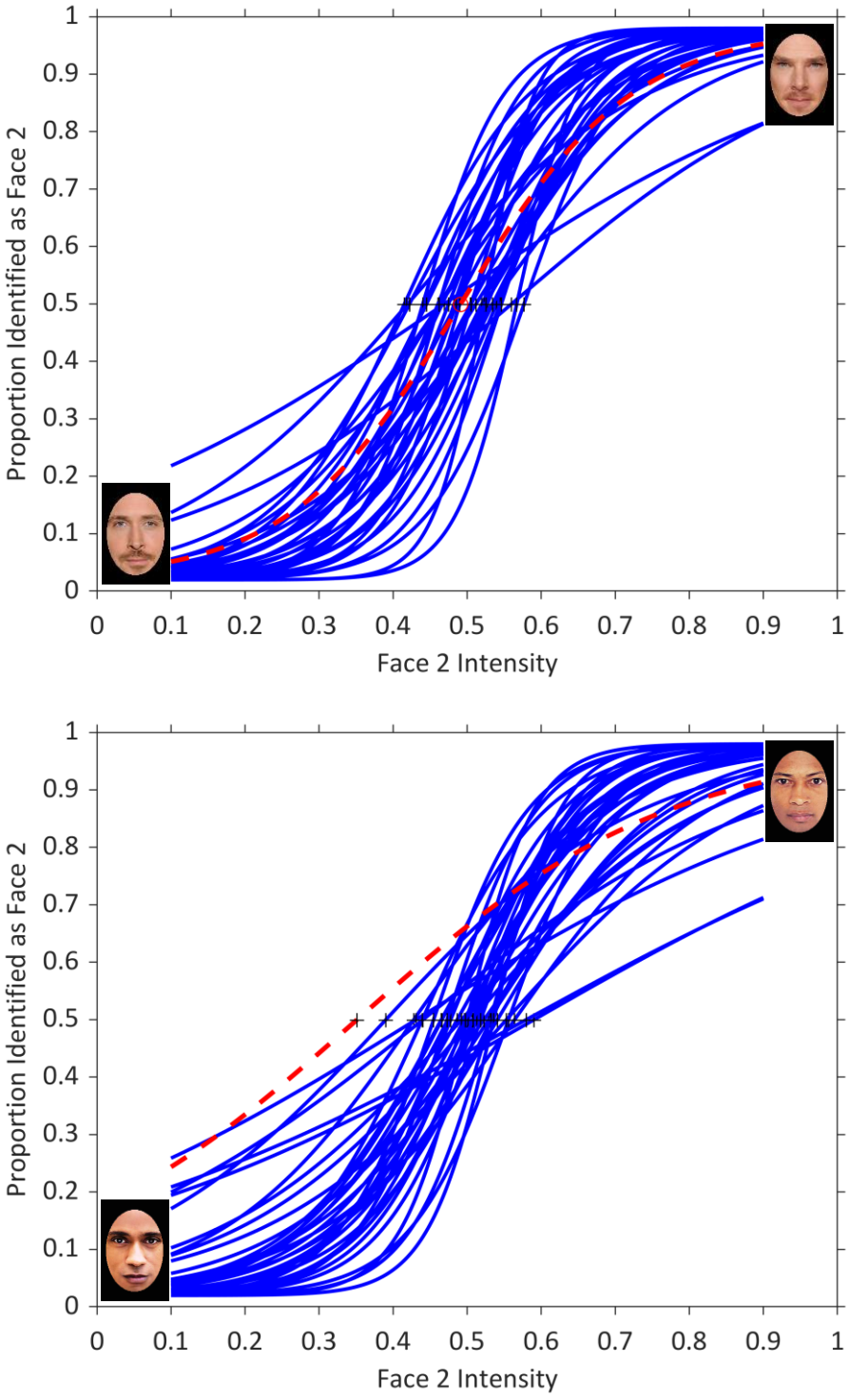


Figure 2-3. Identification data: Best-fitting logistic function for each participant

Top. Identification (one line per participant, with thresholds marked in crosses) of famous faces in controls (blue) and BL (orange). **Bottom**. Identification (one line per participant) of nonfamous faces by controls (blue) and BL (orange).

2.5.1.2.2 Controls have shallow slopes for NF

Following previous CP studies using morphed faces (Y. Lee et al., 2014; Wegrzyn et al., 2015), we analyzed the steepness of the threshold slopes. The difference, 0.52, in the steepness of the average slope for controls at the contrast-detection threshold for FF (M = 3.08, SE = 0.22) and NF (M = 2.57, SE = 0.20) was significant, BCa 95% CI [0.003, 0.981], two-tailed t-test, $t(33)$ = 2.18, p = .036, d = .37. To determine how well the identification of FF and NF aligned with respective logistic functions, we ran a goodness-of-fit routine from the Palamedes toolbox for MATLAB (Prins & Kingdom, 2018) on each participant's data. We then analyzed the aggregate deviation scores in each condition using the chi-square cumulative distribution function, chi2cdf(x,v,'upper'), in MATLAB. We followed guidelines that an unacceptable fit corresponds to a probability value of $p < 0.05$ (Kingdom & Prins, 2016). Data for FF exceeded that value, chi2cdf (235.39, 238, 'upper'), p = 0.5356. By contrast, deviation scores for NF did not reach the benchmark, chi2cdf (374.37, 238, 'upper'), p <.001, indicating that these data points stray from the model fit. Our *a priori* assumption that the logistic function can best fit the identification data in a CP experiment was not met for both morphed face conditions.

2.5.1.2.3 BL's threshold and slope within normal limits for FF, but not NF

Although results indicate that BL had a contrast-detection threshold close to .50 for FF (.49), his performance for NF deviated substantially from that of controls (Table 2-2 and Figure 2-3). In this latter condition, his category boundary was .35. The data indicate that, unlike controls, BL did not switch his responses from Face 1 to Face 2 near the middle of the continuum of noisy exemplars of unfamiliar faces but did so earlier, around the 30–40% intensity of Face 2. To compare the differences in category thresholds between BL and those of controls, we used Crawford and Howell's modified t-test for single cases (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). Using this measure, we found a significant difference between BL's boundary results and those of controls, $t(33)$ = 2.36, p = .01, one-tailed t-test. Indeed, BL's results place him at the 1.22 percentile.

The steepness of BL's slope for FF was within normal limits, $t(33)$ = –0.79, p = 0.218, one-tailed t-test, z_{cc} = –.80. His slope value score (2.08) was at the 21.8 percentile, 95% CI [11.85, 34.16]. In terms of steepness of the NF slope, we did not find evidence that the difference between BL

and controls, 1.43, at this boundary was significant, $t(33) = -1.19$, $p = 0.121$, (one-tailed), $z_{cc} = -1.21$. His slope at the NF threshold was at the 12.13 percentile, 95% CI [4.99, 22.43].

The identification results reported above clearly indicate that controls showed CP effects for FF. Their performance on NF, however, could not be confirmed by a logistic fit of their data. BL also appeared within normal limits for FFs, but his NF threshold was substantially lower than that of controls. BL's skewed categorization performance for NFs seems to indicate his inability to mnemonically discriminate the key perceptual/conceptual information of faces learned in the lab.

2.5.2 Discrimination task

During the perceptual discrimination task, participants were required to differentiate between two highly similar face pair morphs. Prior studies have suggested that perceptual expertise, bolstered by mnemonic discrimination, results in more sharply tuned representations for discrimination (A. Chang et al., 2015). We thought participants would engage in high-interference memory to discriminate between two highly similar morph pairs. We further predicted that patient BL would perform worse than age-matched controls because of focal lesions to areas of the hippocampus known to be implicated in behavioral pattern separation. In concert with classic findings from categorical perception, we also believed that controls would perform with a higher degree of accuracy on between-category face pairs than within-category face pairs (Beal & Keil, 1995). Lastly, we hypothesized that aged-matched controls would perform better with familiar stimuli than with unfamiliar new face pairs (Chang, Murray, & Yassa, 2015).

2.5.2.1 Identification-based within- and between-category discrimination

In order to test whether participants differentially discriminated within- and between-category faces, we elected to create one within-category condition out of 10–30 and 70–90 face pairs and one between-category condition out of 40–60 face pairs. An exception to the 40–60 between-category assignment was made for three controls in the FF category and four controls in the NF category. The between-category face pair was deemed to be at the 50–70 interval for these exceptions, a decision made based on their threshold values at identification. We estimated BL's between-category face pair to be within the 30–50 interval, again based on his identification boundary.

Before proceeding with within-category analysis, we ensured that discrimination accuracy of the 10–30 and 70–90 face pairs was not markedly different by contrasting them using a paired-samples *t*-test. We found that controls' discrimination of FF at the 10–30 endpoint (*M* = .33, *SE* = .05), as well as at the FF 70–90 endpoint (*M* = .38, *SE* = .04), differed by –.05, BCa 95% CI [–.12, .02]. We found no evidence that this difference was significant, *t*(33) = –1.36, *p* = .182, *d* = –.23. Despite speculation that controls had an identification bias towards the NF 90 endpoint, we did not find that the difference between the NF 10–30 within-category face pair (*M* = .45, *SE* = .04) and the NF 70–90 within-category face pair trials (*M* = .42, *SE* = .05), .03, BCa 95% CI [–.03, .08], was significant *t*(33) = .93, *p* = .359, *d* = .17. BL's FF within-category discrimination scores were the same (.25), and his NF within-category discrimination scores for NF 10–30 (.15) and NF 70–90 (.20) differed by 0.5, a difference within the 95% CI for controls. Therefore, we concluded that combining controls' and the patient's 10–30 and 70–90 discrimination trials into within-category conditions was a valid approach.

2.5.2.2 Assessing CP model performance: Predicted versus obtained (proportion correct)

In assessing CP model performance, we found higher than predicted results for controls, but not for patient BL. As shown in Table 2-4 (left panel), the obtained proportion of different pairs correctly identified as different (proportion D|D) was higher than predicted for controls across most within-category intervals (10–30, 20–40, 60–80, 70–90), except for those on either side of the between-category interval (30–50 and 50–70). These latter "shoulder" intervals tracked closely to predicted values. Also, the 40–60 pair was lower than expected for both FF and NF. BL's obtained scores (Table 2-4, right panel) were marginally higher than the expected values for only two image pairs (FF 10–30, FF 70–90 and NF 60–80). BL's responses tracked closely to predicted values (e.g., FF 50–70, NF 50–70) for the remainder of the discrimination trials or were lower than anticipated, particularly for his between-category conditions (FF 40–60 and NF 30–50).

Next, we wanted to determine if BL was able to discriminate beyond his identification abilities. Mean absolute error (MAE) scores provide additional insight into average model-performance error expressed in units of proportion D|D, the variable of interest (Willmott & Matsuura, 2005). Averaged across all FF different intervals, the MAE for controls was .25, 95% CI [.21, .29]; across all NF different intervals, the MAE for controls was .28, 95% CI [.24, .32] (). These

relatively large average differences between modeled values and obtained values lead us to speculate the following about healthy controls: a) they do not discriminate faces to the same equivalence as they identify faces; and/or b) they are biased to respond "same" in a same-different task, thus explaining their inability to rise above chance discrimination across conditions and face-pair intensity levels. BL's average model-performance absolute error (AE) scores for FF (.11) and NF (.15) were smaller than those of controls by .14 and .13, respectively. When considered along with the above observation that BL's obtained scores were typically lower than predicted scores, it appears that BL was unable to discriminate beyond the limits of his identification abilities.

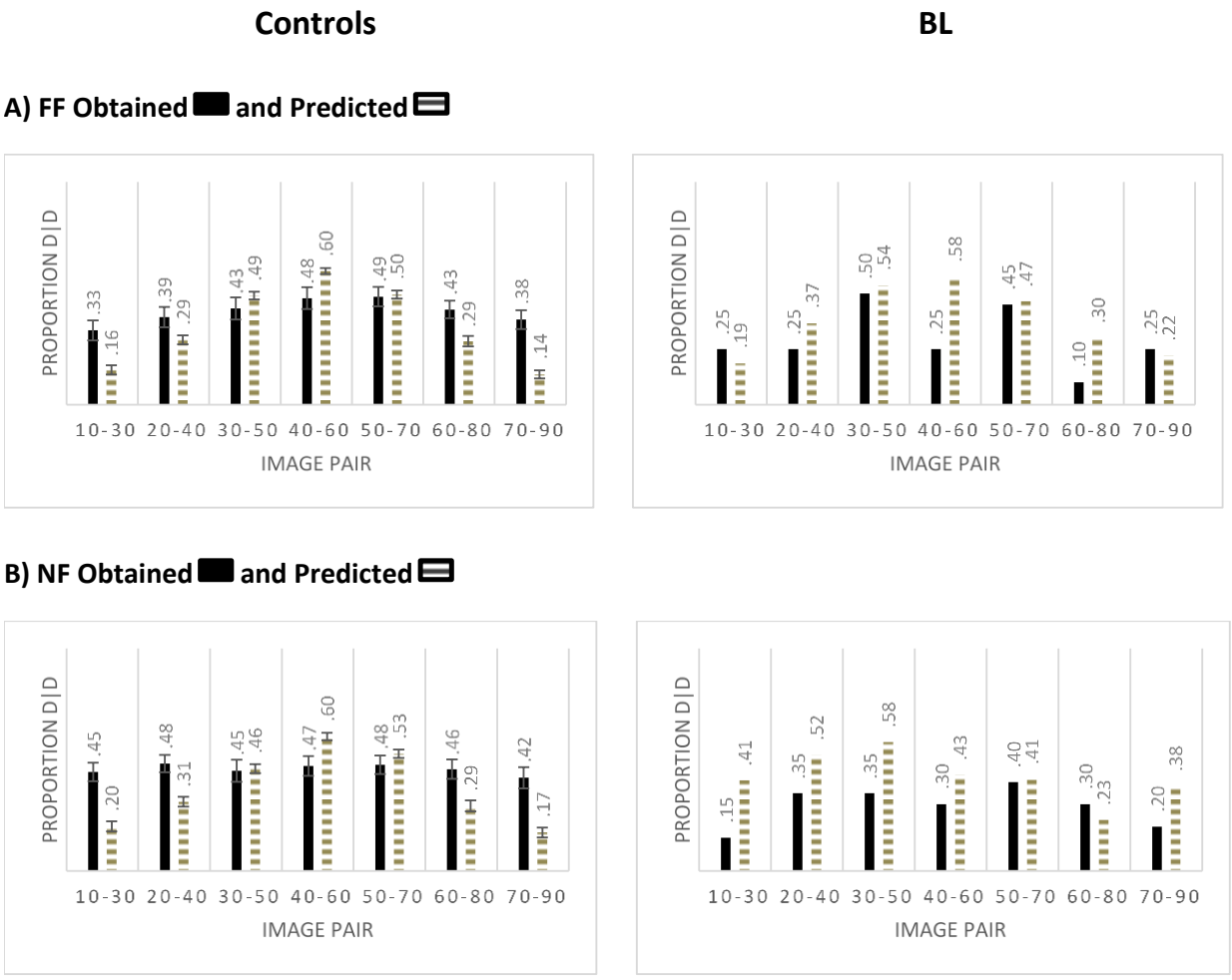


Figure 2-4. Obtained versus predicted discrimination accuracy (proportion correct)
Obtained versus predicted accuracy (proportion correct for different responses to different pairs) for FF (top) and NF (bottom). Control results are in the left column, BL's in the right column.

Table 2-3. Predicted vs. obtained discrimination, (MAE) proportion correct

	FF				NF			
Interval	MAE		Bootstrapped 95% CIs (controls)		MAE		Bootstrapped 95% CIs (controls)	
	Controls	BL	Lower	Upper	Controls	BL	Lower	Upper
10–30	.23	.07	.16	.31	.33	.26	.25	.40
20–40	.25	.12	.19	.31	.27	.17	.19	.34
30–50	.25	.04	.20	.31	.25	.23	.19	.30
40–60	.26	.33	.21	.30	.21	.13	.16	.26
50–70	.23	.02	.18	.28	.21	.01	.17	.27
60–80	.27	.20	.22	.34	.33	.07	.27	.39
70–90	.27	.03	.20	.35	.35	.18	.27	.42
Mean	.25	.11	.21	.29	.28	.15	.24	.32

2.5.2.3 Assessing CP model performance: Within- and between-category discrimination

Controls were 35.79% (FF) and 43.23% (NF) accurate in within-category conditions and 49.61% (FF) and 48.09% (NF) accurate in between-category conditions (Table 2-4). BL achieved 25% discrimination accuracy in both famous face conditions. He was 17.5% accurate in the NF within-category condition and 35% accurate in the NF between-category condition. Middle-older participants' below-chance (50%) performance for within-category faces is to be expected considering within-category compression, a typical CP effect (Harnad, 1987b). However, their inability to rise above chance performance for between-category faces may reflect something different, namely, a response bias that participants typically have toward answering "same" in same-different discrimination paradigms (Kingdom & Prins, 2016; Macmillan, 1987; Macmillan & Creelman, 2005). Therefore, we next analyzed the discrimination data using *d'* methods, which compensate for these forced-choice decision biases.

Table 2-4. Obtained discrimination accuracy: within- and between-categories

	Controls				BL	
Discrimination category	FF		NF		FF	NF
	M	SE	M	SE	M	SE
Within (%)	35.79	3.97	43.23	4.23	25.00	17.50
Between (%)	49.61	4.67	48.09	4.30	25.00	35.00
Within (*d'*)	1.81	0.15	2.19	0.17	0.43	0.0
Between (*d'*)	2.31	0.17	2.22	0.17	1.48	1.16

As the below-chance scores and disconnect between predicted versus obtained results help to illuminate the bias in participant responding evident in same-different tasks, a 2x2 (categorical boundary x familiarity) repeated-measures ANOVA was used to determine if control data varied across discrimination conditions. The dependent variable for this roving, forced-choice task, was discrimination *d'* scores (Kingdom & Prins, 2016; Macmillan & Creelman, 2005).

We found that healthy controls performed significantly better in between-category trials compared to within-category trials, $F(1,33) = 7.45$, $p = .01$, $r = .43$, a medium-sized effect. Face familiarity approached, but did not reach significance, $F(1,33) = 3.82$, $p = .059$, although this contrast yielded a medium-sized effect, $r = .32$. The category boundary x familiarity interaction was significant $F(1,33) = 6.01$, $p = .02$, $r = .39$.

The results above indicate that the categorical boundary had different effects on the discrimination sensitivity of controls depending on their pre-experimental face familiarity. To break down this interaction, we ran tests of simple effects to compare the two levels of face familiarity (FF and NF) for each of the two levels of category (within and between). Post hoc comparisons using the Bonferroni correction indicated that healthy controls were significantly worse ($p < .001$) at discriminating within-category FF ($M = 1.81$, $SE = 0.15$) than between-category FF ($M = 2.31$, $SE = 0.17$). We found no indication that within-category NF ($M = 2.19$, $SE = 0.17$) had a similar perceptual disadvantage relative to between-category NF ($M = 2.22$, $SE = 0.17$), $p = .859$. This last result is unsurprising, as the within-category NF and between-category NF differed by only –0.03, 95% CI [–.34, .28]. Moreover, healthy controls were significantly worse ($p = .002$) at discriminating within-category FF than within-category NF. A similar finding was not evident when comparing between-category famous faces with between-category nonfamous faces, ($p = .514$). See Figure 2-5.

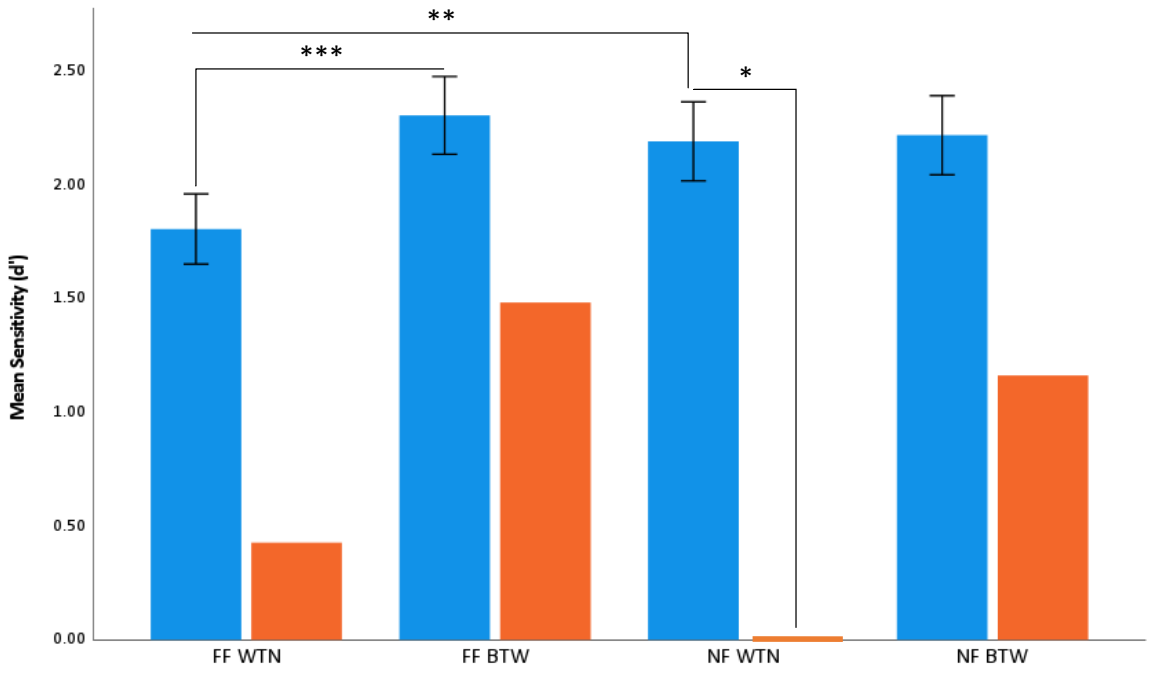


Figure 2-5. Discrimination accuracy (*d'*) for within-category versus between-category faces
FF = famous faces. NF = nonfamous faces. Blue bars = controls. Orange bars = BL.

As can be seen in Table 2-4, BL's lowest *d'* accuracy score was found in within-category NF. BL had a *d'* score of 0 (i.e., random responding) in this condition. Using Crawford and Howell's modified *t*-test for single cases (Crawford & Garthwaite, 2002; Crawford & Howell, 1998), we found this *d'* difference between BL and controls for NF, –2.19, to be significant, $t(33) = -2.13$, $p = 0.02$, one-tailed, $z_{cc} = -2.16$. BL's results place him at the 2nd percentile, 95% CI [0.27, 6.19]. Meanwhile, we could not find evidence that BL's sensitivity to within-category FF was statistically different from that of controls, $t(33) = -1.51$, $p = 0.07$, one-tailed, 7th percentile, 95% CI [2.13, 15.15]. The difference between BL and controls for within-category FF, however, did represent a large effect $z_{cc} = -1.53$, 95% CI [–2.03, –1.03]. Indeed, only one control scored lower than BL in within-category FF *d'* sensitivity. We did not find that BL's performance was significantly different from that of controls in the between-category conditions for either FF or NF.

Table 2-5. Obtained discrimination accuracy (*d'*)

	Control sample (n = 34)			*Significance test (one-tailed)*[a]		*Estimated percentage of the control population obtaining a lower score than BL*[b]		*Estimated effect size (z_{cc})*[c]	
Discrimination category	*Mean*	*SE*	*BL's score*	*t*	*p*	*Point*	*(95% CI)*	*Point*	*(95% CI)*
FF Within	1.81	0.15	0.43	-1.51	.07	7.00	(2.13 to 15.15)	-1.53	(-2.03 to -1.03)
FF Between	2.31	0.17	1.48	-0.81	.21	21.10	(11.30 to 33.36)	-0.83	(-1.21 to -0.43)
NF Within	2.19	0.17	0.00	-2.13	.02	2.02	(0.27 to 6.19)	-2.16	(-2.78 to -1.54)
NF Between	2.22	0.17	1.16	-1.03	.16	15.57	(7.26 to 26.81)	-1.04	(-1.46 to -0.62)

Note. FF = famous faces. NF = nonfamous faces. Controls and BL within = faces averaged across 10–30% and 70–90% face pairs; Controls between = faces in 40–60% face pair (except for three controls at the FF 50–70% face pair and four controls at the NF 50–70% face pair). BL FF between = faces in 40–60% face pair. BL NF between = faces in 30–50% face pair. [a]Crawford & Howell (1998). [b]Crawford & Garthwaite (2002). [c]Crawford, Garthwaite & Porter (2010).

In summary, our evaluation of CP model performance for controls reveals that they show typical CP boundary effects for FF but not NF. As for patient BL, he appears to show boundary effects for both face types, but his responses for within-category NF are difficult to interpret. In the next section we use the obtained *d'* discrimination values to see how well they reflected predicted values from the identification phase of the experiment.

2.5.2.4 Assessing CP Model Performance: Predicted Versus Obtained (*d'*)

As we saw above, controls and BL varied in their mnemonic sensitivity to FF versus NF faces and in within- versus between-categories. We next sought to see how well, if at all, our obtained discrimination results reflected what we predicted from identification, the last operational criterion of CP.

Our findings for predicted versus obtained *d'* scores for within- and between-category conditions show that controls exceeded predicted mnemonic sensitivity values for every condition in both face types (Figure 2-6, left panels). BL's obtained *d'* scores for FF within- and between-category

faces were aligned with (slightly above) predicted values (Figure 2-6, right panel). His NF between-category obtained *d'* discrimination score was somewhat lower than predicted, and his NF within-category *d*' discrimination score, as noted previously, was at floor and lower than predicted.

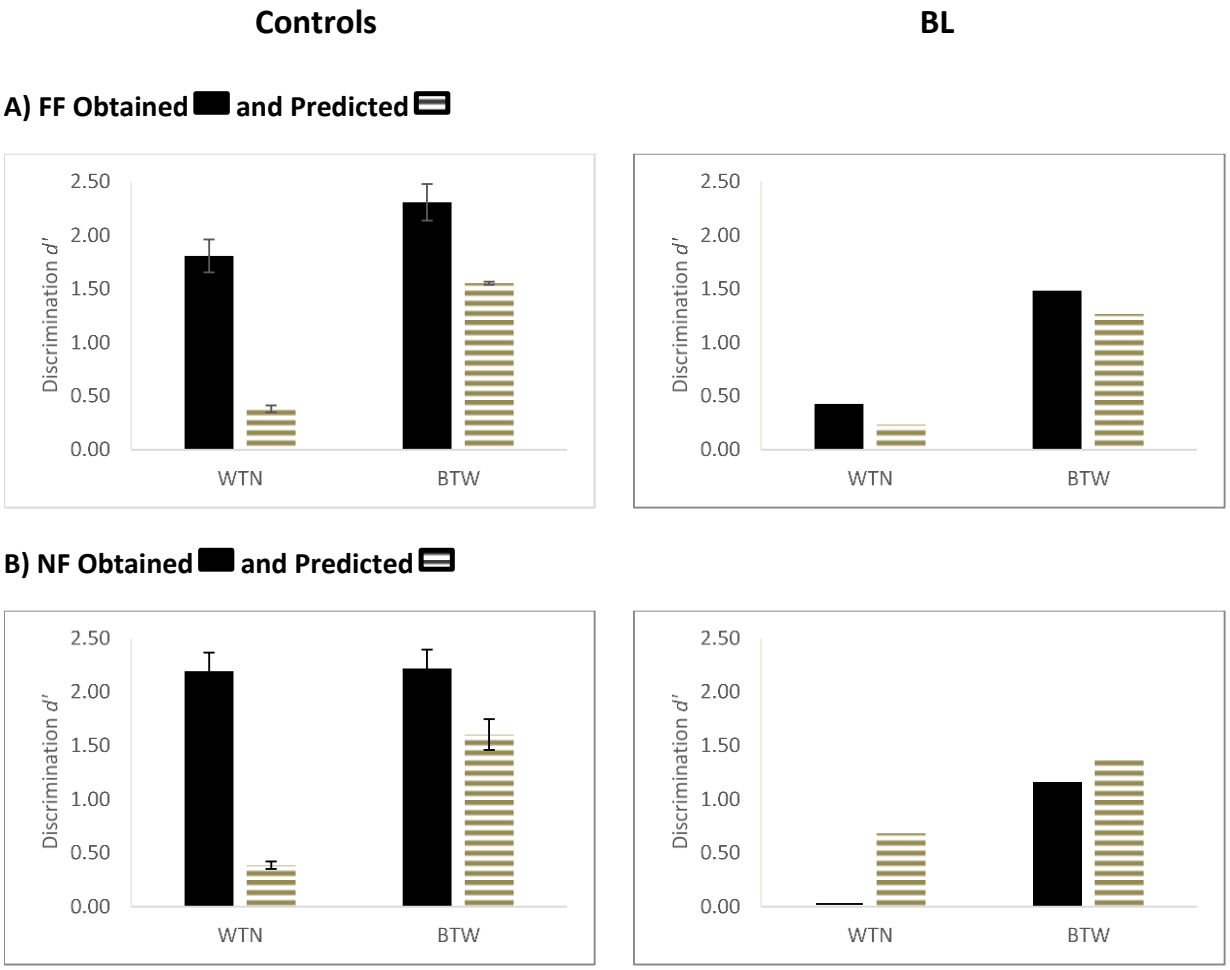


Figure 2-6. Obtained versus predicted discrimination accuracy (*d'*)
Control results are pictured in the left column, BL's findings in the right column.

MAE scores (Table 2-6) provide additional insight into average model-performance error expressed in units of *d'* for this novel analysis of predicted versus obtained sensitivity. For within-category FF, controls had an MAE of 1.44 (33 of 34 controls had obtained values higher than anticipated), 95% BCa [1.19, 1.70] compared with an AE of 0.19 for BL. Clearly, BL's results are outside of the estimated range of 95% of the population. We found controls had an MAE of 1.03 for between-category FF, 95% BCa [0.76, 1.32], compared with an AE of 0.22 for

BL. Again, BL's result is outside of the estimated range of 95% of the population. In response to within-category NF, controls had an MAE of 1.81 (all controls had obtained NF within-category values higher than predicted), 95% BCa [1.50, 2.13] compared with an AE of 0.68 for BL. We found controls had an MAE of 0.89 for between-category NF, 95% BCa [0.65, 1.18], compared to an AE of 0.21 for BL. As with FF, BL's NF results put him outside of the range of 95% of the population.

The above data shows that the CP model is not good at predicting discrimination of faces from identification of faces in neurotypical adults. Actual discrimination results are much better than predicted, a common finding (Macmillan & Creelman, 2005; Massaro, 1987b; R. E. Pastore, 1987). Evidently, controls are not limited by identity labels when making perceptual discriminations in high-interference situations. They seem to be able to integrate featural information, and perhaps information from other dimensions including memory (Massaro, 1987b, 1987a). With BL, however, we do find some evidence of perceptual equivalence between identification and discrimination, a point we consider in greater detail below.

Table 2-6. Predicted vs. Obtained Discrimination (*d'*), (MAE)

	FF				NF			
Interval	MAE		Bootstrapped 95% CIs (controls)		MAE		Bootstrapped 95% CIs (controls)	
	Controls	BL	Lower	Upper	Controls	BL	Lower	Upper
Within	1.44	0.19	1.19	1.70	1.81	0.68	1.50	2.13
Between	1.03	0.22	0.76	1.32	0.89	0.21	0.65	1.18

2.6 Discussion

We investigated if CP, like pattern separation, is modulated by hippocampal DG integrity and is influenced by prior knowledge. As predicted, healthy controls exhibited three of the four criteria necessary to index successful CP effects for FF, including within-category compression and between-category expansion during discrimination (Harnad, 1987b; Studdert-Kennedy et al., 1970). The one criterion that was not met for FF is the close correspondence between actual and predicted discrimination, a criterion that is rarely used or met in the literature on CP (Massaro, 1987b; Studdert-Kennedy et al., 1970). On the other hand, controls' results for NF failed to meet that criterion and most of the other CP benchmarks. These data suggest that familiarity is a factor

in CP of highly confusable faces and illuminate differing perspectives on the subject (Angeli et al., 2008; Campanella et al., 2003; Levin & Beale, 2000). Like controls, BL, an individual with bilateral DG lesions, met the operational criteria demanded for FF (identification thresholds and slopes within normal limits, lower discrimination of within-category faces than between-category ones). Unlike controls, however, BL's FF discrimination and identification abilities were aligned with one another; BL could not discriminate faces better than he could identify them. This CP operational criterion was established during the foundational studies of the phenomenon with unidimensional speech sounds (Liberman et al., 1957; Studdert-Kennedy et al., 1970) but is rarely achieved in that or other domains, including face perception (Campbell et al., 2001; Massaro, 1987a). DG integrity, therefore, is crucial for supporting discrimination of highly confusable faces, suggesting that the perceptual act of CP and the mnemonic act of pattern separation are interrelated via a common hippocampal substrate.

Similar perceptual and mnemonic relationships can be pieced together from process, psychophysics, or neuroanatomical approaches to CP or pattern separation. In a process approach, such interpretation is conceptualized as the tendency for individuals to categorize and discriminate based on stored information, such as category exemplars or prototypes (Angeli et al., 2008; Damper & Harnad, 2000; Goldstone & Hendrickson, 2010). Indeed, early neural network models of CP incorporated mechanisms of associative memory based on prototype models. According to these models, noisy perceptual stimuli are replaced by noise-free prototypes from memory (Damper & Harnad, 2000; Goldstone & Hendrickson, 2010). Within the scope of such approaches, reliance on previously stored exemplar information depends on maintaining the distinctiveness of this information through hippocampal pattern separation (Pickering, 1997). Retrieving a canonical pattern to replace a noisy one would also, presumably, engage the autoassociative circuitry of CA3 (Quiroga, 2017). Pattern separation activity within the DG/CA3, in turn, would track or support CP.

The interrelatedness of CP and pattern separation is emphasized in all phases of the experimental paradigm used to operationalize the phenomenon. For example, the CP task begins with the repeated presentation of morphed faces. In theory, these exemplars of the prototype faces are sparsely coded by pattern separation processes (Yaros et al., 2019). The orthogonal episodic representations of each morphed face — or possibly their identity-defining structural features (L. Chang & Tsao, 2017; Chauhan et al., 2020) — are then projected from the DG onto the CA3

hippocampal cell layer via the mossy fiber pathway (Rolls & Kesner, 2006). Recurrent collaterals within the CA3 ensure the episodic elements are bound together and can be pattern completed from partial cues (Rolls & Kesner, 2006).

In this manner, the CP task resembles a widely used test of pattern separation, the MST (Stark et al., 2015). Unlike tests of CP, however, presentation and discrimination of highly similar stimuli (i.e., unstudied lures) occurs during the retrieval phase of the MST. Nevertheless, the morphed faces in the CP paradigm would undergo pattern separation regardless of whether they were later tested in memory; in effect, the CP discrimination phase is an assessment of how well the faces are pattern separated.

Due to his DG lesion, BL was unable to pattern separate highly similar faces as well as controls during the identification phase. As a result, he lacked the sparse encoding necessary for the perceptual, fine-tuned discrimination required to expand beyond the abstract, conceptual labeling act. Based on BL's memory performance on the MST in a previous study, in which he was able to recognize dissimilar foils (Baker et al., 2016), we surmised that BL could encode coarser face representations during face-name labeling. These more generalized representations may have prompted him to autoassociate highly similar within-category faces to an endpoint identity in memory. This interpretation could explain why BL's discrimination for within-category NF was at floor, and his FF within-category discrimination was near chance.

As BL's pattern separation of exemplars was limited, he was challenged to discriminate morphs based on their perceptual differences. Instead, he relied on successful face-name labelling (for FF) of the endpoint identity that he recognized during identification. In support of this interpretation, BL's FF identification and discrimination were closely aligned. Although BL's purported discrimination strategy was based on finding perceptual differences in the face pairs (see Appendix B:
BL's Face Discrimination Strategy), he seemed only to be able to discriminate the faces to the degree to which they were identified. This represents a CP ideal case rarely achieved through experimentation (Harnad, 1987a; R. E. Pastore, 1987; Studdert-Kennedy et al., 1970).

Controls, too, showed significantly worse discriminability for within-category FF pairs relative to between-category ones. In this way, controls revealed one of the definitional criteria of CP effects (Harnad, 1987b; Studdert-Kennedy et al., 1970), albeit without BL's within-category

indiscriminability and close alignment with identification. This within-category compression of controls might reflect something akin to a "perceptual magnet effect" (Feldman et al., 2009), working upon their neurotypical pattern-separated perceptual abilities. We believe this perceptual pull could be caused by shared connectivity within CA3. It works to elicit "same" rather than "different" judgments, leading to reduced *d'* scores for highly similar within-category images, consistent with the role of CA3 in pattern completion, as was the case with his performance on MST (Baker et al, 2016).

An alternative, but not incompatible, view (particularly applicable for the NF faces) is that such compression reflects the mechanisms inherent in the representational-hierarchical (R-H) model (Saksida & Bussey, 1998, 2010), which delineates the involvement of the perirhinal cortex (PRh) in object perception. These limits are thought to be challenged when visualizing highly similar objects and thus highly confusable if presented simultaneously. When such interference is present, the PRh can become "overloaded," and feature-level representations of objects revert to the inferior temporal cortex (ITC; hence the concept of a hierarchy in the R-H paradigm). High interference can particularly impact perceptual decision-making (Bakkour et al., 2019) and activities of categorization and discrimination. When a novel item is presented that is similar to a previously seen one, the new item may be confused with the old. Without input from the PRh, the ITC must mediate this interference, which it does across broadly tuned neurons, leading to objects with similar perceptual features seeming familiar, or previously seen (Yeung, Ryan, Cowell, & Barense, 2013). An alignment of CP and R-H comes from our speculation that in the visual object domain the within-category, high-interference NF items are operated on, and perceptually "compressed" by the ITC; at the same time, the more distinct, finer-grained, between-category items are discriminated and "expanded" upon by the PRh, with the support of pattern separation/completion processes in the hippocampus.

BL's improved performance for between-category FF, a heightened performance shared with controls, can also be interpreted in terms of his reliance on labeling. These face pairs (i.e., .40–.60) straddled identification boundaries. They had associations split between two concepts rather than one. BL could not pattern complete both of the face pairs to one of the endpoints. Consequently, the perceptual-conceptual tension inherent in these cross-category pairs helped BL (and control participants) to satisfy their conservative internal criterion of "different." Similarly, pattern separation of morphed faces has been found to vary depending on the relative

familiarity and invariance of the faces involved in any particular trial (Bein, Duncan, et al., 2020; A. Chang et al., 2015; Yaros et al., 2019).

Overall, our findings indicate that the role of the hippocampus in face identification and discrimination needs to be taken into account along with the functions of structures within the core face network, such as the lateral occipital cortex, fusiform gyrus, anterior temporal cortex, and prefrontal cortex (L. Chang & Tsao, 2017; Haxby et al., 2000; Kanwisher et al., 1997). Having established that the hippocampus contributes to at least one aspect of face perception, we lay the groundwork for future investigations on how pattern separation interacts with the core face network. Thus, the name of the face, a person's familiarity with the face, and the myriad of meaningful associations and emotional biases or connections humans have for depictions of other humans, such as in the Trump-Putin morph, are equally important. These elements bring the conceptual richness of any face into being, as described in classic cognitive models of face processing (Bruce & Young, 1986; Haxby et al., 2000). For any face, the semantic face-name identity is incredibly important. The ability to disambiguate the nose and eyes of Ryan Gosling from the chin and cheekbones of Benedict Cumberbatch should have little bearing on consciousness if one could not assign a holistic identity to these features. This identity information is associated with faces by the hippocampus and neocortex (Sperling et al., 2001; Zeineh et al., 2003). Intriguing recent finding point to temporal pole as being the location of long-term semantic information about faces (Landi et al., 2021). We believe such semantic knowledge is central to the identification and discrimination of highly similar faces.

A growing literature suggests that the MTL may engage in different mnemonic or perceptual processing expressions, possibly due to its projections to and from the neocortex (Poppenk et al., 2013). Previously, the perirhinal cortex was thought to be the last stop within the MTL for this process, with perceptual contributions of the hippocampus limited to the spatial domain (A. C. H. Lee et al., 2005) or relational processing (Olsen et al., 2016). Using a previously established measure of CP for faces, we draw a parallel between both phases of identification and discrimination for controls and for a person with a focal brain lesion and a deficit in behavioral pattern separation. In doing so, our findings provide strong evidence that the hippocampus, and the DG, in particular, aid in processing faces in a high-interference task. These abilities are necessary for CP. Insofar as CP has been shown to be functionally dependent on perceiving differences and similarities in perceptual data, it appears to be intertwined with mnemonic

pattern separation. The current study brings us closer to understanding this relationship and, more generally, how the hippocampus enables both perception and memory.

Chapter 3 , Study 2

3 Hippocampal mnemonic discrimination across the auditory and visual domains

3.1 Preface

Behavioral pattern separation is operationally defined by our ability to distinguish between episodic memories, or temporally dated, personally experienced past events. In theory, it should not matter whether these episodic memories are within or between categories or within or between modalities. Indeed, complementary learning systems (CLS; McClelland et al., 1995) theorists conceive the hippocampus as representationally agnostic to the modality of information processed when discriminating similar memories (Huffman & Stark, 2014; Hunsaker & Kesner, 2013; Kumaran et al., 2016). However, in practice, the items to be remembered in a pattern separation task, such as the commonly used Mnemonic Similarity Task (MST; Stark, Stevenson, Wu, Rutledge, & Stark, 2015), are semantically and visually related.

After learning about pattern separation, one of my earliest desires was to test its limits by investigating whether mnemonic discrimination can be found in the auditory domain. I conceived of various ways to do this, including using music clips of similar sounds but different bands (AKA the “Beatles versus the Rolling Stones” test). These early conceptions never left the piloting stage for various reasons, including the difficulty of standardizing semantically familiar musical clips to be played to participants. Through consultation with my supervisor, Dr. Shayna Rosenbaum, I eventually settled on using a collection of realistic sounds. These sounds were provided to me from the Alain lab at the Rotman Research Institute

The path of least resistance was to use these sounds in a paradigm the same as the visual standard for behavioral pattern separation, the MST. In this way, the concept of a Mnemonic Auditory Similarity Task (MAST) was born and later implemented in collaboration with Dr. R. Shayna Rosenbaum, Dr. Morris Moscovitch, and Nick Hoang. The prospect of testing the MAST versus the MST became an exciting one. By testing both on the same participants, I could investigate whether the hippocampus may be equally representationally “agnostic” for discriminating

overlapping stimuli presented in either the visual or auditory modality. Furthermore, by testing a patient with focal hippocampal lesions restricted to the DG, we could better localize any potential cross-modality effects in behavioral discrimination.

The hippocampus is inundated by many unique representations a day, including events that we will later remember through recognition of previous experiences. If each of these representations in the hippocampus is encoded distinctly, pattern separation and pattern completion facilitate learning and memory across any perceptual domain (Huffman & Stark, 2014; Hunsaker & Kesner, 2013; O'Reilly & McClelland, 1994; O'Reilly & Rudy, 2001). Therefore, the hippocampal neural mechanisms you use to create a unique memory of where you parked your car on Monday versus Tuesday morning seem be the exact hippocampal neural mechanisms you use to discriminate the memory of the cheery robin song above you as you walked to work on Monday, as opposed to the starling chatter bothering you after you slammed the car door on Tuesday. Using a novel test of auditory behavioral discrimination, I set out to provide the first evidence of such an ability in humans.

3.2 Introduction

In humans, the brain-behavior correlates underpinning pattern separation have been explored in modified recognition memory tests, most of which use visual stimuli (Liu et al., 2015). The MST, for example, taxes the mnemonic discrimination of previously learned images of everyday objects from visually similar lures (Kirwan & Stark, 2007; Stark et al., 2015). Studies using the MST have helped researchers make inferences about pattern separation and its reliance on the hippocampus. For example, older individuals with reduced hippocampal volumes, as well as patients with hippocampal lesions (e.g., to the DG and CA3/CA1 subfields) are impaired relative to younger adults (or age-matched controls) on the MST (Baker et al., 2016; Bakker et al., 2008b; Bennett et al., 2019; Doxey & Kirwan, 2015; Nauer et al., 2020; Riphagen et al., 2020). Based on this evidence, researchers have concluded that the MST and other visual lure discrimination (or mnemonic discrimination) tests are functionally sensitive to hippocampal pattern separation (Kirwan & Stark, 2007; Stark et al., 2013, 2019; Stark & Stark, 2017).

In theory, pattern separation "expansion recoding" (Knierim & Neunuebel, 2016) can be performed on any sensory input to the hippocampus (Hunsaker & Kesner, 2013). Indeed, the multimodal nature of episodic memory suggests that elements from any sensory modality that

arrives on the doorstep of the hippocampus can be sparsely coded by the cellular rooms within the structure (Turk-Browne, 2019). Or so goes the theory. In reality, most tests of pattern mnemonic discrimination in humans use visual stimuli (Liu et al., 2015). Scant experimental evidence exists to support hippocampal pattern separation outside of the visual domain. Notably, these investigations are confined to rodent studies using olfactory inputs (Weeden et al., 2014; Woods et al., 2020). Despite the handful of these animal studies, it is unclear whether pattern separation in humans generalizes in modalities other than vision (Liu et al., 2015).

Auditory stimuli, in particular, are notable for their absence of evidence in mnemonic discrimination tests. Yet, neurons in the mammalian hippocampus are known to respond to discrete sounds (Aronov et al., 2017; Berger et al., 1976; Christian & Deadwyler, 1986; Itskov et al., 2012; Jablonowski et al., 2018; Jirsa et al., 1992; Knight, 1996; Sakurai, 1994; Vinnik et al., 2012). In humans, these hippocampal responses to acoustic inputs can occur during learning episodes (Jablonowski et al., 2018; Kumar et al., 2014). Consequently, patients with lesions to the hippocampus that include the DG are impaired in their ability to discriminate new from old sounds in memory tests (Milner, 1972; Squire et al., 2001). Therefore, it is not incongruent with computational models of hippocampal function that auditory stimuli might be pattern separated within the MTL.

Knowing more about how hearing and memory interact is critical. As evidence grows to support a link between cochlear hearing loss and dementia (Griffiths et al., 2020), as well as hippocampally mediated neurogenesis and long-term memory (Kraus et al., 2010; Manohar et al., 2020), it is crucial that we better understand the degree to which sounds are, or are not discriminated by the hippocampus. These insights will help clinicians better construct and administer pattern separation tests as neuropsychological indicators of hippocampal integrity (Stark et al., 2019). Filling these gaps will also help us better understand the extent of hippocampal processing of highly similar inputs to building a unifying theory of hippocampal-neocortical interactions (Kent et al., 2016). Furthermore, given the critical role ascribed to pattern separation for episodic memory, it is crucial to determine whether pattern separation effects can be detected through visual lure discrimination in memory and other tests that require fine mnemonic and perceptual discrimination. A key question here is whether these effects are related to performance on other tests of episodic memory that decline with age and in hippocampal patients whose deficits resemble age-related disorders.

Pursuing answers to the questions is at the heart of this study. To determine whether human behavioral discrimination occurs in the auditory domain using naturalistic sounds, we constructed the MAST. We tested the MAST against the MST — essentially pitting acoustic versus visual performance of behavioral discrimination — on three groups of adult participants (younger, middle-older, and older) as well as on an individual with a rare hippocampal lesion. We hypothesized that our research would address unanswered questions about pattern separation and the hippocampus's role in learning and memory across visual and auditory modalities. In order to further delineate whether subtleties of interpreting sounds holistically or by elements of pitch and volume, we also tested participants on their experiences of these sounds in discrimination tests.

Based upon findings in recognition memory tests and differences in other head-to-head modality tests (Bigelow & Poremba, 2014; M. Cohen et al., 2009; Stark & Stark, 2017), we predicted a difference in behavioral discrimination for visual versus auditory stimuli, with visual performance (as measured by the MST) being superior. We also forecast we would find a MAST-MST correlation in target versus lure and target versus foil performance, with lure sensitivity yielding the lower score. Such discrimination difficulty was predicted to be consistent across both auditory and visual modalities. This difficulty in discriminating targets from lures is hypothesized to be further exacerbated across the lifespan. Consequently, we also predicted that older adults would perform significantly worse than younger adults. Finally, we expected that relative to age-matched controls, a patient with a lesion to his DG would perform poorly and even worse than the healthy older adults in discriminating targets from lures.

3.3 Materials and methods

3.3.1 Participants — Experiment 1

To evaluate auditory mnemonic discrimination as a proof of concept and as a diminishing ability across the lifespan, we tested 128 participants across three age groups: 1) 18–29 years of age (young adults or YA, $N = 62$), mean age = 20.61 (SD = 2.47 years), 40 females; 2) 48–66 years of age (middle-older adults or MO; $N = 29$), mean age = 56.79 (SD = 4.55 years), 14 females; and, 3) 67–92 years of age (older adults or OA, $N = 37$), mean age = 75.51 (SD = 6.00 years), 24 females. These age groups are similar to the three categories used by Nauer et al. (2020) in their study of mnemonic discrimination across the adult lifespan.

Inclusion criteria required participants to be proficient in English, normal or corrected-to-normal vision and hearing, and no history of neurological or psychological disorders. All participants, except for YAs, were assessed on the Montreal Cognitive Assessment (MoCA). Older adults under 80 had to have a score at or above 26 (out of a 30-point maximum). Participants above 80 were required to have a score at or above 25 (Rossetti et al., 2011). The number of participants used does not include the following exclusions: 16 YAs, 2 MOs, and 10 OAs for either a) a history of head injury, hearing or memory impairment, b) apparent disregard or inattention to instructions, or c) MoCA scores below the cutoff. YAs were recruited through the York University Undergraduate Research Participant Pool (URPP). MOs and OAs were recruited through the community or via the participant database at Baycrest Health Sciences. Participants provided written, informed consent in accordance with the ethics review boards at York University and Baycrest and standards of the Canadian Tri-Council Research Ethics guidelines.

3.3.1.1 Experiment 1 trimmed sample

Sound quality evaluations were administered to a portion of the YA participants from Experiment 1. The performance of these YA participants was used as a baseline to collect a trimmed sample across the other two age categories. These sound quality tests (described below) followed the study and test administration of the MAST. The demographic composition of this subset for YAs was as follows: n = 28, mean age = 20.54 (SD = 2.38 years), 19 females. Most MO participants agreed to the sound quality screens, n = 27, mean age = 56.93 years (SD = 4.56), 13 females. OAs were also represented by most participants from the main testing group, n = 35, mean age = 74.97, SD = 5.70, 23 females.

A trimmed sample of the MO and OA participants — whose sound quality ratings for identical items were within two standard deviations of the YA sound quality rating group — was collected from this subset. The purpose of this trimmed sample was to run auditory tests across all groups with individuals who were matched with the non-subjective sound rating abilities of the YA group. Descriptive statistics for this trimmed sample are as follows: YA, n = 26, mean age = 20.65 (SD = 2.43 years), 18 females; MO, n = 27, mean age = 56.93 (SD = 4.56 years); OA, n = 22, mean age = 74.91 (SD = 6.05 years), 15 females.

3.3.2 Participants — Experiment 2

To compare auditory mnemonic discrimination with visual mnemonic discrimination across the adult lifespan, we used a subset of participants from Experiment 1. These participants were administered both the MAST and the MST. The demographic composition of this subset for YAs was as follows: n = 26, mean age = 21.00 (*SD* = 2.37 years), 18 females. The subset for MOs resulted in *n* = 26 participants, mean age = 56.50 years (*SD* = 4.20), 12 females. OAs were represented by 29 participants, mean age = 74.28, *SD* = 5.28, 20 females.

3.3.2.1 Experiment 2 trimmed sample

As with Experiment 1, we collected a trimmed sample of participants for Experiment 2. These participants were those whose sound quality ratings for identical items were within two standard deviations of the experiment 1 YA group. (Not every YA participant was administered both the sound quality ratings and the MST; the overall pool for those who did both was *n* = 18. Two of these individuals were subsequently eliminated for low sound quality ratings). Descriptive statistics for this sample are as follows: YA, *n* = 16, mean age = 20.94 (*SD* = 2.43 years), 11 females; MO, *n* = 25, mean age = 56.36 (*SD* = 4.24 years), 12 females; OA, *n* = 18, mean age = 73.89 (*SD* = 4.93 years), 12 females.

3.3.2.2 Experiment 2 — Patient BL

To better understand the neural basis of pattern separation in two domains, we examined auditory versus mnemonic discrimination in patient BL. See section 2.3.2 for a description of patient BL, who was 56.72 years old at testing. The inclusion of this patient in Study 2 provided a way to explore the role of the hippocampus in producing distinct mnemonic representations necessary for the behavioral discrimination of overlapping details. More importantly, we sought to identify whether focal lesions to the DG would yield behavioral differences in stimulus discrimination and sensitivity, especially in response to modal changes to the input signals.

3.3.3 Experimental design

3.3.3.1 Mnemonic Auditory Similarity Task (MAST)

To evaluate the auditory mnemonic discrimination abilities of participants relative to their respective control groups, we created the Mnemonic Auditory Similarity Task (MAST). The

MAST is analogous to the visual object-based MST (Kirwan & Stark, 2007; Stark et al., 2015). We used the MST paradigm as a template for programming our experiment. However, we inserted auditory "objects" or 1 s clips of everyday, naturalistic sounds in place of common visual objects.

Like the MST, the MAST consists of a study phase and test phase. At study, participants were presented with a total of 40 easily recognizable, everyday auditory events (e.g., duck quacking, baby crying, fax machine buzzing) played in succession, each presented for 1 second with a corresponding response time of 4 seconds followed by a 0.5-second inter-stimulus interval (ISI). At encoding, participants were asked to classify the sounds as animate (e.g., duck) or inanimate (e.g., piano). At test, participants heard a total of 60 sounds — 20 old or repeated sounds (targets), 20 new sounds (foils), and 20 similar sounds (lures) — played in succession, each presented for 1 second followed by a 0.5 second ISI. After each trial, participants were asked to classify by way of a button press whether the sound was *old*, *similar*, or *new*. See Figure 3-1.

Compared to the MST, the MAST presents fewer stimuli at test (60 sounds versus 128 photographs). We used fewer stimuli to accommodate discrimination fatigue in older adults and amnesic participants, a condition we discovered while piloting the MAST with younger adults. In addition, we acknowledged the reduced number of auditory trials in other behavioral tests of older adults or adults with neurodegenerative disorders (e.g., Goll et al., 2011).

3.3.3.1.1 MAST sound ratings

In a post-experimental session, participants were played pairs of sounds back-to-back. The items in each pair were different from each other, identical to each other, or similar to each other. Participants were asked to compare how similar the sounds were on a Likert scale of 1 to 5. On this scale, 1 equaled no similarity, and 5 was the highest similarity (i.e., identical).

Participants were presented with the stimulus sounds from the MAST, one at a time, and asked to rate each one on vividness for the amount of auditory, visual, and any other sensory details (across the five senses) that may have been elicited in response to each sound. The first rating group asked participants for their subjective reactions to the overall acoustic quality of the two sounds. The second rating was specific to pitch (high vs. low) for the pairs, and the third one was specific to volume (loud vs. quiet). As we detected strong correlations among the three different

sound rating groups, we averaged them into one group with three levels (different sounds, identical sounds, and similar sounds). The second series of rating screens was phrased in terms of subjective vividness during encoding and retrieval. We found the results of this second series challenging to interpret (e.g., many participants could not distinguish which sounds were presented at study versus test), and they have not been reported here.

We administered this posttest for two reasons. The first aim was to quantify participants' conscious ability to report attributes of sounds. This ability is thought to be present in neurotypical adults, but some studies have found this ability absent in amnesiac patients (Howe & Lee, 2021). Our second motive was to obtain a proxy for a hearing or an attentional test, particularly by objectively ascertaining participants' ability to note correctly if two sounds were identical. By including this posttest as a screening measure for trimmed samples, we were also able to control for the influence of perceptual abilities on mnemonic discrimination, a missing element from the MST (Davidson et al., 2019).

3.3.3.2 MST: Visual mnemonic discrimination

Visual mnemonic discrimination was evaluated using the MST (Kirwan & Stark, 2007; Stark et al., 2013, 2015). The MST has been used to test neurotypical adults and participants with hippocampal lesions, and together with fMRI to help establish the neural basis of pattern separation, the brain's way of encoding unique memory traces (Baker et al., 2016; Bakker et al., 2008b; Kirwan et al., 2012; Rolls, 2016). The MST consists of a study phase and test phase, administered following a published protocol (Stark et al., 2013). Participants viewed 128 color images of everyday objects (e.g., picnic basket, fishbowl, saxophone) for 2 seconds each, followed by a 0.5 second ISI during the study phase. For each picture, participants indicated via button press whether the object depicted was primarily an outdoor item (e.g., a picnic basket) or an indoor thing. A test phase followed the study phase. In the test phase, participants were administered a surprise recognition memory test. They were randomly presented with 192 images, each onscreen for 2 seconds, followed by a 0.5 second ISI. The photographs at test included 64 targets (studied objects), 64 unrelated foils, and 64 similar lures. Participants had to classify whether the image was old, new, or similar to the items presented at study.

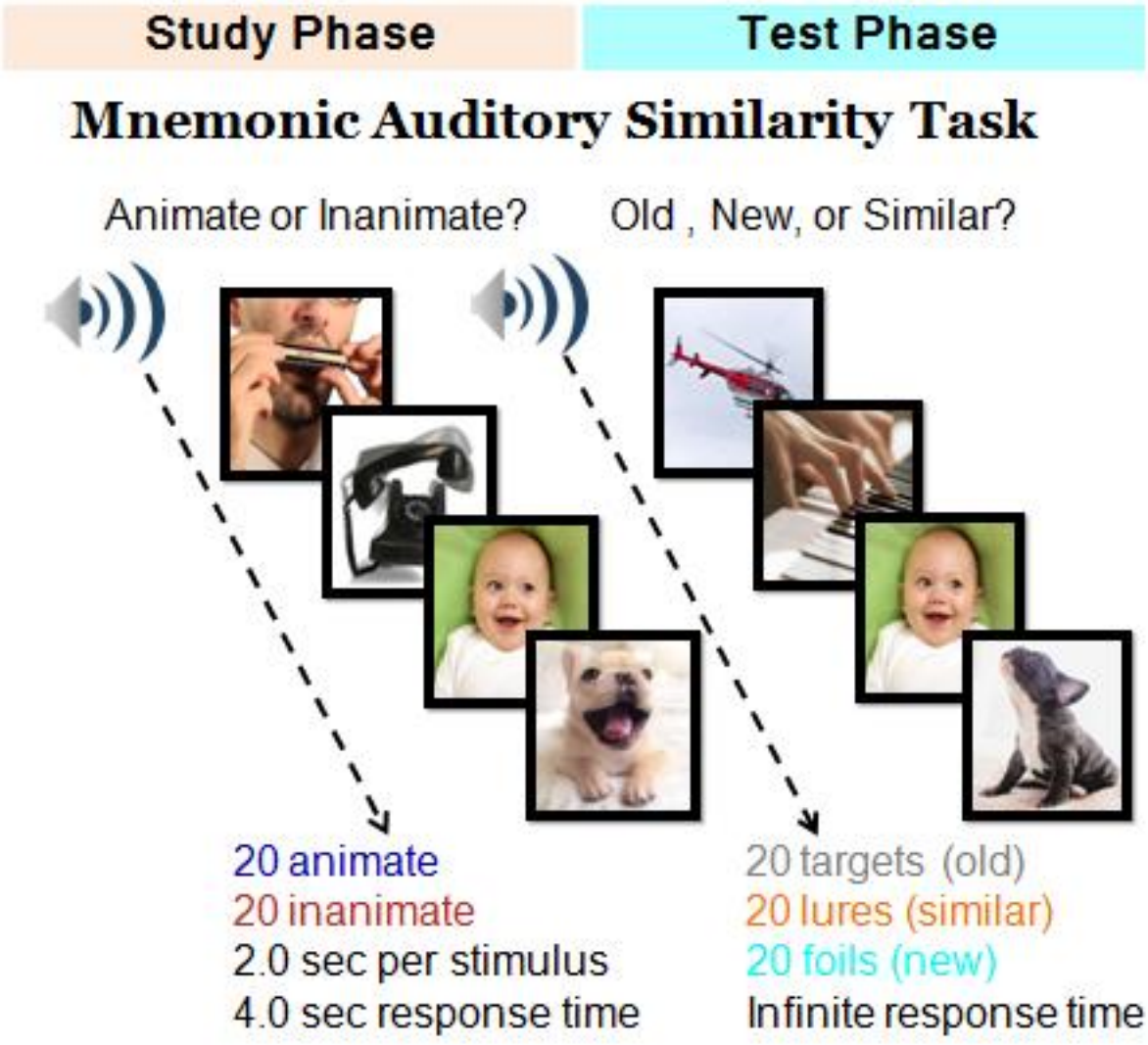


Figure 3-1. Visual depiction of the Mnemonic Auditory Similarity Task (MAST)

3.3.4 Apparatus

The MST was administered as a Windows stand-alone application on either a Lenovo ThinkPad or a Dell Latitude laptop. The MAST was run on identical laptops as a stand-alone application programmed in E-Prime 2.0 (Psychology Software Tools). The sound files on the MAST were presented to participants in a quiet room binaurally through headphones (Bose QuietComfort 25 Over-Ear Noise Cancelling).

3.3.5 Scoring and analysis

3.3.5.1.1 Mnemonic discrimination

Mnemonic discrimination performance on the MST and the MAST was estimated by measuring mean recognition accuracy (proportion correct) across conditions. This statistic reflected the ability of participants to identify foils as new, lures as similar, and targets as old. Calculations were made by totaling the correct number of *old*, *similar*, and *new* responses in the visual or auditory trials and then dividing these by 30 (for the MST) or 20 (for the MAST) to determine proportional accuracy in each condition. We then assessed performance biases on both the MAST and the MST through the Lure Discrimination Index (LDI) score. It rectifies response biases to lures in the face of unlearned items (Stark et al., 2015) by subtracting the proportion of similar responses given to foils from the proportion of similar responses given to lures. In addition to the LDI, we calculated a standard recognition score (REC) by subtracting the proportion of old responses to foils (false alarms) from old responses to targets.

3.3.5.1.2 Memory sensitivity *d'* scores

In order to determine whether differences in mnemonic sensitivity could be detected using signal detection measures (Green & Swets, 1966; Macmillan & Creelman, 2005; Stanislaw & Todorov, 1999), we computed *d'* scores for target items relative to foils *d'* (T,F) and for target items relative to lures *d'* (T,L). These *d'* scores allow for better cross-modality comparisons across studies (Loiotile & Courtney, 2015); hence, these standardized scores facilitated direct MAST and MST comparisons in Experiment 2. Traditional recognition memory sensitivity *d'* (T,F) was calculated in SPSS as the normalized difference between the hit rate for targets versus the false-alarm rate for foils. Target versus lure discrimination sensitivity *d'* (T,L) was calculated as the normalized difference between the hit rate for old items and the rate of calling lure items old.

3.4 Results

3.4.1 Experiment 1

3.4.1.1 Age effects displayed using the MAST

In Experiment 1, we set out to determine whether age-related effects on mnemonic discrimination extend to the auditory modality as they have been found in the visual memory

(Stark et al., 2013, 2015). Marginal means (proportion response) for all conditions across the three age groups for the MAST (participants used in Experiment 1) and the MST (participants from Experiment 2) can be found in Table 3-1. Regardless of age, participants recognized lures at a significantly lower accuracy rate than targets and foils. All MST results in each condition across the three age groups are within one standard deviation (SD) of those reported by Nauer and colleagues (Nauer et al., 2020).

Table 3-1. Experiments 1 and 2, proportion endorsed for each age group and stimulus type
The correct column is shaded; standard errors are in parentheses below.

Age	Study	Targets			Lures			Foils		
group	& *n*	Old	Similar	New	Old	Similar	New	Old	Similar	New
18–29	One	.70	.18	.12	.31	.38	.31	.04	.17	.79
MAST	62	(.02)	(.01)	(.01)	(.02)	(.01)	(.02)	(.01)	(.01)	(.02)
18–29	Two	.66	.20	.14	.28	.37	.35	.05	.15	.80
MAST	26	(.03)	(.02)	(.02)	(.03)	(.02)	(.03)	(.01)	(.02)	(.03)
18–29	Two	.77	.14	.09	.40	.43	.17	.05	.13	.81
MST	26	(.02)	(.01)	(.02)	(.02)	(.03)	(.02)	(.01)	(.02)	(.02)
48-66	One	.61	.23	.16	.32	.38	.30	.06	.18	.76
MAST	29	(.03)	(.02)	(.02)	(.03)	(.04)	(.02)	(.01)	(.02)	(.02)
48-66	Two	.61	.22	.17	.33	.37	.31	.06	.18	.77
MAST	26	(.03)	(.02)	(.02)	(.04)	(.04)	(.03)	(.01)	(.02)	(.02)
48-66	Two	.83	.11	.06	.49	.40	.12	.03	.11	.86
MST	26	(.02)	(.01)	(.01)	(.02)	(.02)	(.02)	(.01)	(.02)	(.02)
67-92	One	.54	.26	.20	.35	.34	.31	.09	.22	.69
MAST	37	(.03)	(.02)	(.02)	(.02)	(.02)	(.02)	(.01)	(.02)	(.03)
67-92	Two	.54	.27	.19	.36	.32	.32	.07	.20	.73
MAST	26	(.03)	(.02)	(.02)	(.02)	(.02)	(.02)	(.01)	(.02)	(.02)
67-92	Two	.84	.09	.07	.61	.23	.16	.06	.09	.85
MST	29	(.02)	(.02)	(.01)	(.03)	(.03)	(.02)	(.01)	(.02)	(.02)

3.4.1.1.1 Auditory mnemonic discrimination

We focused on MAST LDI scores as the most sensitive measures to determine age-related differences in auditory mnemonic discrimination (Stark & Stark, 2017). For LDI scores, Levene's *F* indicated the assumption of homogeneity of variance was not met across the three age groups ($p = .002$). Therefore, to analyze the mean differences among the age categories, we used the obtained Welch's *F* ratio. This robust method corrects for degrees of heterogeneity in a data set (Field, 2013; Welch, 1951). It showed a significant main effect of age on discriminating auditory lures, *Welch's* $F(2, 56.56) = 4.44$, $p = .016$. A significant linear trend in the data, $F(1,125) = 8.12$, $p = .005$, suggested that as age increased, auditory LDI decreased. See Figure 3-2. Post hoc comparisons using the Games-Howell procedure were conducted to determine which pairs of the three LDI means differed significantly. These procedures indicated that OA group members performed significantly worse at auditory lure discrimination ($M = .12$, $SE = .03$) than the YA group ($M = .21$, $SE = .01$; Games-Howell $p = .011$). The OA group also performed worse than the MO group ($M = .19$, $SE = .04$), and the MO group reported results than were below the YA group, but these two post hoc tests did not reach significance using the Games-Howell method ($p > .05$ for both comparisons).

3.4.1.1.2 Auditory recognition memory

We analyzed REC scores to establish whether there were also age-related differences in auditory recognition memory, using a traditional measure often applied to the MST (e.g., Stark & Stark, 2017). Unlike the LDI results, the REC scores did not violate the assumption of homogeneity of variance. A one-way ANOVA indicated there was a significant effect of age on standard recognition of auditory targets, $F(2,125) = 21.80$, $p < .001$, $\omega = .25$. In addition, a significant linear trend in the data, $F(1,125) = 42.84$, $p < .001$, revealed that as age increased, auditory recognition memory decreased proportionately. See Figure 3-2. Post hoc comparisons using the Games-Howell procedure were conducted to determine which pairs of the REC means differed. This test indicated that the OA group ($M = .45$, $SE = .03$) had significantly worse recognition memory for sounds than both the YA group ($M = .66$, $SE = .02$), and the MO group ($M = .55$, $SE = .03$); Games-Howell $p < .05$ for both comparisons. Furthermore, the MO group had significantly worse auditory REC scores than the YA individuals (Games-Howell $p = .018$).

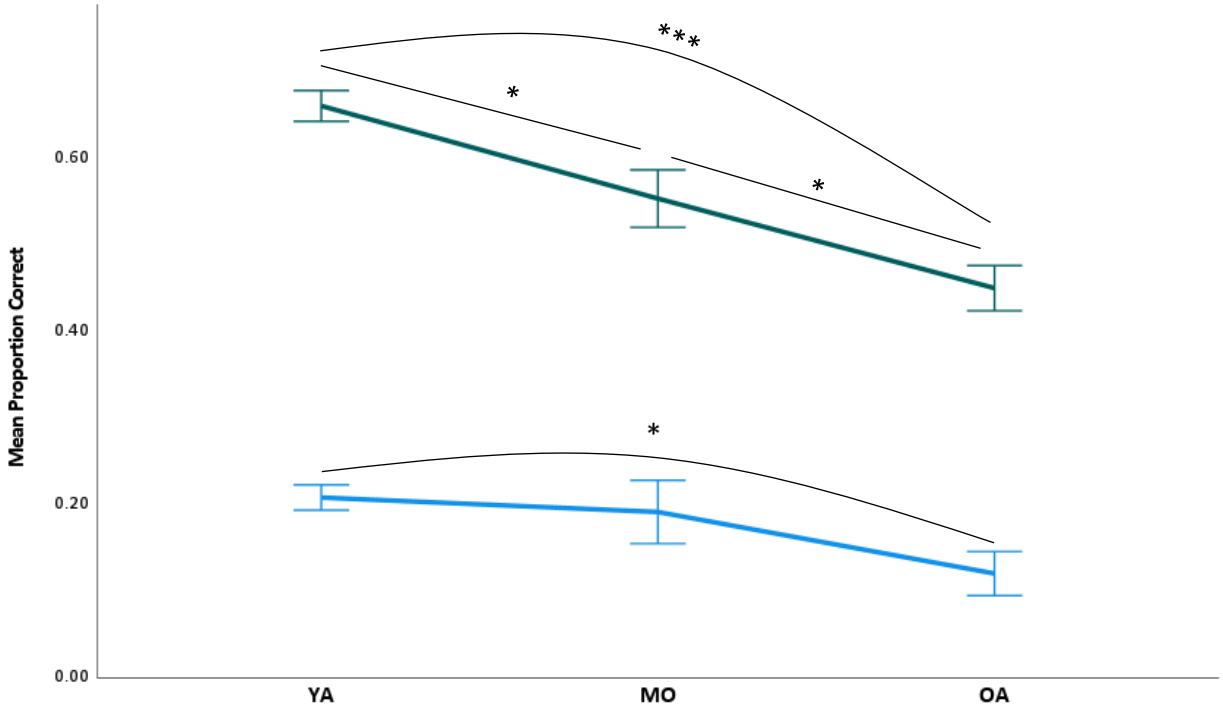


Figure 3-2. Experiment 1: LDI and recognition memory scores

Performance scores for lure discrimination (blue line) and recognition memory (green line) across the three age groups tested. Error bars represent standard error (SE).

3.4.1.2 Auditory memory sensitivity *d'* scores

We investigated mnemonic sensitivity using signal detection methods by contrasting *d'* scores for targets relative to lures *d'* (T,L) and targets relative to foils *d'* (T,F). Levene's *F* confirmed the assumption of homogeneity of variance was met across the three age groups for both these measures. Therefore, we proceeded with a 3x2 mixed design ANOVA (age category x mnemonic sensitivity) to determine the statistical degree to which participants' target identification sensitivity varied over the three age groups.

Collapsed across age, participants were significantly better at discriminating old items relative to foils (M = 1.91, SE = .05) than they were at discriminating old items relative to lures (M = 0.83, SE = .04), $F(1,125) = 650.87$, $p < .001$, $n_p^2 = .84$. However, we failed to find evidence that this difference in sensitivity interacted with the age group of the participant $F(2,125) = 0.61$, $p = .547$, $n_p^2 = .01$. There was, however, a significant difference between age groups for mean sensitivity scores, $F(2,125) = 26.91$, $p < .001$, $n_p^2 = .30$. Post-hoc tests corrected using the

Games-Howell test indicated that the OA group (M = 1.02, SE = .07) performed significantly worse than both the YA group (M = 1.71, SE = .06) and the MO group (M = 1.37, SE = .08; p <.001 and p = .017, respectively). Likewise, participants in the MO group were significantly worse than the YA group (p = .015).

3.4.1.2.1 Correlation with sound ratings

We investigated the relationship between average *d'* sensitivity scores and sound ratings on those participants who completed the MAST, as well as the post-test sound ratings (see section 3.3.3.1.1). Using bivariate Pearson correlations, we found that *d'* (T,L) was significantly related to participants' ability to identify identical sounds as identical , r = .31, 95% BCa CI [.11, .45], p = .003. A weaker yet significant correlation was found between *d'* (T,F) and the ability of participants to identify identical sounds as the same, r = .21, 95%, BCa CI [.03, .41], p = .044. We failed to find evidence that participants' ratings of different sound trials as different or similar sound events as similar correlated with auditory mnemonic sensitivity.

3.4.1.3 Age effects in trimmed sample

Pursuing the investigation of the ability of individuals to identify pairs of sounds as the same, we analyzed the data on participants who completed the sound quality ratings. We trimmed the sample to include only those individuals who performed within two standard deviations of young participants' mean sound quality rating. We chose the YA group as the benchmark because this group performed significantly better than the other two age categories on our tests of auditory mnemonic sensitivity. In effect, this meant that all participants in the trimmed sample had to have an average correct response to identical items across the three sound ratings (pitch, volume, sound quality) equal to or higher than 4.78 out of 5.00 (a 95.60% success rate).

A 3x2 mixed-design ANOVA (age category x sensitivity) was applied to this trimmed sample of participants who performed within normal limits relative to the YA benchmark of 4.78. We again found that participants (averaged over groups) were significantly better at discriminating old items relative to foils (M = 1.92, SE = .06) than they were at discriminating old items relative to lures (M = 0.86, SE = .06). As with the untrimmed sample, the difference in mnemonic sensitivity was significant, $F(1,72) = 371.43$, p <.001, $n_p^2 = .84$. We again failed to find evidence that this difference in sensitivity interacted with age $F(2,72) = 0.76$, p = .473, $n_p^2 = .02$. As with

the untrimmed sample, there was a significant difference between age groups for auditory mean sensitivity scores, $F(2,72) = 10.48$, $p < .001$, $n_p^2 = .23$. Post-hoc tests corrected using the Games-Howell indicated that older adults in the trimmed sample showed average sensitivity scores which were slightly higher than those of the untrimmed sample (untrimmed $M = 1.02$, $SE = .07$; trimmed $M = 1.11$, $SE = .10$). This trimmed subset of OAs continued to significantly underperform the YA group ($M = 1.72$, $SE = .09$; $p < .001$). A replication of the MO group's significantly worse performance ($M = 1.35$, $SE = .09$) in comparison to the YA group was also found ($p = .021$).

When accounting for perceptual abilities to identify sounds, the primary difference between the whole and trimmed samples was that the OA group's weaker performance in auditory mnemonic sensitivity in the trimmed sample failed to reach significance ($p = .207$) when using a Games-Howell pairwise comparison with the MO group.

3.4.2 Experiment 2

By testing a subset of participants from Experiment 1 on both the MAST and the MST, we were able to make inferences about relative perceptual and mnemonic abilities of healthy adults across the lifespan. Furthermore, we could make these comparisons with groups similar in sample sizes ($n = 26$, 26, and 29 in YA, MO, and OA categories, respectively). Additionally, the testing of patient BL in Experiment 3 provided a way to gauge the involvement of hippocampal subfields known to facilitate pattern separation in the visual modality in auditory mnemonic discrimination and sensitivity.

3.4.2.1 Age effects in auditory and visual memory

3.4.2.1.1 Auditory and visual mnemonic discrimination

To see if age effects could be found both in auditory and visual memory in the same participants, we again began our analysis on LDI and REC scores. Marginal mean accuracy for recognition memory discrimination and sensitivity for this subset of participants can be found in Table 3-2.

For auditory LDI scores, Levene's F again indicated the assumption of homogeneity of variance was violated across the three age groups for auditory LDI scores ($p = .022$). A one-way ANOVA using a robust method to correct this heterogeneity specified a significant main effect of age on

the ability to discriminate auditory lures, *Welch's F*(2,49.61) = 3.96, p = .025. Multiple comparisons using the Games-Howell procedure indicated that the OA group (M = .12, SE = .03) performed significantly worse (p = .018) on auditory lure discrimination than younger adults (M = .23, SE = .02). Although the OA group members were weaker on average in auditory lure discrimination than the MO individuals (M = .19, SE = .04), we failed to find evidence that the difference between OA and MO groups was significant (p = .311). In addition, the relatively poor performance of the MO group compared to the YA group failed to reach significance. (p = .738). The above results of significant versus non-significant pairwise comparisons parallel those found in Experiment 1.

Table 3-2. Experiment 2: Mnemonic discrimination and sensitivity by age group
Standard errors are in parentheses below.

Age group	**LDI**	**REC**	***d'* T,L**	***d'* T,F**
18–29 MAST	.23 (.02)	.61 (.03)	1.13 (.08)	2.09 (0.09)
18–29 MST	.30 (.03)	.71 (.03)	1.03 (.08)	2.44 (.11)
46-64 MAST	.19 (.04)	.55 (.04)	0.82 (0.12)	1.91 (0.12)
46-64 MST	.29 (.02)	.80 (.02)	1.06 (.07)	2.89 (.11)
66-92 MAST	.12 (.03)	.47 (.03)	0.49 (0.08)	1.64 (0.07)
66-92 MST	.16 (.02)	.78 (.02)	0.77 (0.07)	2.70 (0.09)
BL MAST	.15	0	0	0
BL MST	–.21	.64	0.29	1.97

Visual LDI scores from the MST did not violate the assumption of equal variances. Therefore, we ran a one-way ANOVA to determine whether there were age-related differences in LDI scores, as has been found in previous investigations using this metric (Stark et al., 2015). Results revealed a main effect of age group on the ability to discriminate visual lures, F(2,78) = 8.80, p <.001, $n_p^2 = .18$. Multiple comparisons using the Games-Howell procedure showed that the OA group (M = .16, SE = .02) had significantly worse LDI scores than both the YA (M = .30, SE = .03; p = .004) and the MO groups (M = .29, SE = .02; p <.001). MO means were very similar to

the younger group and the difference in visual discrimination for the two groups was not found to be significant (p = .953).

3.4.2.1.2 Auditory and visual recognition memory

Auditory and visual REC scores in Experiment 2 met the assumption of homogeneity of variance across the three age groups (p > .05). Therefore, one-way ANOVAs were used to determine whether there were differences in means across the three age groups. For auditory REC, there was a significant effect of age on standard recognition of auditory targets, $F(2,78) = 5.15$, p = .008, $n_p^2 = .12$. Post hoc comparisons using the Games-Howell method indicated that the OA group (M = .47, SE = .03) had significantly worse REC scores than the YA group (M = .61, SE = .03; p = .003). Although the OA group had lower mean REC scores than the MO group (M = .55, SE = .03) and the MO group had weaker performance than the YA group, the pairwise differences failed to reach statistical significance (p >.05).

As with the auditory values, traditional recognition memory scores from the MST also exhibited a main effect of age category, $F(2,78) = 4.11$, p = .02, $n_p^2 = .10$. We detected a significant quadratic tendency in the data, $F(1,78) = 4.06$, p = .047, indicating a curvilinear trend. Indeed, multiple comparisons showed that YAs (M = .71, SE = .02) had lower average visual REC scores than OAs (M = .78, SE = .02), although the difference in their scores was not found to be significant (p = .116). A different story was found between the YA group and the MO group. The former group performed significantly worse on visual REC scores than the MO group (M = .80, SE = .02). The difference between these two groups was significant (p = .031).

3.4.2.1.3 Mnemonic sensitivity for auditory vs. visual memory

As well as evaluating mnemonic discrimination in experiment two, we also assessed whether age-related effects on mnemonic sensitivity (as measured by *d'*) are different for auditory versus visual stimuli. To see if we could find a significant main effect of the modality of stimuli on mnemonic sensitivity, we first used paired-samples *t*-tests to contrast *d'* scores for the MAST and the MST. Irrespective of age category, participants performed worse at lure mnemonic sensitivity for everyday sounds (M = 0.81, SE = .06) than for everyday visual objects (M = 0.95, SE = .04; Figure 4). The difference in *d'* sensitivity means, –0.15, 95% BCa CI [–.28, –.01], was significant $t(80) = –2.27$, p = .026, albeit a small effect d = –0.25. A study of foil mnemonic

sensitivity differences across modality illustrated that participants were worse at recognizing *d'* for targets relative to foils in the auditory relative to the visual domain. The mean difference in *d'* (T,F), –0.81, 95% BCa CI [–0.94, –.68] was significant, $t(80) = -11.70$, $p < .001$, and represented a large effect, $d = -1.30$. See Figure 3-3.

Despite the significant differences in performance in mnemonic sensitivity across the auditory and visual domains, *d'* comparative pairs values had medium correlations. As measured using the bivariate Pearson correlation, we found that *d'* (T,L) of sound objects was significantly related to *d'* (T,L) of visual objects, $r = .30$, 95% BCa CI [.04, .51], $p = .007$. See Figure 3-4. In addition, the auditory *d'* (T,F) trials were significantly correlated with the visual trials for *d'* (T,F), $r = .36$, 95%, BCa CI [.19, .51], $p = .001$.

3.4.2.1.4 Auditory versus visual memory sensitivity

3.4.2.1.4.1 Auditory versus visual mnemonic sensitivity to lures

Our computation of *d'* scores allowed for the direct testing of memory sensitivity in the acoustic versus visual domains. A review of mean participant sensitivity to discriminating target items from foils and lures (see Table 3-2) shows that they progressively declined over the three groups tested. Two separate 3x2 mixed-design ANOVAs, with factors of age and modality, were run on the *d'* scores for targets relative to lures *d'*(T,L) and targets relative to foils *d'*(T,F). We aimed to determine the statistical degree to which participants' auditory memory sensitivity varied across the lifespan.

The *d'* (T,L) results exhibited a main effect of age, $F(2,78) = 12.92$, $p < .001$, $n_p^2 = .25$, and a main effect of modality, $F(1,78) = 5.08$, $p = .027$, $n_p^2 = .06$. These results must be interpreted in light of a significant age x modality interaction, $F(2,78) = 3.63$, $p = .031$, $n_p^2 = .09$. Post hoc comparisons using the Bonferroni correction indicated that younger adults' mean *d'* (T,L) scores for the MAST ($M = 1.13$, $SE = .08$) were slightly higher than their mean *d'* (T,L) sensitivity scores for the MST ($M = 1.03$, $SE = .08$). The difference between the two means failed to reach levels of significance ($p = .380$).

Differences between groups, however, amplify in the other age categories. MO adults were significantly worse at lure sensitivity in the auditory domain ($M = 0.82$, $SE = .12$) than the visual one ($M = 1.06$, $SE = .07$; $p = .034$). OAs reported poor sensitivity at detecting targets relative to

lures in both the auditory (*M* = 0.49, *SE* = .08) and visual (*M* = .77, *SE* = .07) modalities. However, they were significantly worse the auditory domain, *d'* (T,L), *p* = .009.

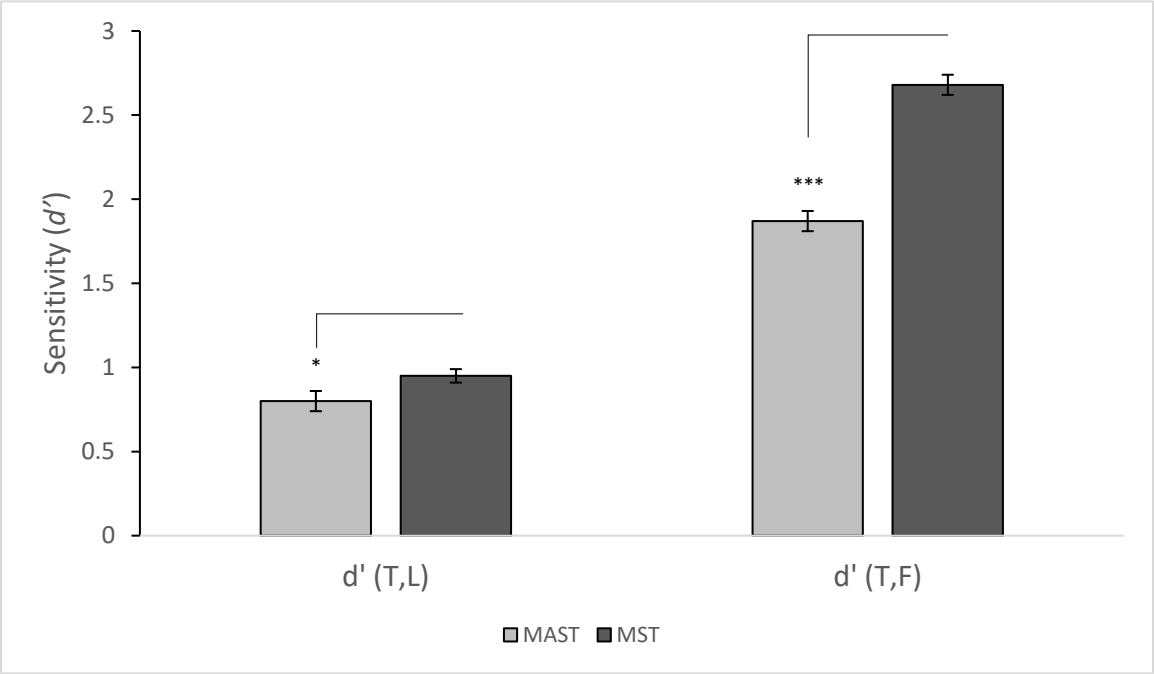


Figure 3-3. Experiment 2: MAST and MST lure and recognition mnemonic sensitivity
Performance averaged across all participants. Error bars represent standard error (SE).

For simple effects of lure discrimination by modality, we found that auditory *d'* (T,L) scores for the OA group were significantly worse than auditory *d'* (T,L) for both the YA group (*p* <.001) and the MO group (*p* = .046). We failed to find evidence that the MO group was significantly different than the YA group (*p* = .082). These MAST results found parallels with the MST findings: visual *d'* (T,L) scores for the OA group were again significantly worse than the YA group (*p* = .034) and the MO group (*p* = .017). The marginal difference between visual mnemonic sensitivity for the MO group compared to the YA group failed to reach significance using the post hoc comparisons (*p* = 1.00)

3.4.2.1.4.2 Auditory versus visual mnemonic sensitivity to foils

Unlike mnemonic sensitivity to targets relative to lures, *d'* (T,F) results did not exhibit a similar main effect of age group, $F(2,78) = 1.89$, $p = .158$, $n_p^2 = .05$, although these results must again be interpreted within the context of a main effect of modality, $F(1,78) = 176.01$, $p < .001$, $n_p^2 =$

.69, and a modality x age interaction, $F(2,78) = 13.80$, $p < .001$, $n_p^2 = .26$. Post hoc comparisons using the Bonferroni correction indicated the YA group mean *d'* (T,F) scores for the MAST ($M = 2.09$, $SE = .09$) were worse than their mean scores for the MST ($M = 2.44$, $SE = .11$). The difference between the two means, –0.35 ($SE = .11$), was significant ($p = .001$). We also found that the MO group *d'* (T,F) scores for the MAST ($M = 1.91$, $SE = .12$) were significantly worse ($p < .001$) than that group's *d'* (T,F) performance for the MST ($M = 2.89$, $SE = .11$). Similarly, the OA group had significantly worse performance ($p < .001$) in detecting auditory targets from foils ($M = 1.64$, $SE = .07$) compared to their sensitivity for discriminating visual targets relative to foils ($M = 2.70$, $SE = .09$).

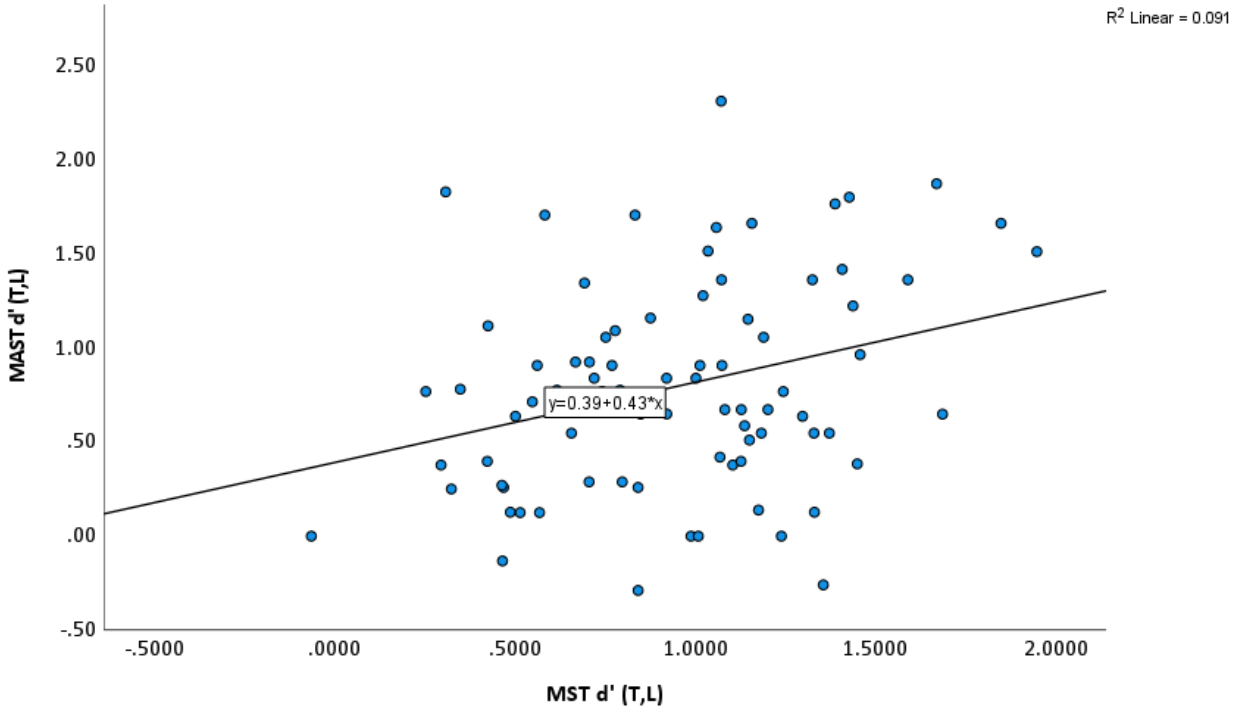


Figure 3-4. Experiment 2: Correlation between MAST and MST *d'* scores

Interestingly, recognition memory sensitivity for visual objects was lowest for the YA group, whereas it peaked in this group for the auditory stimuli and then declined in a linear fashion across the MO and OA groups. We find this relationship further quantified in the data when comparing the MAST *d'* (T,F) for OAs compared to that of the YAs. The OA group showed significantly worse MAST *d'* (T,F) performance than the YA group ($p = .005$). The OA group also had lower sensitivity to auditory foils than the MO group, but this difference was not

significant (p = .157). For their turn, the MO individuals had lower auditory *d'* (T,F) means than the YA group, but we again failed to find evidence this difference was significant (p = .628).

In contrast, visual mnemonic sensitivity for targets relative to foils showed that this ability increases in middle-to-older age and then plateaus in older age. For example, we found that the YA group members were significantly worse than those in the MO group for their sensitivity to target items relative to foils (p = .009). The YA individuals were also worse than the OA participants for *d'* (T,L), although the difference between the groups failed to reach significance (p = .227). The OA group performed slightly worse than the MO group, but again, this comparison could not reach significance (p = .535).

3.4.2.2 Age effects in trimmed sample

We re-ran the analyses from sections 3.4.2.1.4.1 and 3.4.2.1.4.2 on a trimmed sample of Experiment 2 participants (see 3.3.2.1 for a description of this sample). Two separate 3x2 mixed-design ANOVAs (age category x sensitivity) were applied to this group.

3.4.2.2.1 Auditory versus visual mnemonic sensitivity to lures

As with the untrimmed sample, the *d'* (T,L) results exhibited a main effect of age, $F(2,56)$ = 7.63, p = .001, n_p^2 = .21. However, unlike the untrimmed sample, we failed to find a main effect of modality, $F(1,56)$ = 1.95, p = .168, n_p^2 = .03, nor a significant age x modality interaction, $F(2,56)$ = 1.37, p = .263, n_p^2 = .05. See Figure 3-5. Post hoc comparisons using the Games-Howell procedure indicated that the OA group (M = .63, SE = .09) showed significantly worse (p < .001) performance for mean *d'* (T,L) scores than younger adults (M = 1.12, SE = .09). The individuals in the OA group also performed significantly worse (p = .032) in average lure sensitivity than the MO group (M = .94, SE = .07). The difference between the average means for the MO and YA groups failed to reach levels of significance (p = .277).

3.4.2.2.1.1 Auditory versus visual mnemonic sensitivity to foils

Results of our investigation of auditory versus visual mnemonic sensitivity to foils for the trimmed sample were unchanged (in terms of significance detected) from those for the untrimmed sample.

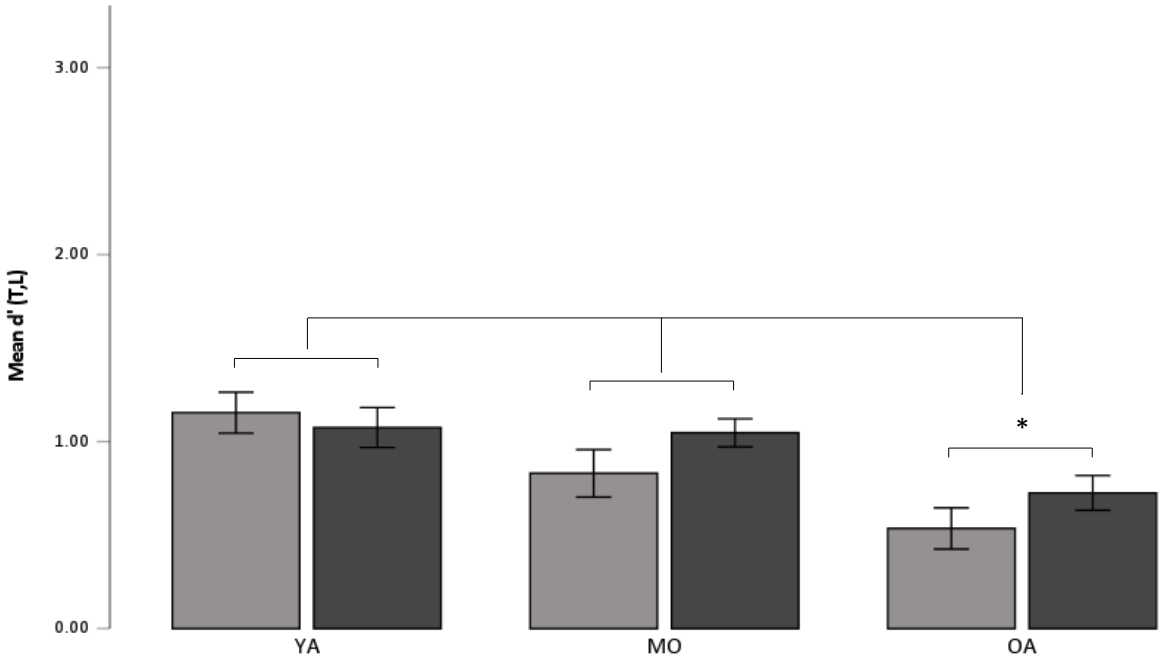


Figure 3-5. Experiment 2 (trimmed sample): MAST vs. MST lure sensitivity
Mean mnemonic sensitivity (Y-axis) of targets relative to lures, *d'* (T,L). MAST results are represented by the light bar, MST results by the dark bar. Error bars represent standard error.

As with the larger sample, the *d'* (T,F) sample trimmed by participants' perceptual sound quality ratings did not exhibit a main effect of age group, $F(2,56) = 0.71$, $p = .498$, $n_p^2 = .02$. These results must again be interpreted within the context of a main effect of modality, $F(1,56) = 112.53$, $p < .001$, $n_p^2 = .67$, and a modality x age interaction, $F(2,56) = 9.86$, $p < .001$, $n_p^2 = .26$. Post hoc comparisons using the Bonferroni correction indicated the YA group mean *d'* (T,F) scores for the MAST ($M = 2.15$, $SE = .13$) were worse than their mean scores for the MST ($M = 2.45$, $SE = .14$). The difference between the two means, –0.30 ($SE = .14$), was significant ($p = .036$). We also found that the MO group *d'* (T,F) scores for the MAST ($M = 1.88$, $SE = .11$) were significantly worse ($p < .001$) than that group's *d'* (T,F) performance for the MST ($M = 2.86$, $SE = .11$). Similarly, the OA group had significantly worse performance ($p < .001$) in detecting auditory targets from foils ($M = 1.66$, $SE = .12$) compared to their sensitivity for discriminating visual targets relative to foils ($M = 2.74$, $SE = .13$). See Figure 3-6.**Error! Reference source not found.**

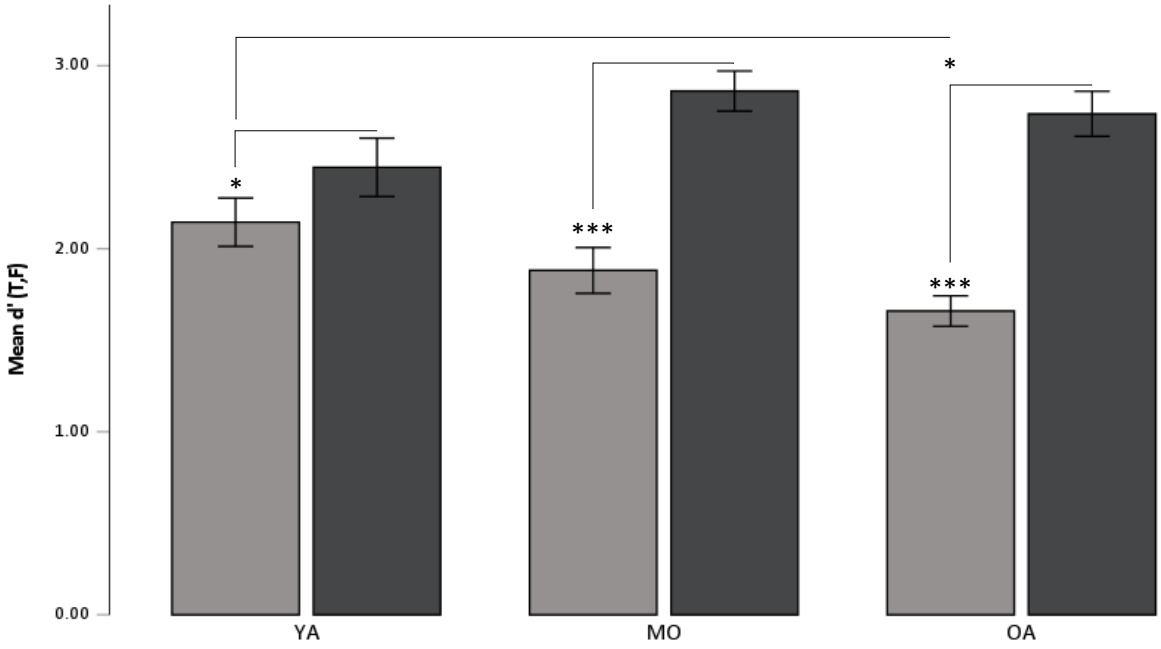


Figure 3-6. Experiment 2 (trimmed Sample): MAST vs. MST foil sensitivity
Mean mnemonic sensitivity (Y-axis) of targets relative to foils, *d'* (T,F). MAST results are represented by the light bar, MST results by the dark bar. Error bars represent standard error.

Again, as is illustrated in Figure 3-6, recognition memory sensitivity for visual objects was highest for the MO group, followed closely by the OA individuals. In contrast, auditory recognition memory sensitivity peaked with the YA group and then declined in a linear fashion. We find this relationship further quantified in the data when comparing the MAST *d'* (T,F) for OAs compared to that of the YAs. Post hoc comparisons using the Bonferroni correction indicated the OA group showed significantly worse MAST *d'* (T,F) performance than the YA group (p = .030). The OA group also had lower sensitivity to auditory foils than the MO group, but this difference was not significant (p = .543). For their turn, the MO individuals had lower auditory *d'* (T,F) means than the YA group, but we again failed to find evidence this difference was significant (p = .379).

Remarkably, the main difference between the trimmed and untrimmed sample for *d'* (T,F) performance was in the visual, not the auditory domain. Whereas we found significant differences between YA and MO participants in simple effects of *d'* (T,F) for the untrimmed MST sample, these findings were not apparent in the smaller trimmed sample. The YA group

members were worse than those in the MO group for their sensitivity to target items relative to foils, but the difference between the two age groups failed to reach significance (p = ..075). The OA group performed slightly worse than the MO group, but again, this comparison could not reach significance (p = 1.00).

3.4.3 Patient BL: a dissociation between lure versus foil discrimination and sensitivity across modalities

We were interested in determining if critical regions of the hippocampus / MTL are implicated in facilitating mnemonic recognition and discrimination. Therefore we tested an amnesic patient (BL) on both the MAST and the MST. We compared his results with those of the untrimmed MO group from Experiment 2 (see Table 3-2). (In regard to BL's sound quality rating, his aggregate sound quality rating of 4.88 was within limits used to define the trimmed sample. His lowest sound quality rating score was for pitch. Here we did find that his ability to identify two sounds as having identical acoustic properties was significantly worse than controls).

To compare auditory lure discrimination as measured by the LDI for BL with the mean of the MO control group, we applied Crawford and Howell's modified *t*-test for single cases (Crawford et al., 2010; Crawford & Garthwaite, 2002; Crawford & Howell, 1998). Using this measure, we could not find that the difference, –0.04, between BL and controls for the ability to discriminate highly similar sounds was significant, $t(25) = –0.19$, $p = 0.424$, one-tailed *t*-test, $z_{cc} = –0.20$. Indeed, BL's results place him at the 42.41 percentile, 95% CI [28.00, 57.65]. In contrast, BL was significantly worse ($M_{\text{diff}} = –.55$) in his auditory recognition memory (REC) performance compared to the MO group, $t(25) = –2.94$, $p = .003$, one-tailed t-test, $z_{cc} = –3.00$. These REC results place BL at the 0.35 percentile, 95% CI [.005, 1.872]. The data indicate that BL's source memory for whether a sound was old or new was impaired. See Table 3-3.

Consistent with Baker et al. (2016), BL's visual lure discrimination was impaired relative to controls on LDI scores, $t(25) = –4.32$, $p < .001$, one-tailed *t*-test, $z_{cc} = –4.40$. BL's suboptimal results place him at the 0.01 percentile, 95% CI [<.001, 0.089]. BL's visual recognition memory (REC) score was not found to be significantly different than controls, $t(25) = –1.44$, $p = .081$, one-tailed *t*-test, $z_{cc} = –1.44$. Still, his visual recognition performance placed BL relatively low in percentile terms, with the estimated percentage of the neurotypical population falling below BL's score being 8.07%, 95% CI [2.16, 18.23].

Table 3-3. Patient BL vs. MO controls

	Control sample (n = 26)		*BL's score*	*Significance test (one-tailed)*[a]		*Estimated percentage of the control population obtaining a lower score than BL*[b]		*Estimated effect size (z_{cc})*[c]	
Test	*Mean*	*SD*		*t*	*p*	*Point*	*(95% CI)*	*Point*	*(95% CI)*
LDI – MAST	.19	.20	.15	-0.19	.42	42.41	(27.98 to 57.65)	-0.20	(-0.58 to -0.19)
LDI – MST	.29	.11	-.21	-4.32	<.001	0.01	(<.001 to .089)	-4.40	(-5.67 to -3.12)
REC – MAST	.55	.18	0	-2.94	.003	0.35	(.005 to 1.872)	-3.00	(-3.90 to -2.08)
REC – MST	.80	.11	.64	-1.44	.081	8.07	(2.16 to 18.23)	-1.47	(-2.02 to -0.91)
d' (T,L) MAST	.82	.62	0	-1.29	.10	10.45	(3.32 to 21.80)	-1.31	(-1.84 to -0.78)
d' (T,L) MST	1.06	.37	0.29	-2.02	.027	2.73	(.31 to 8.63)	-2.06	(-2.73 to -1.36)
d' (T,F) MAST	1.91	.63	0	-2.97	.003	0.32	(.004 to 1.77)	-3.03	(-3.94 to -2.10)
d' (T,F) MST	2.89	.56	1.97	-1.61	.060	5.97	(1.29 to 14.86	-1.64	(-2.23 to -1.04)

Notes. [a]Crawford & Howell (1998), [b]Crawford & Garthwaite (2002). [c]Crawford, Garthwaite & Porter (2010).

As was noted above, computation of *d'* scores allowed us to run direct tests of memory sensitivity in the auditory versus visual domains. We applied our calculation of these *d'* scores on the trials comparing mnemonic sensitivity of BL and the MO control group within the auditory and visual modalities. In respect to auditory lure sensitivity, we failed to find evidence that BL's mean *d'* (T,L) score was significantly different than controls, $t(25) = -1.29$, $p = .104$, one-tailed *t*-test, $z_{cc} = -1.31$, which places BL at the 10.45 percentile, 95% CI [3.32, 21.80]. In contrast, BL's mnemonic sensitivity to auditory targets relative to foils was significantly worse than controls, $t(25) = -2.97$, $p = .003$, one-tailed *t*-test, $z_{cc} = -3.03$, 0.324 percentile, 95% CI [.004, 1.773]. As with his visual LDI scores, BL's visual *d'* (T,L) performance was significantly worse than controls, $t(25) = -2.02$, $p = .027$, one-tailed *t*-test, $z_{cc} = -2.06$, 2.73 percentile, 95% CI

[0.31, 8.63]. Yet, we failed to find evidence that BL's visual recognition memory sensitivity, like his visual REC scores, was significantly different than controls, $t(25) = -1.61$, $p = .060$, one-tailed t-test, $z_{cc} = -1.64$, 5.97 percentile, 95% CI [1.29, 14.86].

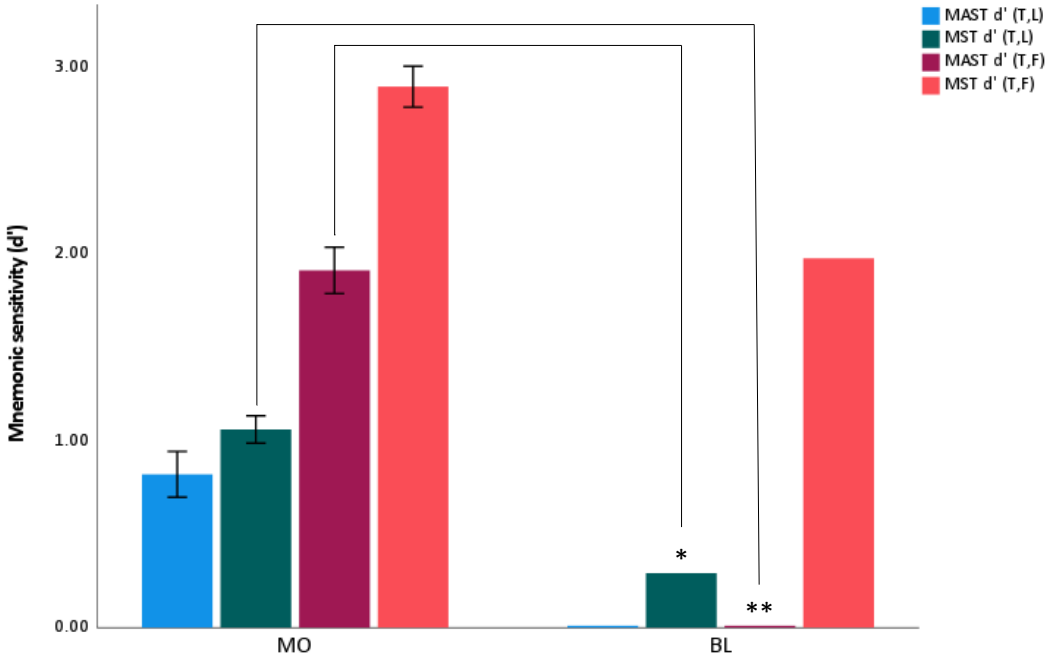


Figure 3-7. Experiment 2: Mean mnemonic sensitivity for MO controls and patient BL
Error bars represent standard error (SE).

3.5 Discussion

Over two experiments, we set out to test whether mnemonic discrimination and sensitivity in the auditory domain have similar performance declines across the lifespan as has been found in the visual domain (Nauer et al., 2020; Riphagen et al., 2020; Stark et al., 2013, 2015). Furthermore, we investigated whether variations in ability can be found in a patient with an established behavioral pattern separation deficit. The tools we used to determine these abilities in all participants were an established test of visual behavioral pattern separation (MST; Kirwan & Stark, 2007; Stark et al., 2015) and a novel test of auditory mnemonic discrimination and sensitivity, the MAST, modeled after the MST.

In experiment one, we established that the auditory MAST, like the visual MST, can be used to detect age-related declines in mnemonic discrimination (as measured by a conventional lure discrimination index using an untrimmed sample) in older adults compared to young adults. Yet,

the MAST failed to find significant differences for auditory lure discrimination between young adults and middle-older adults or between middle-older participants and older ones. These results suggest differences in auditory mnemonic discrimination for semantically overlapping sounds are most apparent when testing participants at extreme ends of the lifespan. In terms of mnemonic sensitivity, as measured by SDT methods (*d'*), we found that combined *d'* scores (for targets relative to lures and targets relative to foils) significantly declined over the three age groups tested. These age-related effects varied slightly when we trimmed the sample of participants by their auditory perceptual abilities. Here, we failed to find a difference in mnemonic sensitivity scores between the middle-older adults and older adults.

In experiment two, we ran a subset of participants on both the MAST and the MST. For the MAST, we found similar age effects for mnemonic discrimination as was found in experiment one. For the MST, visual mnemonic lure discrimination declines across the three age groups were apparent and paralleled linear decreases with age found in a study with three similar age categories (Nauer et al., 2020). As for traditional recognition memory discrimination using naturalistic sounds, we found that OAs were significantly worse than YAs at recognizing whether an everyday sound was previously encountered. Recognition memory results for visual objects, however, did not decline with aging. The only significant difference to be found was between the YA and the MO group, with the younger adults performing significantly worse than adults in middle-older age. The absence of evidence for visual recognition memory deficits between the YA group and the OA group supports findings of a lack of age-related recognition memory declines across the lifespan (Nauer et al., 2020; Stark et al., 2013).

3.5.1 Modality effects: Agnostic hippocampus for sound and vision

3.5.1.1 Targets versus lures

In direct testing of the MAST and the MST in the untrimmed sample, we found that target vs. lure sensitivity scores, *d'* (T,L), were similar for both sounds of objects and pictures of things in the YA participants. However, significant variations in ability were found in the MO and OA age groups. In these older individuals, acoustic performance was significantly worse than visual performance. This finding of a significant discrimination difficulty for target items relative to highly auditory lures seems to contradict the postulation that mnemonic representations of sensory/perceptual stimuli should occur across modalities as per the attributes model of the

memory system (Hunsaker & Kesner, 2013). We say *seems to contradict*, because these significant modality differences in the older age groups vanished when we controlled for auditory perceptual abilities in a trimmed sample. Rather than challenging the notion that the hippocampus is representationally agnostic to stimulus modality (Huffman & Stark, 2014; Larocque et al., 2013), our results with this trimmed sample seem to support this theory.

3.5.1.2 Targets versus foils

Unlike target vs. lure mnemonic sensitivity, traditional memory sensitivity *d'* scores, *d'* (T,F) showed a frank dissociation between modality of the stimuli used. Participants' ability to identify targets relative to foils was significantly worse for sounds of objects in comparison to pictures of objects. This deficit was found in all three age categories in both the larger and the trimmed samples. These findings appear to support previous research showing that auditory recognition memory is weaker than visual recognition memory (Bigelow & Poremba, 2014; Gloede et al., 2017; Cohen et al., 2011). Why is this so? One possibility is that auditory recognition memory relies on multiple areas of the brain outside of the hippocampus (e.g., Zimmermann, Moscovitch, & Alain, 2016), making its processing within the MTL less robust than that of visual information. Alternately, auditory recognition memory could be more dependent on hippocampal subfields, and we expand on this argument below.

3.5.2 Aging effects: Converging evidence for lure but not foil performance

3.5.2.1 Targets versus lures

We found that the OA group had significantly poorer performance for target versus lure sensitivity than the YA and MO groups for auditory and visual items. (The only exception to this finding being in the trimmed sample, where we failed to find significant differences between the OA and MO groups.) Our research, then, provides converging evidence for auditory and visual age-related declines in lure mnemonic sensitivity across the lifespan. In interpreting these results, we reason that the OA group's lower mnemonic sensitivity to lures reflects a dependency on a hippocampus that has lost volume and otherwise deteriorated with age due to neurobiological alterations (Bettio et al., 2017; Raz et al., 1998). These age-related changes are theorized to significantly impact mnemonic discrimination in the visual domain (Nauer et al., 2020; Stark et al., 2013, 2015). We provide developing evidence of concomitant deficits in the auditory environment.

3.5.2.2 Targets versus foils

Traditional memory sensitivity *d'* scores showed aging effects interacted with the modality of the test stimuli. Older adults in the MAST, but not the MST, were significantly worse than their younger counterparts in foil sensitivity. This cross-lifespan finding of auditory recognition decline was apparent in both the larger sample and a trimmed sample which accounted for potential hearing deficits. This result appears challenging to interpret in light of our speculation above about auditory foil discrimination being less reliant on the hippocampus. However, as we argue below in discussing BL's result, we speculate the decline in auditory sensitivity for targets relative to foils is partly attributable to an aging or inefficient hippocampus.

As for *d'* (T,F) results for the MST, results again diverged from the MAST. The only significant difference found when measuring visual *d'* (T,F) was with the MO group, which appeared (in the untrimmed but not trimmed sample) to have significantly better mnemonic sensitivity relative to foil items than the YA group. There were no significant differences between age categories for visual *d'* (T,F) in the trimmed sample, which might have been attributable to the lower power of the smaller sample to detect age-related differences in recognizing a common object as previously encountered. However, previous studies using the MST or similar paradigms have found variable within- and between-group visual recognition memory results (e.g., Holden et al., 2013). Furthermore, a recent meta-analysis of aging and recognition memory (Fraundorf et al., 2019) identified multiple variables that influence recognition memory in aging, including the semantic richness of the material to be studied.

3.5.3 Focal lesion effects: Auditory and visual dissociations?

One of the aims of Study 2 was to investigate whether there was a causal role of the human hippocampal DG subfield in discriminating studied items from similar unstudied items in both the auditory and visual domains. We pursued this goal through testing patient BL, an individual with hippocampal lesions selective to the DG who has been found to show selective behavioral discrimination impairment on the MST, as well as a bias toward pattern completion (Baker et al., 2016).

3.5.3.1 Targets versus lures

When comparing amnesiac patient BL to healthy, age-matched MO controls, we replicated his lure discrimination difficulty for visual objects compared to age matched-controls (Baker et al., 2016). By analyzing his sensitivity to target items relative to foils, we also replicated the finding that patient BL's visual recognition memory is within normal limits of healthy controls. In other words, in our novel analyses, that of auditory lure mnemonic discrimination and sensitivity, we found that BL's poor (i.e., floor) performance at discriminating similar sounds was not significantly different than controls as measured by his LDI and *d'* (T,L) scores. Due to the variability in the MO group for identifying similar naturalistic sounds, BL's total absence of sensitivity did not register as significantly different than control results.

The inability to detect a mnemonic discrimination deficit with BL using the MAST could point to a potential limitation of this novel paradigm: the variability found within the age categories, particularly with the middle-older adults. These individuals had a SE of .04 for auditory LDI scores, which was twice as high as .02 recorded for the YA group. Less variability was found in the visual realm, where MST LDI scores had a SE of .02 for the MO individuals. Middle-aged adults are under-represented in associative recognition memory tasks (Nordin et al., 2017; Riphagen et al., 2020), so it is difficult for us to determine whether the variability in our sample was a typical result of this age group or an interaction between participants in the MO and the auditory stimuli used. Future testing that attempts to normalize a larger sample of naturalistic sounds with participants in the 40–66 age range would shed more light on this issue, particularly in light of individuals' idiosyncratic brain-behaviour mnemonic discrimination performance in midlife (Riphagen et al., 2020). Lessening the variability in the data would also help to determine whether a 0 score is actually indicative of impaired auditory lure sensitivity in a patient with a focal hippocampal lesion.

3.5.3.2 Targets versus foils

BL's results when comparing auditory target items relative to foils exposed additional deficits, which may also contribute to this lure discrimination deficits for sounds. His frank impairments in mnemonic discrimination, as measured by the traditional REC score, and his significantly worse performance in mnemonic sensitivity for targets versus foils as measured by *d'* (T,F) appear to implicate the DG as playing a crucial role in auditory recognition memory. Such a

finding would seem to indicate a dissociation between the DG's function for auditory versus visual recognition memory, as a similar deficit was not found for BL in response to visual recognition memory assessment using the MST.

Not all of these results are surprising. The dependency of auditory recognition memory on the hippocampus on has been established in a variety of patient studies, including at least one conducted with Henry Molaison (Milner, 1972). That patient was famous for having his hippocampus (and areas of his surrounding MTL) surgically removed. Squire and colleagues (Squire et al., 2001), in an investigation with amnesiac patients, also showed that lesions restricted to the hippocampus could severely impair auditory recognition memory for sounds. However, the authors note that these deficits are exacerbated in individuals with lesions, including the broader MTL. Squire et al. (citing Suzuki and Amaral, 1994) noted that one of the avenues for auditory (but not visual) inputs to the MTL is through projections to the anterior TH region of the parahippocampal cortex.

In nonhuman mammals, indirect projections have been found which connect the auditory cortex to the hippocampus via the parahippocampus (Cenquizca & Swanson, 2007; Insausti & Amaral, 2008). A recent study in humans and monkeys found a common effective connectivity signature directly from the auditory cortex directly to the ventrolateral prefrontal cortex and indirectly to the hippocampus via the parahippocampal gyrus (Rocchi et al., 2021). The established projections from the parahippocampal cortex to the lateral entorhinal cortex (van Strien et al., 2009; Witter et al., 2017) and from there to hippocampal subfields via the perforant path (Hainmueller & Bartos, 2020) may explain why a lesion to the DG may severely impact auditory recognition memory in humans, as it appears to have done in patient BL.

Other clues of DG sensitivity to auditory inputs are found in studies which have not directly set out to investigate memory. Recently, Kurioka and colleagues offered evidence that auditory deprivation in rodents severely impairs neurogenesis in the DG (Kurioka et al., 2021). A similar decrease in hippocampal neurogenesis was found in rats after loud noises that diminished the neural output of the cochlea (Manohar et al., 2020). These rats with "blast-induced hearing loss" also had difficulties remembering spatial information (Manohar et al., 2020). It appears through both these studies that a link exists between how acoustic inputs and the DG are interrelated, to the extent that neural plasticity in the hippocampus can be drastically affected when hearing is

impaired. As we learn more about the role hearing impairment plays in mild cognitive impairment and dementia, these and future studies will help pinpoint interventions that might defer such cognitive slowing. This study with patient BL helps lay the groundwork for future human studies on the involvement of the DG in this context.

Chapter 4 , Study 3

4 Mismatch negativity predicts pattern separation

4.1 Preface

We are so tuned to sensory changes in our environment that we can detect novelty within hundreds of milliseconds. To what extent does our capacity to automatically discriminate auditory stimuli influence our ability to differentiate highly similar inputs belonging to separate yet overlapping events into discrete episodes at encoding, a process known as pattern separation? In Study 3, I combine a behavioral paradigm with the brain's perceptual discrimination index, known as mismatch negativity (MMN), to determine if prediction error is a component enabling mnemonic discrimination.

In collaboration with Dr. R. Shayna Rosenbaum, Dr. Claude Alain, Deena Herman, and Jaime Cazes, I expand upon the question — posed in Study 2 — of whether mnemonic discrimination can be detected using auditory inputs. To make the investigation more process pure, my colleagues and I used auditory stimuli stripped of any semantic associations. In addition, we structured the experiment to offer insights into neural activity at encoding through the use of scalp-recorded EEG technology.

An exciting thing about Study 3 was that it provided a way to formalize the link between brain signals that detect perceptual differences (MMN) and memory mechanisms thought to orthogonalize similar inputs (pattern separation). Until now, these phenomena have been studied separately, even though they bear a striking resemblance. As with Study 2, the quest was to unite disparate literatures and reduce theoretical redundancies across fields. A candidate framework I offer is that of prediction error. Prediction errors, a constant in the MMN signal, are thought to shape perception, and it seemed conceivable to me that they also facilitate pattern separation.

Study 2, then, is a novel addition to the pattern separation field for three reasons. Firstly, it uses abstract auditory stimuli. Secondly, it tracks neuroelectric brain activity at encoding. Thirdly, it offers a unifying framework between mismatch detection and our ability to differentiate highly similar memories.

4.2 Introduction

It has been over 45 years since a Finnish research team discovered that our brain's ability to discriminate auditory stimuli could be indexed by the mismatch negativity (MMN) signature (Näätänen et al., 1978). It reveals itself in EEG experiments whenever an oddball event violates predictions established from preceding events (Picton et al., 2000). These auditory oddballs generate an MMN response peaking approximately 125–225 ms after the onset of the deviant stimulus (Garrido et al., 2009; Picton et al., 2000; Schröger, 1994). The MMN amplitude and latency vary as a function of the perceptual distance between standard and deviant sounds, as well as the irregularity of the deviant relative to the standard (Alain et al., 1998; Baldeweg et al., 2004; Picton et al., 2000). For decades, investigators have found the MMN to be a reliable change-detection, event-related potential (ERP) component (Näätänen, 2019). However, researchers have yet to establish a clear relationship between the MMN and subsequent long-term memory effects. The inability to draw such a conclusion sets the MMN apart from other "difference due to memory" (Dm) ERPs (Paller et al., 1987). These Dm ERPs have been found to index the successful encoding of long-term declarative memories in response to incidental learning tasks (Brady et al., 2019; Olofsson et al., 2008; Paller et al., 1987, 1988; West, 2011). Whether ERP old/new effects can also be correlated with the brain's ability to reduce interference among similar memories at encoding or retrieval (also known as pattern separation or mnemonic discrimination) is an ongoing yet unresolved research question (Anderson et al., 2017; Morcom, 2015).

MMN experiments with clinical populations provide some suggestion that the MMN response transcends its role as an index of perceptual discrimination and relates to higher-order cognitive processes, such as long-term memory (Alain et al., 1998; Baldeweg & Hirsch, 2015; Näätänen, 2019). The MMN might do so in neurotypical adults by interacting with the cognitive mechanisms involved in the domains of statistical learning (Saffran et al., 1996) and implicit learning (Reber, 1993). These overlapping theoretical approaches describe how humans incidentally learn by acting upon or adapting to consistent environmental stimuli (Perruchet & Pacton, 2006). Statistical and implicit learning, however, rely on humans attending to the to-be-learned stimuli in their environments, even if such attention is below the level of conscious awareness (Frensch & Runger, 2003; Perruchet & Pacton, 2006). We propose that the preattentive or preconscious (Näätänen et al., 2011) elements of MMN, particularly the

mechanisms of prediction error and predictive coding, are at the heart of the statistical inferences underlying statistical and implicit learning; further, we propose that these preattentive elements enable the neurobiological mechanisms of long-term memory, or personally experienced past events (Tulving, 1983), in particular pattern separation, a memory process by which similar or overlapping information is disambiguated into unique events at encoding (Rolls, 2016).

There are hints in the literature that the MMN might enable pattern separation or pattern completion (recollection of memories from partial cues; Rolls, 2016). Data from animal models suggest mismatch responses manifested within the auditory cortex are detected by the hippocampus (Ruusuvirta et al., 2013), an area essential for episodic memory (Rosenbaum et al., 2008; Vargha-Khadem et al., 1997), possibly within the DG or CA1/CA3 (Bein, Duncan, et al., 2020; Hindy et al., 2016). Additional links between the MMN and elements of episodic memory can be inferred from human studies. These show that a model of hierarchical inference may explain the neuronal mechanisms responsible for MMN generation (i.e., predictive coding and predictive error; Cacciaglia et al., 2019; Garrido et al., 2009). Indeed, a leading theory of the MMN response is that it involves the interplay of predictive coding, or top-down perceptual inferences, with prediction error, or neural responses following violations of expected inputs (Friston, 2003, 2005; Garrido et al., 2009), including in the hippocampus (Kok et al., 2017; Kok & Turk-Browne, 2018). Experiments used to investigate the MMN offer a non-attentive learning situation involving unique patterns of stimuli that vary in a systematic, quantifiable way.

In the current investigation, participants were presented with standard and deviant (i.e., oddball) sound patterns, and an associated MMN was computed. We hypothesized that the MMN strength would indicate a robust representation of the standard and deviant sound patterns in memory. Those acoustic representations were further investigated by correlating MMN amplitudes with the results from a surprise recognition memory test using previously heard old items (targets) and new sound patterns. The new patterns were similar to the old ones (lures) or markedly distinct from target items and lures (foils). In fMRI studies of pattern separation in the visual domain, activity in the DG/CA3 region has been associated with correction rejection rates of both lures and foils (Bakker et al., 2008a). Through investigating participants' sensitivity to abstract and highly similar sounds, we hoped to establish, for the first time, that prediction errors associated with preconscious auditory discrimination reflected in the MMN might enable conscious

recognition memory of target items relative to foil, as well as mnemonic discrimination of target items relative to lures.

4.3 Materials and Methods

4.3.1 Participants

To determine if the MMN relates to behavioral discrimination, 36 healthy adults (18–32 years, 19 female) took part in an experiment that included passive listening at study and a recognition task at test. Participants were recruited through the Undergraduate Research Participant Pool at York University and within the broader community. Participants were provided with credit towards their first-year psychology course or were paid $15 per hour. Informed consent was obtained in accordance with the ethics review boards at York University and Baycrest and conformed to the standards of the Canadian Tri-Council Research Ethics guidelines. We excluded six participants from the final data analysis for the following reasons: one fell asleep during EEG recording, two had pitch discrimination deficits, one was left-handed, one had a shorter interstimulus interval than other participants that could have affected performance, and one failed to understand test instructions. Data analysis, therefore, included 30 individuals (18 females) with an average age of 22 (*SD* = 4.4). This sample size is similar to previous investigations using a comparable age range (Gottselig et al., 2004; Hindy et al., 2016; Todd et al., 2014). All participants were right-handed, and none reported learning disabilities or neuropsychological disorders. Participants were screened for anxiety and depression symptoms using the Generalized Anxiety Disorder 7-item scale (GAD7) and the Patient Health Questionnaire Depression 8-item scale (PHQ8). Three participants reported a current diagnosis of a mood disorder, but only one of the three exceeded the severity threshold of 15 on both tests. Before ERP acquisition, we administered an audiogram; all participants had normal pure-tone thresholds of ≤ 25 decibels (dB) hearing level (HL) at each octave frequency from 250 to 8000 Hz in both ears.

4.3.2 Pre- and post-tests

4.3.2.1 Pre-test: mnemonic similarity task (MST)

To ascertain participant's behavioral discrimination abilities in a non-auditory domain, we evaluated participants using the MST (Stark et al., 2015). The MST was administered on a laptop

running Windows 7. Participants were randomly assigned one of two MST stimulus sets and then administered the task following an established protocol (Stark et al., 2013, 2015). See section 3.3.3.2 for a summary of this protocol. One participant was excluded from the final MST data analysis for failing to understand test instructions, resulting in a comparative sample size of n = 29 (18 female) for the MST.

4.3.2.2 Post-test: Same-different forced-choice discrimination task

We concluded our experiment with a discrimination task. We intended to ensure that the participants could discriminate the micropatterns from one another when they were presented back-to-back. During the task, two micropatterns were played in succession and participants were asked whether they were the same or different. Participants indicated their answers via an arrow key. Every micropattern was presented against itself and every other micropattern. There were 42 unique combinations of different micropatterns (as the different pairs could be presented in a different order). Trials were randomly presented twice, leading to 84 discrimination trials. One female participant was unable to complete this task; therefore, analysis was conducted on 29 participants.

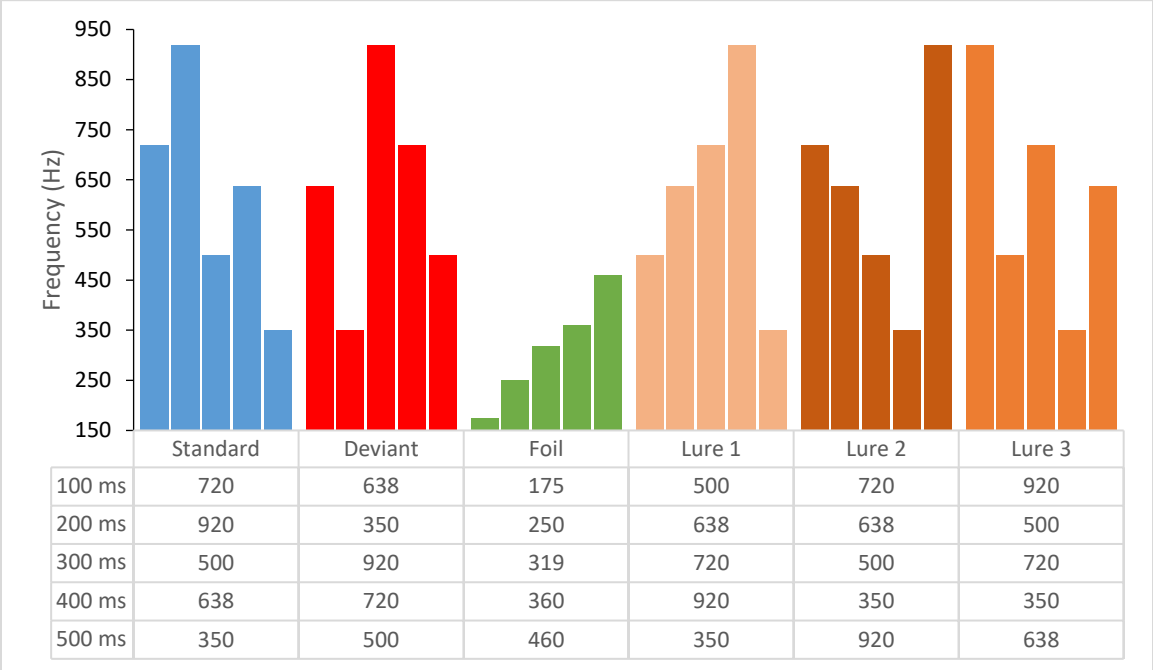
4.3.3 Experimental tasks

4.3.3.1 Stimuli

The stimuli used to generate the MMN were auditory micropatterns (Näätänen et al., 1993; Schröger, 1994; Schröger et al., 1992; Watson et al., 1975), constructed using a sequence of five, 100-ms tones. All micropatterns were generated using Audacity(R) 2.3.3. Six different auditory micropatterns were used in our study. Each consisted of a different temporal arrangement of 100-ms tones (Figure 4-2), with a 10-ms fade in and 10-ms fade out to prevent click sounds associated with abrupt frequency changes. The five tones had frequencies of 350 Hz, 500 Hz, 638 Hz, 720 Hz, and 920 Hz, similar in range to those used in previous auditory pattern studies (e.g., Leek & Watson, 1988; Schröger, 1994; Schröger et al., 1992; Watson et al., 1975).

We designed each of the micropatterns to be similar (in terms of mean frequency) and be discriminable (in terms of pitch contour). For example, the contour of the standard micropattern was M-shaped (i.e., up, down, up, down). In contrast, the temporal pattern of the deviant micropattern was more U-shaped (i.e., down, up, down, down). At test, we presented an

additional four micropatterns (three lures and a foil). The lures were assembled so as to be highly similar to the two micropatterns presented at study. Lure one and lure two switched contour direction once, and lure three switched contour twice. The easily distinguishable foil had a straight increasing contour from low to high. Its five tonal frequencies were pitched down 12 semitones making it sound low and distinct from the other micropatterns.



	Standard	Deviant	Foil	Lure 1	Lure 2	Lure 3
100 ms	720	638	175	500	720	920
200 ms	920	350	250	638	638	500
300 ms	500	920	319	720	500	720
400 ms	638	720	360	920	350	350
500 ms	350	500	460	350	920	638

Figure 4-1. Schematic Illustration of the 500-ms Micropatterns

4.3.3.2 Study phase: Passive auditory memory encoding

We divided the experiment into two phases. During the initial listening (study) phase, we presented one micropattern 70% of the time (700 trials). It was designated as the "standard." A second micropattern, delivered 30% of the time (300 trials), was the de facto "deviant." We played the micropatterns while participants watched 25 minutes of a muted movie (*Toy Story*) (Lasseter, 2005). Participants viewed the film from where they sat in a double-walled, sound-attenuating booth. We instructed participants to attend to the visually engaging movie. Our aim was to prevent attention-elicited ERP signals that might obscure the MMN. At the same time, participants were exposed to the auditory input of the standard and deviant micropattern trials. Each 500-ms trial was separated by a jittered (900 – 1150 ms) interstimulus interval (ISI).

4.3.4 EEG recording and analysis

We used EEG to record ERPs to determine if a MMN signal, elicited by deviation from preceding stimuli, predicted participants' ability to discriminate the micropatterns presented at study from the lures and foils presented at test. During the study phase, we recorded ERPs for each micropattern trial. The EEG was recorded from 76 scalp electrodes using a BioSemi Active Two acquisition system (BioSemi V.O.F., Amsterdam, Netherlands) with a bandpass of 0.16-100 Hz and a sampling rate of 512 Hz. Electrode positions were based on the International 10–20 system (Silverman, 1963). Horizontal and vertical eye positions were recorded by electrooculography using four electrodes positioned around each eye. Two additional electrodes were placed on the left and right mastoids. EEG recording was grounded by an active Common Mode Sense electrode and a passive Driven Right Leg electrode. EEG recordings were processed offline using Brain Electrical Source Analysis 7.0 software (BESA 7.0; MEGIS GmbH, Gräfelfing, Germany).

The EEG data were visually inspected to identify segments contaminated by imperfect readings. If noisy electrodes were detected, they were interpolated using values from surrounding ones (no more than eight interpolations per participant). The EEG was then re-referenced to the average of all electrodes and digitally filtered with 1 Hz high-pass filter (forward, 6dB/octave) and 40 Hz low-pass filter (zero phase, 24 dB/octave). For each participant, a set of ocular movements was identified from the continuous EEG recording and used to generate spatial components that best account for eye movements. The spatial topographies were then subtracted from the continuous EEG to correct for lateral and vertical eye movements as well as for eye blinks. After correcting for eye movements, the EEG was scanned for artifacts. The data were parsed into 500-ms epochs, including 100 ms of pre-stimulus activity. Those including deflections exceeding ± 60 μV were marked and excluded from further analysis. The remaining epochs were averaged according to electrode position and stimulus type. Each average was baseline-corrected with respect to a 200-ms pre-stimulus baseline interval. Approximately 5-10% of trials were rejected for each participant.

The ERP results from the time domain and the distributed source analysis (see below) were exported into BESA Statistics 2.0 for statistical analyses. This program identifies clusters in time, frequency, and space using a series of *t*-tests that compare the ERP amplitudes between

experimental conditions at every time point. This preliminary step identified clusters both in time (adjacent time points) and space (adjacent electrodes) where the ERPs differed between the conditions. The channel diameter was set at 4 cm, which led to approximately four neighbors per channel. We used a cluster alpha of .05 for cluster building. A Monte-Carlo resampling technique (Maris & Oostenveld, 2007) was then used to identify those clusters that had higher values than 95% of all clusters derived by random permutation of the data. The number of permutations was set at 1,000.

The cluster-based statistics revealed a significant difference between standard and deviant micropatterns, with the three strongest MMN signals approximately 250, 350 ms and 650 ms after onset of the first tone in the micropattern. Figure 2B shows the group mean ERPs elicited by the standard and deviant micropatterns and the corresponding difference wave. The standard and deviant amplitudes were calculated as a mean voltage averaged over an approximate 50-ms period on either side of the peak latencies in the individual participant waveforms collected from three fronto-central and three frontal electrodes (FCz, Fz, F1, F2, FC1, FC2), where the largest response was obtained. The MMN amplitude for each individual was calculated by subtracting the mean standard amplitude from the mean deviant amplitude across these electrodes during this 100-ms window. For the purpose of correlation analyses, we chose to focus on the second and strongest MMN signal, referred henceforth as the MMN.

4.3.5 ERP source analysis

BESA 7.0 was used to estimate distributed source activity for ERPs elicited by the standard and deviant trials. To enhance accuracy and reduce noise, we used distributed source analysis for each participant and each condition. We modelled the standard and deviant events and then compared the strength of the source activity. This was done using an iterative application of Low-Resolution Electromagnetic Tomography (LORETA), which reduces the source space in each iteration. The imaging approach, termed Classical LORETA Analysis Recursively Applied (CLARA), provides more focal localizations of the brain activity and can separate sources located in close vicinity. The voxel size in Talairach space was 7 mm; this default setting is appropriate for the distributed images in most situations. The regularization parameters that account for the noise in the data were set with a single value decomposition cutoff at 0.01%. We used a four-shell ellipsoidal head model with head radius of 85 mm, and thickness for scalp,

bone and cerebrospinal fluid of 6, 7, 1 mm, respectively. The relative conductivities were 0.33, 0.33, 0.0042, and 1 for brain, scalp, bone and cerebrospinal fluid, respectively.

4.3.6 Test phase: Recognition Memory Test

During the test phase, participants were presented with the standard and deviant (target) micropatterns from the passive listening phase, randomly intermixed with four unstudied (new) micropatterns. As was noted in section 2.4.1, three of the new micropatterns were similar to the standard and deviant and were designated as lures, while a fourth — more distinct in pitch and temporal arrangement — was deemed to be the foil.

The test phase assessed the recognition memory of the participants for the micropatterns. Participants were presented with a micropattern and asked, “Did you hear this tone during the movie?” Participants were then instructed to respond “Yes” by pressing the left arrow key, or “No” by pressing the right arrow key. The six micropatterns (two old, three lures, and one foil) were presented ten times each throughout the test phase, for a total of 60 trials, in randomized order, with a 500-ms interval between stimulus presentation and instruction screens. The correct response to hearing the standard or deviant micropatterns was the left arrow key. The correct response to the three lure micropatterns and the foil micropattern was the right arrow key.

4.4 Analysis

Analysis of the recognition and discrimination data were done using IBM SPSS Statistics 27, except *A* scores, which were calculated using a Microsoft Excel spreadsheet (Mueller, n.d.). The relationship between *d’* sensitivity and MMN1 amplitudes was conducted using bivariate Pearson correlations. (Negative correlations being indicative of a positive relationship between *d’* and the MMN values.) Where appropriate, effect sizes for all analyses have been reported and interpreted according to accepted guidelines (Field, 2013). Confidence intervals for correlations were computed, including using the bias-corrected accelerated (BCa) option in SPSS. Other analysis measures for the experimental tasks are described below.

4.4.1 Proportional responses: Loglinear method

Participant performance in all conditions was corrected through the application of the loglinear rule (Hautus, 1995). This method converts response frequencies by adding 0.5 to each frequency

and dividing by *N*+1 (where *N* is the number of trials in each condition). This method was developed to respond to extreme values (i.e., hit rate = 1; false alarm = 0) in experiments that use techniques derived from signal detection theory (SDT). Although its primary purpose in SDT is to mitigate infinite *d'* values (Hautus, 1995; Macmillan & Creelman, 2005; Snodgrass & Corwin, 1988; Stanislaw & Todorov, 1999), the loglinear approach is recommended even when SDT measures are not calculated (Snodgrass & Corwin, 1988). Hence, we have applied the above transformation to the proportion of correct responses (i.e., hit rates and correct rejections) and the proportion of incorrect responses (i.e., misses and false alarms) during recognition memory analyses. Response time analysis and MST scores were not corrected in this manner.

4.4.2 Sensitivity indexes

The two response choice ("yes"/"no") recognition memory component of our study allows for the calculation of SDT sensitivity indexes (*d'* and alternatives) based on single hit and false-alarm rates per condition (Green & Swets, 1966; Macmillan & Creelman, 2005; Stanislaw & Todorov, 1999). We calculated the statistic *d'* in SPSS as the normalized difference between the hit rate (*H*) versus the false-alarm rate (*F*). Values of *d'* can range from 0 (no sensitivity) to approximately 4.65 (perfect sensitivity). We supplemented our *d'* investigation with an analysis using the SDT measure, *A* (Zhang & Mueller, 2005). *A*, which is equivalent to the average areas of minimum and maximum receiver operating characteristic (ROC) curves through a point, does not assume equal variances across conditions (Zhang & Mueller, 2005). For this area-based measure of sensitivity, perfect performance is indicated with a score of 1.0 and random or undistinguishable performance by a score of 0.5 (Zhang & Mueller, 2005). Promoters of *d'* variants, such as *A'* (Grier, 1971; Pollack & Norman, 1964), have been criticized for creating the mistaken impression that these variants are non-parametric (MacMillan & Creelman, 1996; R. Pastore et al., 2003). Nonetheless, these variants have been applied in recognition memory experiments, including studies of visual pattern separation as a more rigorous complement to *d'* (e.g., Stark et al., 2015). Such measures of sensitivity are also recognized as a viable alternative when the memory strength distributions of lures and targets cannot be assumed to be Gaussian in form and/or where there are ceiling or floor effects evident in the data (Mickes et al., 2007; Zhang & Mueller, 2005).

4.5 Results

4.5.1 EEG results and source analysis

We anticipated and found that the presentation of the unexpected deviant — calculated as the difference between the standard and deviant waveforms (Näätänen, 2019) — elicited a negative deflection in the ERP waveform. We found the MMN was concentrated in six frontocentral electrodes with three peaks, approximately 250, 350 ms and 600 ms after onset of the first tone in the deviant micropattern. Schröger (2007) suggested that the auditory environment is parsed into 300 ms units, which might explain the finding of two strong MMN signals at the 350 and 650 ms mark. Since earlier segments of higher intensity sound sequences are thought to be more salient in memory and sensory sound discrimination (Shestakova et al., 2003), we focused analyses on the strongest, and second earliest, of the three peaks, at the 350 ms point, as it was expected to be more predictive of behavioral performance than the other two peak signals.

Using an iterative application of low-resolution electromagnetic tomography (BESA v7.0), we found that standard and deviant sounds were associated with source activity in the auditory cortex of the superior temporal gyrus. The contrast in activity between the standard and deviant, however, revealed greater source activity for the deviant in the superior temporal gyrus and the MTL (See Figure 4-2).

4.5.2 Recognition rates and discrimination

4.5.2.1 Collapsing treatment levels

Before investigating participants' mnemonic sensitivity levels, we investigated the appropriateness of combining levels of old items (targets) and similar items (lures) into binned conditions. Our primary criterion guiding this decision was the similarity of accuracy rates (hits or correct rejections). We began with an examination of the old stimuli. A review of the boxplots and of the probability-probability (P-P) plots (Field, 2013) of the standard hit rates (M = .91, SE = .01) and deviant hit rates (M = .85, SE = .02) indicated that both distributions deviated from normality.

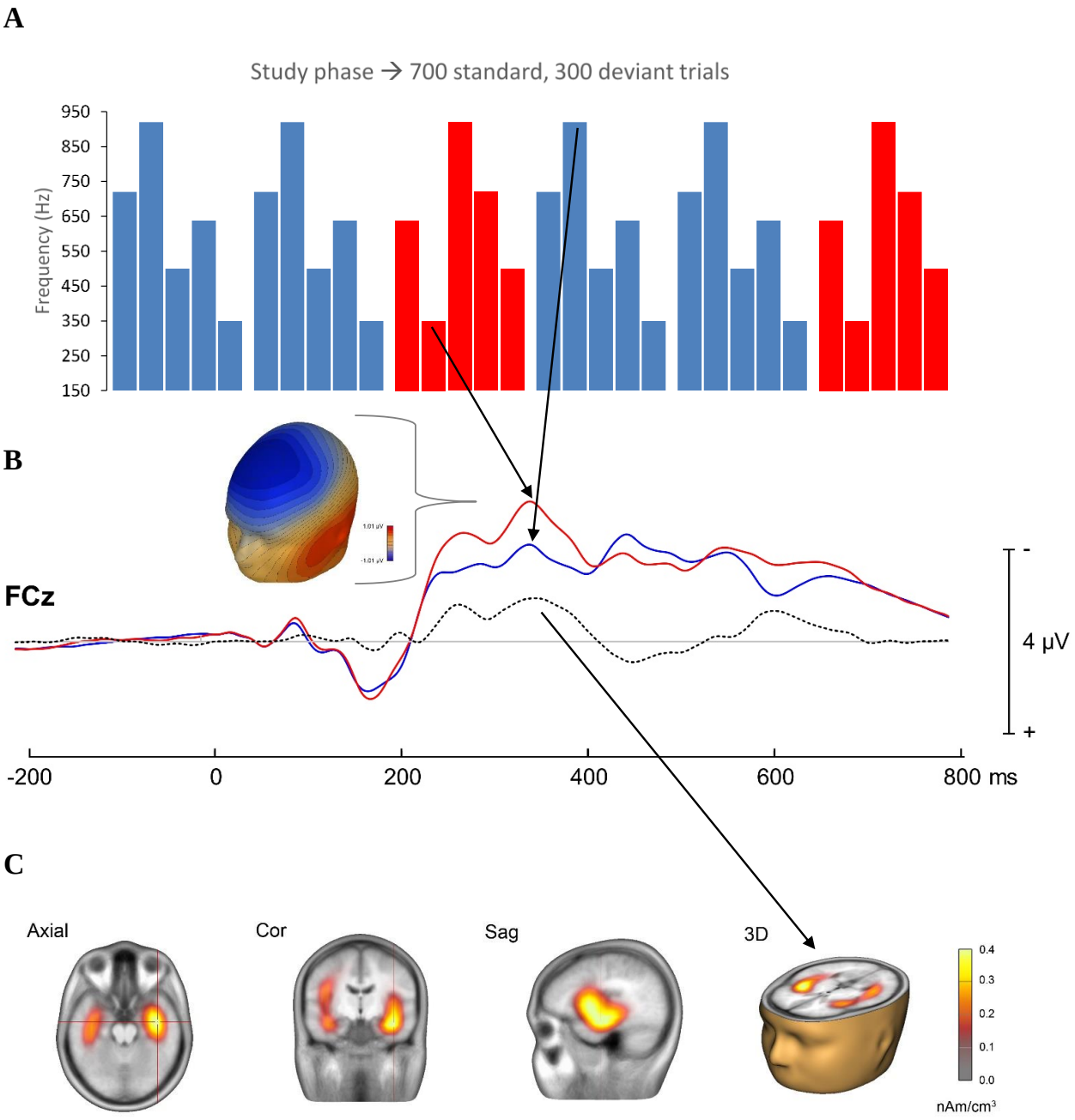


Figure 4-2. Micropatterns at study

Notes: (A) Schematic illustration of the 500-ms standard and deviant micropatterns. (B) Grand average frontal-central pole (FCz) ERPs in response to the standard (blue line) and the deviant (red line) micropatterns. Black arrows indicate the 200 ms tone; detection of the mismatch here is responsible for the MMN1 amplitude spike at approximately 350 ms, 150 ms after the onset of the mismatch with the deviant micropattern. The dotted black line indicates the MMN waveform. (C) Four views of the CLARA source analysis of the difference in activity between deviant and standard conditions (300-400 ms latency). Red and yellow shading represents areas where deviant micropattern activity is significantly greater ($p<.001$) than standard micropattern activity.

The apparent cause was the pile-up of high scores. Consistent with this supposition, we found the standard hit rates were negatively skewed (p <.001); deviants also exhibited a concentration of high scores, although to a lesser degree (p = .043). To determine whether there was a significant difference between hit rates for these old items, the non-parametric sign test — which makes few assumptions about normality (Howell, 2010) — was used to detect if deviant micropatterns had lower accuracy rates than standard ones. The measure failed to show any difference between the standard and deviant hit rates, z = –1.835, exact binomial p (2-tailed) = .064. Consequently, we derived one treatment level for old items by combining the standard and deviant scores into one target condition. We failed to find significant evidence of skewness (p = .103) in the hit rates for the resulting target condition (M = .88, SE = .01). See Figure 4-3.

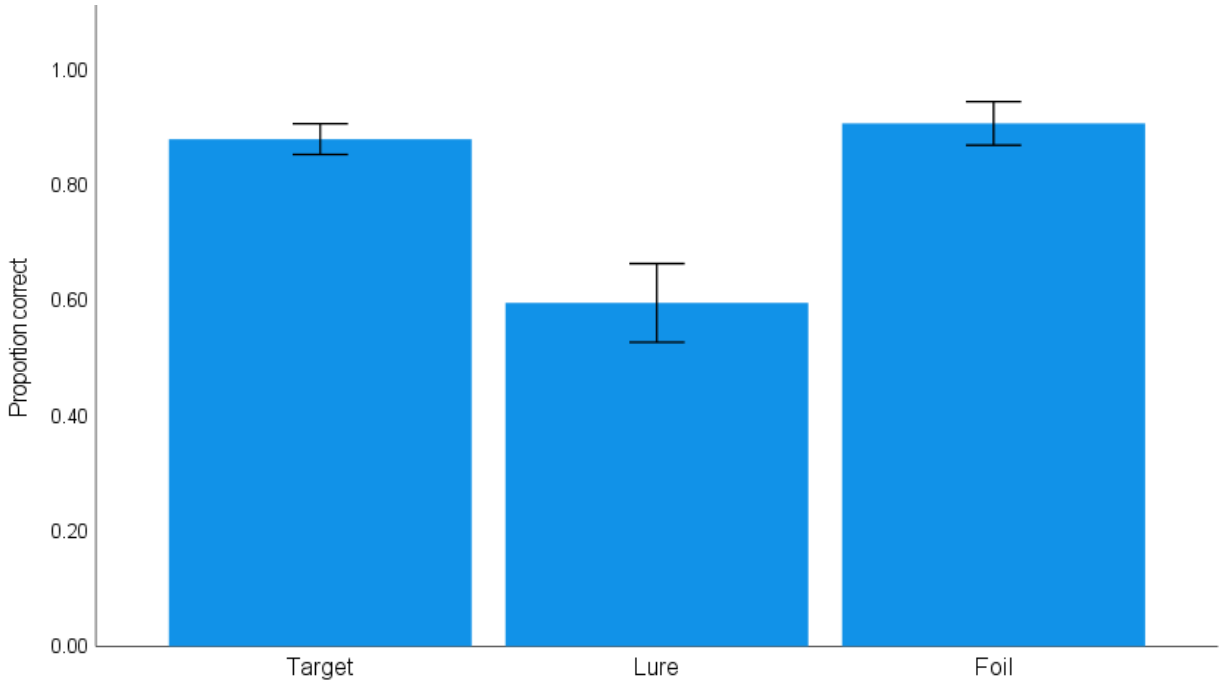


Figure 4-3. Recognition memory accuracy (proportion correct)

Regarding lures, a review of the boxplots and P-P plots of correct rejections for lure 1 (M = .57, SE = .05) and lure 3 (M = .54, SE = .04), suggested that accuracy rates for these two treatment levels were normally distributed. Greater hit rate variability was found in Lure 2 (M = .68, SE = .06). It likewise showed evidence of non-normality and negative skew (p = .035). However, the nonparametric sign test did not indicate that the difference between lure 2 and lure 1 correct rejections, z = 1.20, was significantly different, exact binomial p (2-tailed) = .230. Furthermore,

the difference between lure 2 and lure 3, $z = 1.70$, was not significantly different, binomial p (2-tailed) = .09. Therefore, we combined all three lure levels into one derived lure condition. We failed to find significant evidence of non-normality or skewness ($p = .966$) in the hit rates for the resulting lure condition ($M = .60$; $SE = .03$).

As expected, foils were found to have a high correct rejection rates ($M = .91$, $SE = .02$). The concentration of high foil values resulted in a negatively skewed distribution ($p < .001$).

4.5.2.2 Reaction times

We analyze reaction times (RTs) in order to help determine participants' sensitivity to the acoustic difference between sounds (Aaltonen et al., 1987; Barascud et al., 2016; Savela et al., 2003; Winkler et al., 1999). The consensus among researchers is that the greater difference between the sound or sound patterns, the shorter latency time to respond to a behavioral task during an MMN study (Savela et al., 2003). In studies of visual pattern separation, longer RTs are associated with lure correct rejections relative to target hits (Kirwan & Stark, 2007). It has been speculated that the additional time involved in correctly discriminating lures (but not foils) is related to a "recall-to-reject" strategy (S. Clark & Gronlund, 1996; Kirwan & Stark, 2007; Norman & O'Reilly, 2003; Rotello & Heit, 1999). Central to this process is the act of recalling an encoded memory trace as a comparator for similar items. This process takes more time than correctly rejecting highly dissimilar foils. Neuroimaging studies have found the DG/CA3 region of the hippocampus to be active during such correct rejection of similar lures (Bakker et al. 2008).

With the goal of ascertaining whether there were any variations in RTs of targets ($M = 655.14$, $SE = 56.71$), lures ($M = 916.74$, $SE = 83.70$) and foils ($M = 589.85$, $SE = 44.02$), we entered average participant RTs (in ms) for hits and correct rejections into a 1X3 ANOVA. The differences in RT among the three conditions was significant, $F(2, 58) = 11.61$, $p < .001$, $\eta_p^2 = .29$, (Figure 4-4). Post hoc tests using the Bonferroni correction revealed that the mean difference between the RTs for targets and lures, –288.32, 95% CI [–496.86 –79.78], was significant ($p = .004$). In addition, the mean difference between the RTs for foils and lures, –353.35, 95% CI [–580.18, –126.53], was significant ($p = .001$). We failed to find evidence, however, that the mean RT difference between targets and foils, 65.03, 95% CI [–86.95 217.02], was significant ($p = .858$). The results suggest the lures (but not the targets they resembled) were processed in a

slower, more deliberate way, possibly due to the additional time required to detect subtle differences between the sounds in a recall-to-reject strategy. We ran a paired-samples *t*-test to help determine whether correct rejections for lures, which might involve additional processing time (Morcom, 2015), led to even slower RTs. (Before running the test, we excluded one participant who did not have any lure false alarms.) On average, participants responded more slowly to lure micropatterns they incorrectly perceived as target ones (M = 1088.89, SE = 122.12) compared to lure micropatterns they correctly recognized as new ones (M = 923.33, SE = 101.67). We failed to find evidence, however, that this fraction of a second difference, 165.55 ms, BCa 95% CI [–43.28, 396.16] was significant, $t(28) = 1.37$, $p = .180$, $d = .26$. See Figure 4-4.

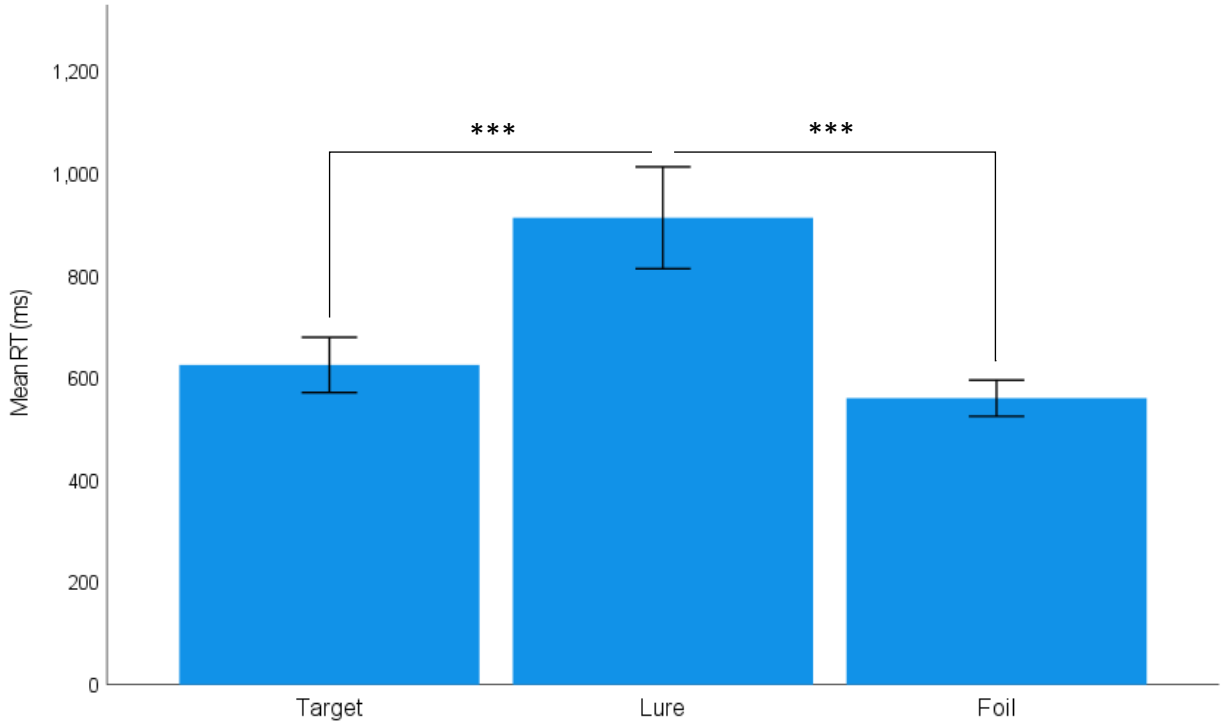


Figure 4-4. Reaction times for hits and correct rejections by condition

4.5.2.3 Recognition memory discrimination — signal detection results

In order to compare recognition memory performance of passively studied old micropatterns versus unstudied lures and foils we incorporated methods from SDT described in section 2.5.2. Our dependent variables were two indexes of SDT sensitivity to the pattern of yes (old) and no (new) responses: *d'* and *A*. The independent variables were target micropatterns (T) versus lure

micropatterns (L) or target items versus foil micropatterns (F). Using paired-samples *t*-tests, we found participants showed higher sensitivity to the old/new difference when recognizing target micropatterns relative to the foil, *d'* (T,F), *M* = 2.70, *SE* = .11, than they were at identifying target micropatterns relative to the lures, *d'* (T,L), *M* = 1.53, *SE* = .11. This difference, 1.17, (BCa) 95% CI [.95, 1.37], was significant $t(29) = 10.58$, $p < .001$, and represented a large-sized effect, $d = 1.93$. Using the *A* measure of detection sensitivity (Zhang & Mueller, 2005), we again found that participants had greater sensitivity in recognizing the target micropatterns relative to the foils, *A* (T,F), *M* = .93, *SE* = .01, than they were at identifying target micropatterns relative to the lures *A* (T,L), *M* = .82, *SE* = .01. This difference, .11, (BCa) 95% CI [.09, .14], was significant $t(29) = 8.81$, $p < .001$, $d = 1.61$.

4.5.2.4 Recognition memory discrimination — correlation with MMN signal

To disentangle the MMN representation and its relationship with recognition memory discrimination, we correlated the MMN peak amplitudes with *d'* and *A* scores. We found the MMN was significantly related to lure discrimination, *d'* (T,L), $r = –.54$, 95% BCa CI [–.78, –.19], $p = .002$, and to foil discrimination, *d'* (O,F), $r = –.37$, 95% BCa CI [–.58, –.08], $p = .047$. Using the purportedly more rigorous measure of *A*, we found the MMN was again significantly related to lure discrimination, *A'* (T,L), $r = –.48$, 95% BCa CI [–.76, –.17], $p = .008$ (Figure 4-5). We failed to find evidence, however, that the MMN correlated with foil discrimination, *A* (T,F), $r = –.28$, 95% BCa CI [–.49, –.06], $p = .135$. This primary finding that the MMN and *d'* (T,L) and *A* (T,L) are correlated is consistent with our prediction that strong mnemonic representation is formed from the MMN and that it may predict recognition memory specificity.

4.5.3 Pre- and post-tests

4.5.3.1 MST

In this test of visual object behavioral pattern separation, participants were able to identify 79.70% (*SE* = 2.37%) of the targets as old, 50.04% (*SE* = 3.14%) of the lures as similar, and 80.55% (*SE* = 2.41%) of the foils as new. These results are comparable to the target/lure/foil accuracy rates of 81.2%/47.6%/82.0%, found in a group of 26 healthy adults (16 females), 20–39 years of age, tested by Stark et al. (2013). Performance on the MST was further evaluated through the Lure Discrimination Index (LDI) score (Stark et al., 2015). The LDI is calculated by subtracting the percentage of incorrect similar responses to foil trials from the percentage of

correct similar responses for lure trials. Consequently, the LDI represents the percent of lure trials correctly identified, while accounting for false alarm responses. The average LDI score was 35.25% (*SE* = 3.04%), compared to approximately 36.0% for the younger adult group tested by Stark and colleagues (2013; the LDI is referred to as the BPS in this paper). Performance on the MST was also evaluated through traditional recognition memory performance (REC) by calculating the difference between the proportion of targets endorsed as "old' less the proportion of foils named as "old". The average REC score was 75.04% (*SE* = 2.67%), compared to approximately 78.6% for the younger adult group tested by Stark and colleagues (2013).

4.5.3.2 Same-different forced-choice discrimination task

Participants showed high discrimination rates (*M* = 96.63%, *SE* = 0.86%) averaged across the 21 pairs in this post-test, with slightly higher overall rates for discriminating same stimuli as "same" (*M* = 97.70%, *SE* = 0.57%) versus discriminating different stimuli as "different" (*M* = 96.21%, *SE* = 1.18%).

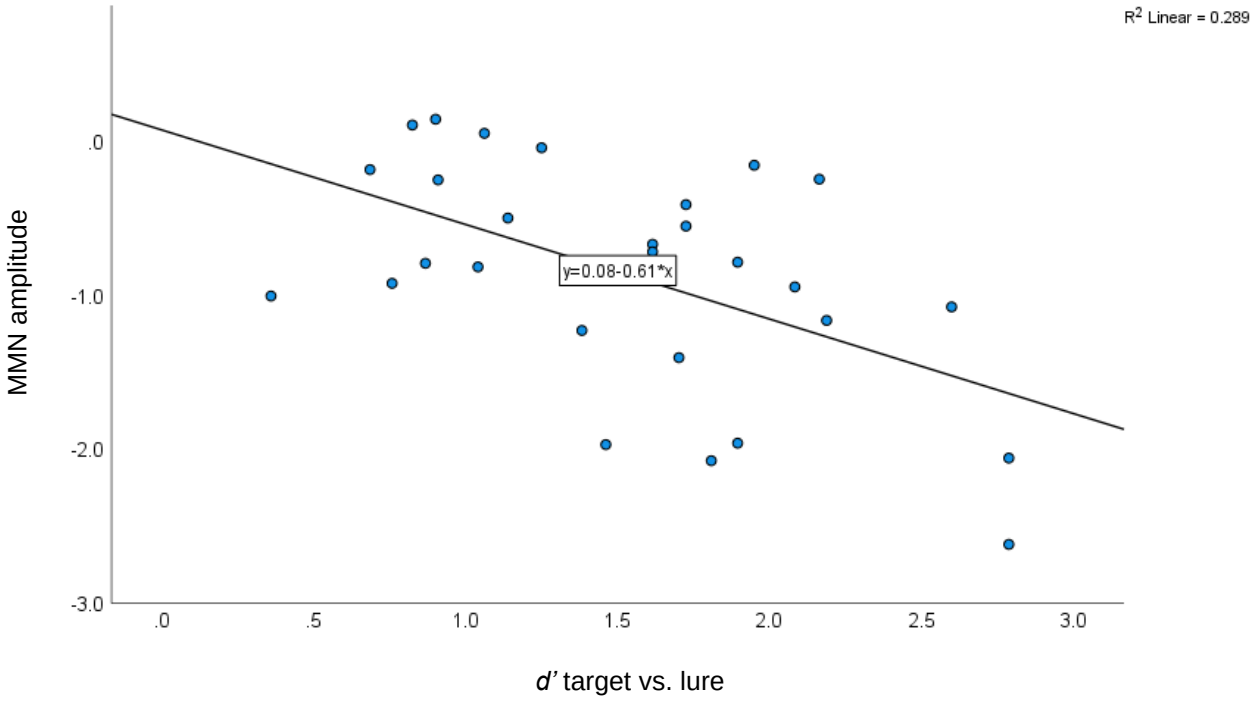


Figure 4-5. Scatterplot of MMN correlation with *d'* (T,L)

4.6 Discussion

We set out to investigate whether the strength of the MMN at encoding correlates with recognition memory performance. We show that the strength of the auditory MMN predicts subsequent memory in healthy young adults, a novel finding. We do so by demonstrating a significant correlation between MMN amplitudes and mnemonic discrimination of acoustic information in recognition memory. This result indicates that the MMN reflects participants' ability to encode a lasting representation of the standard versus deviant; this representation has a monotonic relationship with the ability to subsequently differentiate old items from unstudied tonal patterns, even those which are highly similar but unstudied. Such a finding advances our understanding of the preattentive MMN signal by connecting it with conscious cognitive abilities. We also promote new avenues of research possibilities for ERP studies of learning and memory encoding by grounding our results in developing theories of predictive error within the hippocampus.

Previous studies have interpreted the MMN difference wave as an index of discrimination and change detection, localized in the frontal and auditory cortices (Näätänen, 2019). However, evidence is lacking for the significance of the amplitude of the MMN in predicting hippocampally mediated episodic memory discrimination in neurotypical humans. Indeed, most studies that have found a link between the MMN and higher-order cognitive abilities are those that focused on clinical populations, particularly people with schizophrenia or bipolar disorder (Alain et al., 1998; Baldeweg & Hirsch, 2015) or older adults with neurodegenerative conditions (e.g., Laptinskaya et al., 2018). A theory derived from some of these experiments is that the MMN is sensitive to a deficient N-methyl-D-aspartate (NMDA) receptor function in cortical areas of the brain. MMN investigators speculate that this NMDA deficit impairs synaptic plasticity and prevents memory encoding and higher-order cognition in the clinical conditions studied and in age-related neurological conditions such as Alzheimer's disease (Baldeweg & Hirsch, 2015; Näätänen et al., 2012; Näätänen, Kujala, Kreegipuu, et al., 2011; Stephan et al., 2006).

Evidence from a transgenic mouse model has shown that NMDA receptors in the granule cells of the hippocampal DG are likewise crucial to pattern separation of visual inputs (McHugh et al., 2007). There is further evidence that the MMN signal in rats is elicited in both the auditory

cortex and the DG, subiculum, and CA1 cellular layers (Ruusuvirta et al., 2013). In humans, these hippocampal subfields play essential roles in pattern separation/pattern completion of visual objects (Baker et al., 2016; Bakker et al., 2008b; Rolls, 2016). Based on our observations, these MTL areas might also be sensitive to discriminating acoustic information in response to the MMN signal in humans. Our findings indicate that individual differences in the increase of MMN amplitude in response to standard vs. deviant micropatterns correlate with performance variability in behavioral pattern separation. An MMN-NMDA-DG link could facilitate this mnemonic discrimination of abstract auditory stimuli. Such a link would provide the rationale for our finding that the MMN predicts higher order cognition in a neurotypical population, as has been previously found in neuroatypical groups (Baldeweg & Hirsch, 2015).

Our electrophysiological results — and source strength activity in the auditory cortex and MTLs — then, may reflect deviance or mismatch detection registered by the hippocampus at encoding. This inference is supported by ERP findings of hippocampal sensitivity to oddball verbal events (Vila-Ballo et al., 2017). The CA1 of the hippocampus receives input from the DG via the CA3 (Rolls, 2016). It also back projects onto the neocortex to activate modality-specific cortical areas involved in episodic memory (Hindy et al., 2016; Rolls, 2016). Thus, the auditory cortical source of the MMN might represent the back projections from the CA1 to the auditory cortex in service of the representation of the deviant in memory (Parras et al., 2017; Vila-Ballo et al., 2017), in the same way abstract visual information is hypothesized to interact with the visual cortex (Hindy et al., 2016).

A complementary, yet novel explanation for the relationship between the MMN and mnemonic discrimination is in the context of prediction coding (Friston, 2003, 2005; Garrido et al., 2009; Hohwy, 2013). Within this framework, the MMN is conceptualized as a detectable signal when the brain's predictive coding mechanism fails to predict anomalous, bottom-up input, resulting in prediction errors (Friston, 2003, 2005; Garrido et al., 2009). A growing body of research has found that prediction errors influence episodic memory (Sinclair & Barense, 2018). Importantly, prediction error minimization has been theorized to facilitate difference-based coding rather than stimulus-based coding (Northoff, 2013), possibly by biasing hippocampal subfields to certain receptive states (Bein, Duncan, et al., 2020). In addition, the integration of predictive coding into neurobiological models of the MMN depends on NMDA-dependent plasticity to modulate synaptic weights in response to prediction errors (Wacongne et al., 2012).

In our paradigm, the bottom-up input sustaining predictive coding would be the regularly occurring standard micropattern. As participants sat in a soundproof booth, watching a movie and passively being exposed to the repetitive standard, they became attuned to the acoustic regularity within their environment. When the deviant micropattern violated these regularities, prediction errors occurred and were registered by the MMN. Our analysis suggests that the magnitude of this MMN predicts mnemonic discrimination. We speculate but cannot verify that the neural responses following the deviant — or prediction error minimization (Friston, 2003, 2005, 2010) — are responsible for this recognition memory performance. Support for this thought may be found in vision science. Here, prediction errors in response to violations of perceptual expectations have been found to bias hippocampal CA3 and CA1 subfields (Bein, Duncan, et al., 2020). These biases lead to "states," whereby the hippocampus is more conducive to pattern separation or pattern completion (Bein, Duncan, et al., 2020). In our study, the deviant auditory input's predictive errors would similarly bias hippocampal subfields towards sparse encoding (Bein et al., 2020; Kok & Turk-Browne, 2018). These specific representations which would facilitate more precise discrimination in high-interference memory situations (i.e., pattern separation), along with other, less demanding memory judgments.

As for these less demanding memory judgments — the sensitivity to foils relative to targets — our evidence of a significant effect using a *d'* measure was not corroborated with a non-parametric measure of sensitivity. The inability to detect an effect using both tests may be attributable to overall high accuracy rates for foils. These rates make that condition insensitive to a potential correlation with MMN amplitudes. Alternatively, it could be that the pitched-down foil was so distinctive that it did not rely on a recall-to-reject post-retrieval process, which is more demanding of the memory trace detected by the MMN. This assumption is reinforced by the RTs for the foils, which were significantly faster than the lures, and not found to be significantly different than target RTs.

Overall, our findings of a significant relationship between the MMN amplitude for pre-experimentally unknown, incidentally encoded auditory stimuli and mnemonic discrimination of micropatterns lends credence to our position that the MMN could be a direct measure of acoustic pattern separation at encoding. This mechanism helps discriminate between highly similar lures vs. targets and possibly less similar foils vs. targets. To our knowledge, this is the first study to examine the nature of pattern separation with novel auditory stimuli and to describe the MMN as

a neural signature of recognition memory discriminability. This link is significant, as much of our knowledge of mnemonic discrimination in human recognition memory comes from studies that use semantically recognizable visual stimuli (Liu et al., 2015). For example, the MST evaluates performance using pictures of everyday objects (e.g., picnic basket, fishbowl, saxophone). Despite the reliability and ubiquity of studies on mnemonic discrimination of visual stimuli using the MST, it is unclear if this process generalizes to other modalities (Liu et al., 2015). Evidence of a significant correlation between the MMN and mnemonic discrimination, *d'* (T,L), illustrates that mnemonic discrimination is not a modality-specific ability, dependent on conceptual processing conferred by semantic stimuli. Instead, the enhanced encoding reflected in the MMN waveform is resilient to interference from highly similar inputs and facilitates behavioral pattern separation of incidentally learned, pre-experimentally novel, auditory information. This finding substantiates our paradigm as a test of behavioral pattern separation for abstract auditory objects, with potentially similar reliability as the MST for visual objects. A leading view is that the MMN is an overall barometer of neuronal dynamics and brain plasticity (Garrido et al., 2009; Näätänen, 2019). Our study suggests that such perceptual and mnemonic malleability is a manifestation of pattern separation, prediction error, and match-mismatch detection — all different iterations of similar neurophysiological, hippocampally dependent processes.

Chapter 5

5 General discussion

5.1 Summary

In this dissertation, I set out to investigate the multimodal nature and limits of pattern separation and whether they are dependent on processing within the hippocampus as theorized by classical theories of pattern separation/pattern completion (O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011). By combining different research techniques, I hypothesized that I could better investigate the purported functions and neural correlates of pattern separation. To do so, it was necessary to address three primary research questions during the conceptualization of the three studies described here. The first two relate to whether presumed deficits in pattern separation/pattern completion — following hippocampal lesions or through age-related hippocampal deterioration — can:

1. Interact with perception as they do with memory (Aim 1); and,
2. Extend to modalities other than vision, notably audition (Aim 2).

The last research question pursued the question of whether pattern separation, as evidenced by lure discrimination:

3. Can be detected using abstract stimuli (Aim 3).

This section will elaborate on the studies' main findings and discuss how they provide insight into the aims above. I will further expand on some of the key points discussed in the dissertation, including what BL's performance reveals about the necessity of the DG in pattern separation and perception. Finally, I will discuss how these results integrate with two theories of hippocampal involvement in pattern separation throughout the hippocampus and in connection with the neocortex. Finally, I outline some of the clinical implications of these findings and future research to address outstanding issues.

5.1.1 Deficits in pattern separation affect perception as well as memory

In Study 1, I showed how hippocampal involvement in categorical perception of faces might depend on mnemonic and perceptual discrimination. I tested BL, an individual with selective bilateral DG lesions, and age-matched controls. Participants were administered morphed images of famous and nonfamous faces in a standard categorical perception (CP) identification and discrimination experiment (Studdert-Kennedy et al., 1970). All participants exhibited nonlinear identification of famous faces with a midpoint category boundary. However, controls identified newly learned nonfamous faces with lesser fidelity, while BL showed an unusual shift in his category boundary.

The complementary learning systems (CLS; McClelland et al., 1995) theory conceives the hippocampus as being agnostic to the modality of information processed when encoding similar memories (Huffman & Stark, 2014; Hunsaker & Kesner, 2013; Larocque et al., 2013). Yet, the first human neuroimaging study of pattern separation (Kirwan & Stark, 2007) found slightly different activation patterns within the hippocampus for faces relative to objects. Indeed, activation patterns associated with faces were more diffuse, leading to later conjecture that the orthogonalization of faces happens upstream of the hippocampus, likely in the fusiform face area (Kirwan et al., 2012).

Faces have also been associated with different behavioral response profiles when contrasted with objects in pattern separation tests (Kirwan et al., 2012; Kirwan & Stark, 2007). For example, healthy controls were significantly more likely to respond “similar” to face foils than to object foils, even if their overall lure discrimination was intact (Kirwan et al., 2012). These differences, however, did not lead to significant overall category differences in lure discrimination in controls (Kirwan et al., 2012; Kirwan & Stark, 2007), although patients with hippocampal damage exhibit predicted lure discrimination deficits for both faces and objects (Kirwan et al., 2012).

Huffman and Stark conducted more intentional testing of CLS using objects and faces to investigate differences in the degree of pattern separation in the hippocampus and the “summed similarity” in the broader MTL (Huffman & Stark, 2014). Their experiment had the advantage of high-resolution fMRI and multivariate pattern analysis. Results revealed significant differences in classification accuracy (i.e., generalization of similar stimuli) for faces versus objects/scenes in the parahippocampal and perirhinal cortices (Huffman & Stark, 2014). Similar category

discrimination was not detected in the hippocampus, although activity in that region did distinguish between images of all types and a non-mnemonic baseline (Huffman & Stark, 2014). More recently, high-resolution fMRI suggests that prior knowledge mediates the role of the hippocampus — in conjunction with cortical face processing areas — in differentiating highly confusable faces (Bein, Reggev, et al., 2020).

A pillar of the CLS theory, reinforced by Huffman and Stark (2014), is that the neocortex, including extra-hippocampal areas in the MTL (e.g., the perirhinal cortex), are responsible for categorizing or summing similar information (Huffman & Stark, 2014). This supposition is relevant to Study 1. In the first part of the CP experiment, we found that prior knowledge helped participants categorize faces. Both controls and BL, who has a focal hippocampal lesion but an intact perirhinal cortex, identified famous faces with an expected 50% category boundary between face morphs. BL and controls, however, were less competent at categorizing nonfamous faces.

We found the most remarkable performance divergence between BL and controls in the discrimination of faces. In theory, discrimination should place fewer demands on memory, as participants looked at two faces side-by-side and only had to respond whether they were the same or different. Yet, we found that BL could not improve beyond his categorization accuracy to discriminate faces as distinct. If the faces were of the same category, he was likely to identify them as similar. On the other hand, controls, who presumably relied on their ability to pattern separate faces and combined these with higher-order cortical representations, could make these perceptual distinctions. These results suggest that hippocampally mediated pattern separation is necessary for perceptual discrimination beyond the limits of categorization or prior conceptual knowledge about faces.

Study 1 thus provides an essential missing link in understanding the perceptual and mnemonic processes involved in face processing by the DG. Traditionally considered a declarative memory structure, our findings show that the hippocampus may also contribute to visual perception.

5.1.2 Evidence exists for pattern separation in the auditory modality

In Study 2, we compared the performance of neurotypical younger, middle-older, and older adults and patient BL on an original recognition memory paradigm using auditory stimuli. As

was noted previously, CLS theorists conceive of the hippocampus as being agnostic to the modality of information processed when encoding similar memories (Hunsaker and Kesner, 2013; Huffman and Stark, 2014; LaRocque et al., 2013). However, visual items are most often used in behavioral tests of pattern separation tasks, such as the commonly used MST (Stark et al., 2015). Speculation exists that the hippocampus is biased towards processing inputs from the visual domain (Zammit et al., 2017). Indeed, the hippocampus has well-established afferents from the ventral visual stream, and it has been purported to play a specialized role in spatial memory and complex spatial perception, which is highly visual in humans (A. C. H. Lee et al., 2012; Saksida & Bussey, 2010). Thus, behavioral studies of pattern separation that use the MST may be limited in their generalizability to other domains (Liu et al., 2015).

A novel task, the Mnemonic Auditory Similarity Task (MAST), was developed to detect recognition memory for auditory stimuli of participants. At test, participants were asked to distinguish among semantically recognizable auditory stimuli that were previously heard (targets), were highly similar to those previously heard (lures), or were new and semantically different from targets or lures (foils). Regardless of age, participants recognized lures at a significantly lower accuracy rate than targets and foils. This lure discrimination difficulty paralleled similar results found in the visual modality (Bakker et al., 2008a; Kirwan & Stark, 2007; Stark et al., 2013). In addition, similar to previous visual memory studies in healthy younger and older adults (Stark et al., 2015; Yassa, Lacy, et al., 2011), there was an age-related decline in performance accuracy for auditory lure discrimination. This finding suggests that the hippocampus may play a similar role in pattern separation of highly similar sounds as it does with highly similar visual images.

In testing performance on the MAST and the MST across the three age groups, we found that target vs. lure sensitivity scores in young adults were similar for both sounds and pictures of everyday objects. However, significant variations in ability were found in the middle-older and older age groups. In these individuals, acoustic performance was significantly worse than visual performance. However, these modality differences vanished when we controlled for auditory perceptual abilities in a trimmed sample. Thus, rather than challenging the notion that the hippocampus is representationally agnostic to stimulus modality (Huffman & Stark, 2014; Larocque et al., 2013), our results seem to support this theory when the age-related auditory decline is taken into account.

BL's results for target items relative to lures and foils raised additional questions related to the theoretically agnostic nature of the hippocampus. Although we could not find a significant impairment in BL's lure sensitivity relative to controls, his performance was at floor, exhibiting a total lack of behavioral discrimination. In addition, BL was significantly worse than controls in recognition memory performance for acoustic but not visual objects. We speculate that BL's frank impairments in mnemonic discrimination, as measured by traditional metrics and signal detection analysis, might have uncovered an unexpected finding: the DG plays a crucial role in auditory recognition memory. Such a finding would also seem to indicate a dissociation between the DG's function in acoustic versus visual recognition memory, as a similar deficit was not found for BL in response to visual recognition memory assessment using the MST.

Indirect and direct connectivity thought to support episodic memory between the human auditory cortex and hippocampus has been found in humans and monkeys (Munoz-Lopez et al., 2010; Rocchi et al., 2021). However, the interconnectivity between human hippocampal subfields, which might support recognition memory for sounds, has yet to be established. As technological advancements are made in functional imaging, I expect that the connectivity involved in delineating all sensory information (including auditory) within the hippocampus will be defined more precisely. Until then, this finding of a potential recognition memory disruption caused by a lesion to the DG offers initial human evidence of a brain-behaviour relationship between the DG and the auditory cortex in recognition memory of everyday sounds.

5.1.3 Pattern separation can be detected using abstract auditory stimuli

In humans, behavioral pattern separation is classically illustrated by assessing participants' ability to differentiate pre-experimentally known visual objects studied from those that were unstudied, some of which are visually and semantically similar to the studied items (Bakker et al., 2008a; Stark et al., 2015). In Study 2, we provided evidence that auditory lure discrimination declines across the lifespan, suggesting that age-related declines found in visual behavioral discrimination (Stark et al., 2015) are also detectable in at least one other category. The sounds used in Study 2 had strong semantic associations, as do the visual objects included in the MST. However, the use of stimuli with pre-existing semantic representations risks biasing participants towards pattern completion in behavioral tests of pattern separation (Deuker et al., 2014; Hunsaker & Kesner, 2013; Liu et al., 2015).

Study 3 set out to control for the potential bias inherent in semantically familiar sounds by using micropatterns of pure tones. By doing so, we removed any mnemonic advantage conferred by deeper-level processing of semantically meaningful items. Participants heard the clusters of sounds for the first time on the day of the experiment. The micropatterns were not musical and avoided the emotional richness or memorability of musical passages, which activate the hippocampus and the broader MTL (Levitin & Tirovolas, 2009). Devoid of pre-experimental semantic familiarity, these micropatterns met the goal of being process pure (Deuker et al., 2014). At study, we measured ERPs of young adults as they passively listened to the standard and deviant micropatterns. We controlled for possible confounds due to attention by instructing participants to attend to a movie being played without an audible soundtrack. During the 20 minutes they watched the movie, the young adults were presented with standard and deviant sound patterns, and an associated MMN was computed.

The second test phase of the experiment was adopted from a typical visual pattern separation behavioral paradigm (Kirwan & Stark, 2007; Stark et al., 2013, 2015). During this part of the experiment, participants completed a surprise memory test in which they were presented with target micropatterns, highly similar lures, and relatively different foils. We found the healthy young adults exhibited a high degree of sensitivity at recognizing target items relative to foils. Unexpectedly, we found an even stronger correlation between the MMN amplitude and recognition accuracy for target micropatterns versus lures than for target items versus foils. These findings suggest that the MMN translates to recognition memory discrimination, possibly facilitated by mechanisms of prediction error (Friston, 2010; Garrido et al., 2009).

There are hints in the literature that the MMN interacts with long-term memory (Näätänen & Kreegipuu, 2010; Snyder & Michelon, 2006). We believe this extends to the signs of pattern separation we found in Study 3. Evidence for similar interactions can be found in studies using phoneme stimuli (Cheour et al., 1998; Näätänen et al., 1997). In these experiments, a larger-amplitude MMN appears when a phoneme deviant is in a participant's mother tongue, relative to when it is a vowel sound from outside a native language. Furthermore, the MMN provides evidence that the ability to discriminate familiar phonemes from unfamiliar, but highly similar, phonemes is learned before 12 months of age (Cheour et al., 1998; but see also Cooray et al., 2015). These findings lead to our conjecture that the MMN also reflects behavioral pattern separation of long-term memory traces of speech sounds.

In animal experiments (Ruusuvirta et al., 1995, 2013), the MMN has been found to activate the hippocampus, a brain structure crucial to episodic memory integrity (Rosenbaum et al., 2008; Vargha-Khadem et al., 1997). Specific hippocampal subfields engaged include the DG (Ruusuvirta et al., 2013), which, as I have stressed throughout this work, is a part of the hippocampus on which pattern separation depends.

In a mouse study, significant hippocampal activity was found when the rodents were presented with random, relative to self-generated, auditory stimuli (Rummell et al., 2016), suggesting that the hippocampus may also subserve novelty detection/suppression modulation. Such activity would align the MMN within the larger predictive coding framework. This theory hypothesizes that neural responses are shaped by expectations in advance of, and prediction errors following the presentation of, sensory input (Garrido et al., 2009). Interestingly, prediction errors in human participants in response to a violation of expectations of visual stimuli have also been found to involve hippocampal subfields (Bein, Duncan, et al., 2020).

Efforts to casually link the MMN with episodic memory processes beyond language acquisition in neurotypical humans, however, have been untested. We confirmed a link between MMN brain dynamics and behavioral pattern separation to test our prediction that the MMN signal mediates both recognition memory and behavioral pattern separation in healthy young adults. In doing so, we show that pattern separation is not a modality-specific ability, nor is it dependent on conceptual processing conferred by semantic stimuli.

5.2 Further interpretation and implications

The research reported throughout chapters 2 to 4 of my dissertation speaks to several influential theories and previous empirical findings, which I elaborate upon in this section.

5.2.1 Complementary Learning Systems (CLS)

In many ways, the CLS account of the functional organization of memory (McClelland et al., 1995) is intertwined with the rise of the study of pattern separation. Indeed, the CLS account drew upon ideas proposed by David Marr (Kumaran et al., 2016; McClelland et al., 1995), who was also a key figure in explicating pattern separation/completion concepts (Becker, 2017; Hasselmo & Hinman, 2016; Marr, 1971). Furthermore, the CLS account was developed and refined by individuals involved in computational modeling of pattern separation (Kumaran et al.,

2016; McClelland et al., 1995; Norman & O'Reilly, 2003). The CLS account also integrates models of computational systems of human perception and cognition (including learning and memory) known as connectionist or Parallel Distributed Processing (PDP) models (McClelland & Cleeremans, 2010; Rumelhart & McClelland, 1986). These connectionist models propose interconnected layers or patterns of units (e.g., neuronal clusters) that exhibit neuron-like behaviour when interacting with units in other parts of the brain (Banich, 2011). As was stressed in 5.1.2, the CLS propounds that the hippocampus is agnostic to the modality of the sensory input it processes (Huffman & Stark, 2014). This approach is not incompatible with O'Keefe and Nadel's position that "the hippocampus is the core of a neural memory system providing an objective spatial framework within which *the items and events of an organism's experience are located and interrelated*," (O'Keefe & Nadel, 1978, p. 1; emphasis mine).

One of the central tenets of the CLS computational framework is that the brain has a fast and slow system of representing and retrieving memories (McClelland et al., 1995; Schapiro et al., 2017). The hippocampus in general, and the DG and the CA3 in particular, are part of the fast learning system. The DG allows for rapid learning by arbitrarily and automatically orthogonalizing distinct (i.e., pattern-separated) representations for each memory episode to minimize interference. These patterns are transmitted to the CA3, where specific experiences can be reinstated (or auto-associated) from partial cues. (Within connectionist models, pattern completion is also a central aspect of recurrent and inter-connected networks within the neocortex; e.g., Palmer, 1999; Rolls, 2008). The neural connectivity within this system adapts and changes much more rapidly than synaptic connections among the slow system or units within the neocortex (Frankland & Bontempi, 2005; McClelland et al., 1995; Yassa & Reagh, 2013). Connections from the hippocampus to the broader MTL or neocortex (see Figure 1-3), however, provide for more gradual, incremental generalization, which facilitates categorization. This process relies on layering overlapping representations or on the assimilation of novel inputs so as to generalize about how they relate to similar representations. Thus, the CLS model can account for both specificity and generalizability of memories, as well as the modification of existing memories based on new statistical regularities within the environment (Kumaran et al., 2016; McClelland et al., 1995; Norman & O'Reilly, 2003).

Importantly, the CLS framework predicts that patients with focal lesions to the hippocampus (which spare the perirhinal cortex) should be impaired in modified recognition tests with related

lures. These high-interference items would not be pattern separatable and thus would be perceived as similar (Norman, 2010). Studied items (targets), however, would be discriminable from new, unstudied items (foils) as the studied items would have a finer tuned neural signature in the perirhinal cortex, even after only one exposure (Brown et al., 1987; Norman, 2010; Norman & O'Reilly, 2003; Viskontas et al., 2006).

Since its articulation as an account of human learning and memory in the mid-1990s (McClelland et al., 1995), the CLS theory has been expanded and reinterpreted in critical ways. For example, in its reliance on hippocampal-neocortical interactions, the CLS account has been seen to be compatible with "non-connectionist," cross-cortical systems of learning and memory (McClelland, 2000), including the Competitive Trace Theory (Yassa & Reagh, 2013). The CLS account is also acknowledged as a close cousin to the representational-hierarchical framework of the cortical organization (Cowell et al., 2010; Kent et al., 2016; Saksida & Bussey, 2010) discussed in section 2.6. However, the CLS model is less specific on how representations of visual objects culminate in the perirhinal cortex, the termination point for the ventral visual stream hierarchy (Norman, 2010).

A significant update of the CLS theory by Kumaran, Hassabis, and McClelland in 2016 expanded the role of the hippocampus within the context of the CLS. One of the updates Kumaran and colleagues proposed — citing a decade or so of new data and empirical considerations of the CLS (e.g., Eichenbaum, 2004; Kumaran & McClelland, 2012; Schapiro et al., 2014; Zeithamova et al., 2012) — is that hippocampus supports "some forms of generalization that go beyond those originally envisaged" (Kumaran et al., 2016, p. 512). The mechanisms by which this generalization occurs within the hippocampus are the subject of current theoretical debate and ongoing investigation. However, two leading candidate processes (which might not be mutually exclusive) are the recurrence of pattern separated codes in the DG/CA3 with the EC (Kumaran et al., 2016; Kumaran & McClelland, 2012) and within the synthesis of generalities by the hippocampus through statistical learning. The latter process, potentially intertwined with the CLS, can learn regularities from environmental cues over time (Schapiro et al., 2014, 2017; Schapiro & Turk-Browne, 2015). The time necessary to form these generalities in the hippocampus can be much faster (on the order of minutes) than was initially envisioned for neocortical learning (Kumaran et al., 2016; Schapiro & Turk-Browne, 2015). Interestingly, there is evidence that statistical learning may be supported within the hippocampus

by the EC to CA1 monosynaptic pathway (Schapiro et al., 2017), which is believed to be intact in patient BL.

5.2.1.1 Support for the CLS account: Study 1

The CP results in Study 1 can be interpreted in light of the CLS. Participants likely relied upon neocortical representations of pre-experimentally known FF during identification, perhaps residing in the temporal pole (Landi et al., 2021). This act of categorization, where humans recognize the functional "purpose" (e.g., being that famous movie star, politician, singer, etc.) with a semantically known conceptual set of properties (e.g., who was in that movie, who was our last prime minister, who sings now in Vegas, who has that wide nose), is informed by experience and is thought to be the ultimate goal of perception (Palmer, 1999). Participants' (including patient BL) responses were in a typical sigmoidal function for the FF condition. In a connectionist CLS model approach, the sigmoidal function is indicative of the weighted all-or-none communication between units in a neural network (Rolls, 2008). As BL's identification performance was not found to be significantly different than that of controls, the CLS supposition of the neocortex being representationally categorical for faces and not necessarily dependent on rapid hippocampal learning (Huffman & Stark, 2014) is borne out.

However, the NF condition would not have had enough exposure (at least in the original CLS conception) to obtain the slow learning necessary to possess these neocortical associations. These faces were learned on the day of testing, and thus their identification elements were those which had been learned quickly, pattern separated by the hippocampus. This reliance on fast learning may explain why the controls' identification of NF did not follow a sigmoidal function as did FF. Hippocampally based representations could also account for the ability of participants to discriminate the within-category and between-category faces with equal skill. The NF were distinguishable, then, but they lacked generalizability. Paradoxically, this lack of overlapping representations seems to have helped the NFs discriminability within the context of a CP experiment. The NF, in effect, had little interference from neocortical identification associations and thus did not appear to be similarly tied to one identity.

On the other hand, BL lacked the circuitry to pattern separate the NF. In theory, he was doubly disadvantaged, as he could not reply upon either neocortical generalities or hippocampal specificity. As a result, he could not categorize the NFs at a reasonable boundary when asked, as

he had no conceptual or perceptual representation of the identities. His discrimination performance reflected his impaired identification, with the caveat that one could also interpret his results as being "ideal" CP. This ideal derives from his zero sensitivity at within-category discrimination (i.e., all the within-category faces looked identical to BL). Alternatively, these results could be interpreted in terms of what we know about BL's intact hippocampal subfields (Baker et al., 2016). Suppose his EC to DG/CA1 pathways are still intact, as I believe they are. In that case, BL could still encode coarse representations of the faces or generalize about the NFs based on statistical learning along the monosynaptic pathway. The result would be potentially overactive pattern completion/generalization without the mediating effect of pattern separation. In this scenario, we would see that there would be little, if no, discriminability of the within-category NF.

5.2.1.2 Challenges to the CLS account: Study 2 and Study 3

Huffman and Stark (Huffman & Stark, 2014), in their positioning of pattern separation within the CLS account, famously referred to the hippocampus as "representationally agnostic" (Huffman & Stark, 2014). This term distinguished the functions of these hippocampal subfields from areas of the neocortex that are "representationally categorical" and show classification accuracy between categories of inputs (e.g., faces versus scenes). This agnostic conception of the hippocampus regarding pattern separation dates back to seminal theories of pattern separation and pattern completion (e.g., Marr, 1971; O'Reilly & McClelland, 1994). The agnostic view has also been articulated in different ways by those who propose that pattern separation is a process that operates on information across any sensory or perceptual domain (Hunsaker & Kesner, 2013; Kent et al., 2016). Failure to provide evidence of such agnosticism would threaten the positioning of pattern separation within the CLS framework. In addition, such an absence of evidence could limit our understanding of pattern separation. Rather than being an agnostic process, it would be confined to the visual object or visuospatial world. These are the type of stimuli that have most often been used in human and animal testing to support the operationalization of pattern separation (Liu et al., 2015).

In Study 2, I provided support that the hippocampus is representationally agnostic by showing that everyday sounds show similar lure discrimination difficulties across the lifespan as do everyday visual objects. Notably, young adults did not differ in their lure discrimination ability

between modalities. This result appears to implicate hippocampal decline as the cause of behavioral pattern separation deficits for everyday sounds. This is a significant finding, as auditory stimuli, to my knowledge, have not been used until now in human mnemonic discrimination tests. Yet, unlike the visual objects, we also found that overall recognition memory performance for auditory objects was significantly worse in the older adult groups than the young adult group.

Further complicating the question was that patient BL had even worse auditory recognition memory performance than age-matched controls. His lure discrimination was at floor but was not statistically different from that of controls, possibly due to variability in the control data or a lack of power in the MAST test. Both issues could be addressed by increasing the sample size of the number of participants tested (Howell, 2010).

The role of the hippocampus in recognition memory has been the subject of considerable debate (Bird, 2017; Brown et al., 2010; Burwell & Furtak, 2008; I. A. Clark & Maguire, 2016; Norman, 2010; Ranganath, 2010; Sauvage et al., 2008; Wixted & Squire, 2004; Yonelinas et al., 2010). Studies of humans with focal hippocampal damage have contributed data suggesting that the hippocampus is necessary (Kopelman et al., 2007; Manns et al., 2003). Evidence for a "dual-process" — the theory that the hippocampus is essential for recall but not recognition (Yonelinas, 2001) — also exists (Baddeley et al., 2001; Mayes et al., 2002; Patai et al., 2015; Vargha-Khadem et al., 1997). In a previous study using the MST (Baker et al., 2016) and in Study 2, BL exhibited visual object recognition memory performance (i.e., ability to identify targets as old) comparable to age-matched controls. However, others have found that recognition memory performance for auditory recognition memory is impaired in hippocampal amnesiacs (e.g., Squire et al., 2001). Animal studies are also often divided on this issue, with further nuances identified by the task and stimuli involved (Eichenbaum, 2004).

An extensive account of the CLS model as applied to recognition memory, including one that accommodates findings in hippocampal amnesiacs (Norman & O'Reilly, 2003), includes a multi-faceted account with several key variables. These variables include the type of paradigm used in a behavioral study, pre-experimental familiarity with the stimuli (which affects encoding), and the extent of the lesion and its location within hippocampal subfields. Within the model proposed by Norman and O'Reilly, it is difficult to say whether BL's performance supports the CLS

approach to recognition memory for auditory stimuli. However, other studies of auditory recognition memory have consistently shown that recognition memory for sounds is worse than visual objects (Bigelow & Poremba, 2014; Gloede et al., 2017). More direct testing of behavioral pattern separation across modalities is needed to tease apart these modality-specific differences. A potential area of focus would be to investigate pitch detection. This ability has been found to be a variable of interest in behavioral discrimination studies with rodents (e.g., Aronov et al., 2017).

5.3 MMN, predictive coding, and pattern separation

We recorded ERPs of healthy young participants using a novel task that measures auditory pattern separation of pre-experimentally unknown stimuli. Our goal was to determine if, during the study phase, a mismatch negativity (MMN) signal, elicited by deviation from preceding stimuli, predicts participants' ability to discriminate studied items from highly similar, unstudied items.

A component of ERPs, the MMN is associated with a change-detection process driven by prediction errors. A leading theory of the MMN response is that it involves the interplay of predictive coding, neural difference responses following the onset of change detection with prediction error, or neural expectancy responses in advance of sensory input (Garrido et al., 2009; Näätänen, 2019; Näätänen et al., 1978). Hindy, Ng, and Turk-Browne (2016) discovered that predictive coding links perceptual mismatches. These occur between erroneous mnemonic expectations — expressed through pattern completion in the CA3 — with perceptual inputs of abstract visual images (Hindy et al., 2016). In this way, prediction errors registered in the hippocampus for visual inputs may initially reflect arbitrary binding of co-occurring events; these representations may sharpen over time as they are consolidated within the visual cortex (Hindy et al., 2019).

Nevertheless, in humans, it is unclear if the MMN, which signals a change in input at perception, plays a causal role in maintaining a separation of overlapping auditory representations in long-term memory. Tentative evidence supports the notion that the hippocampus plays a role in learning complex acoustic patterns (Barascud et al., 2016; Geiser et al., 2014). Furthermore, MMN experiments with clinical populations have provided some suggestions that the MMN response transcends its role as an index of perceptual discrimination and relates to higher-order

cognitive processes, such as long-term memory (Alain et al., 1998; Baldeweg & Hirsch, 2015; Näätänen, 2019). However, speculation that the MMN correlates with behavioral discrimination of sounds has not been subjected to empirical testing.

In Study 3, we answer the outstanding question of whether the MMN extends beyond its role as an index of perceptual discrimination and correlates with higher-order cognitive processes, such as episodic memory. We establish for the first time that automatic auditory discrimination is related to behavioral pattern separation in episodic memory. By linking MMN amplitudes with a surprise recognition memory test using previously heard and new sound patterns, our investigation also shows that our capacity to discriminate abstract auditory inputs, as measured by MMN, translates into new, unique memories.

5.4 Clinical Implications

As our aging population increases, so will the number of individuals who will suffer age-related cognitive impairment. One of the most common among them is a decline or loss of episodic memory, characterized by an inability to recall past personal experiences in detail, specificity, and precision. Similar losses of detail, specificity, and accuracy are also observed in perception. The evidence provided throughout this dissertation suggests that age-related decline in specificity and precision, and possibly in perceptual detail, is related to deficiencies in pattern separation. This loss of specificity may lead to reliance on gist rather than detailed information.

Pattern separation is thought to depend on the functional integrity of the hippocampus, particularly the DG, which atrophies in aging and age-related neurological disease, including amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD). Recent research has shown that the hippocampus and related MTL structures are implicated in perception in addition to memory (Aly et al., 2013; Graham et al., 2010; Murray et al., 2007; Turk-Browne, 2019) but, to my knowledge, no one has examined if that is true also of pattern separation. We provide evidence that impaired pattern separation also contributes to perceptual deficits seen in older adults over and above those caused by deterioration of peripheral sensory mechanisms through testing patient BL.

Although a deficit in pattern separation has been proposed as one of the main causes of memory decline with age, the test typically used to assess pattern separation, the MST, is a visual one.

Older adults and people with aMCI and AD all show deficient performance on the MST, because they have difficulty distinguishing targets from similar foils. Previously, it was not known if comparable deficits would also be observed in perception. Given the critical role ascribed to pattern separation for episodic memory, it is crucial to determine whether its effects can be detected not only with the MST, useful as it is, but also with other tests that require fine mnemonic and perceptual discrimination and whether these effects are related to performance on other tests of episodic memory that decline with age and age-related disorders such as aMCI and AD.

Knowledge gained from this research could directly inform the development of tools for clinical assessment and intervention, particularly concerning auditory function. Mounting evidence points to the relationship between hearing loss and dementia (Griffiths et al., 2020; Lin et al., 2011; Livingston et al., 2017; Loughrey et al., 2018). We provide data showing that the mnemonic discrimination and recognition — both likely mediated by the hippocampus — decline with age and may be detectible as early as midlife (see also Griffiths et al., 2020). Through building on these findings, future research could point to ways to mediate hearing loss as an independent risk factor for dementia (Griffiths et al., 2020), perhaps through fitness activities that boost neurogenesis within the DG (Han et al., 2016; Marlatt et al., 2012).

5.5 Limitations and future directions

Although the findings across all three studies have succeeded in whole or in part in meeting the main aims of my dissertation, some limitations are apparent. A discussion of these limitations also points to future directions for potential follow-on studies.

Regarding the CP study (Chapter 2), a companion pattern separation study run at the same time would have helped disentangle the findings. Such a study would build on previous pattern separation studies using faces as stimuli, with a variation of adding famous and nonfamous faces into the mix or faces that vary by social dimension or ethnicity.

It is well established that humans rapidly and effortlessly make generalities (many of them accurate) between another person’s facial features or expressions and that person’s character or personality (Zebrowitz & Montepare, 2015). In looking upon another’s face, we also commonly seek social information about that person’s age, sex, and attractiveness. In response to such

widespread first impressions, social psychologist Leslie Zebrowitz formulated the "overgeneralization hypothesis" (Zebrowitz, 1997). Zebrowitz's hypothesis posits that humans are attuned to certain psychological qualities in others and may overgeneralize or overinterpret facial structures resembling these qualities. For example, we may create stereotypes of faces that project a certain level of fitness, particular emotions, or identity or remind us of babies (Zebrowitz & Montepare, 2015). Others have expanded upon Zebrowitz's overgeneralization effects to look at other nonverbal information we perceive in faces and which may initiate our attitudes or behaviors towards others (Bjornsdottir & Rule, 2017; Zebrowitz & Montepare, 2015). For example, Bjornsdottir and Rule (Bjornsdottir & Rule, 2017) studied young adults' ability to infer social class from first impressions of faces. The subtle cues participants gleaned from these faces correlated with stereotypes that more affluent faces appear happier than poorer ones, even though the expressions on rich and poor faces were ostensibly neutral.

As convincing as Bjornsdottir and Rule were on identifying social class as a dimension that can be conceptualized within Zebrowitz's "overgeneralization hypothesis" (Zebrowitz, 1997), the researchers failed to illustrate whether social class is a dimension that is discrete or continuous, or how various degrees of wealth may influence first impressions. Therefore, one way of studying how we infer social class would be within the context of a CP experiment, accompanied by a companion pattern separation study.

A related research question would be whether the ethnicity of the participants might interact with these determinations (e.g., Friesen et al., 2019). Here the phenomenon being explored would be the cross-race effect (CRE; also known as the other-race effect; Malpass & Kravitz, 1969). The CRE has been investigated in many studies of facial perception; a common finding is that recognition memory is stronger for same-race (SR) compared to cross-race (CR) faces (Hugenberg et al., 2012; Meissner & Brigham, 2001). Although infrequently studied in CP studies, Levin and Angelone found that categorical effects were more apparent when moving from one race to another (e.g., white faces to black faces) than when morphing from one white face or one black face to another white face or another black face (Levin & Angelone, 2002). If a similar effect influences judgments of faces with varying social class, then I would expect to find an interaction in categorical identification and discrimination due to the race of the participants viewing the target faces in such an experiment.

Additionally, much speculation occurred in the CP study as to the neural correlates potentially involved in categorization and discrimination and the extent to which these perceptual activities are potentially involved with pattern separation. A companion study with participants undergoing ultra-high-resolution fMRI during both phases of the study would reveal hippocampal dependencies during the identification and discrimination phases.

The MAST study (Chapter 3) is another paradigm that could be adapted for a neuroimaging experiment to better understand the brain mechanisms of pattern separation in the non-visual domain. However, before that takes place, further refinement of the MAST may be needed. Just as the visual object-based MST has undergone rigorous improvement to select stimuli with varying degrees of similarity (divided into lure bins), the MAST could be improved by norming the stimuli. In addition, the paradigm could be expanded by introducing at least a dozen or more sounds to each condition (e.g., 32 trials each of repetitions, similar lures, and novel foils), which could allow for sharper performance distinctions among conditions. In piloting the task, we found that participants had a hard time with more than 20 sounds per condition. However, longer presentations of trials might help participants form representations of the sound files.

Our novel use of the MMN signal to measures auditory pattern separation of pre-experimentally unknown stimuli had promising results with young adults. I had planned to test and report how their results would compare with a cohort of middle-older adults, as well as patient BL.[1] I am confident our lab will finish this testing in the coming years. A comparison between age groups and additional patients with focal lesions within and without the hippocampus can also be conducted at that time.

As part of this follow-up study, several limitations of the present paradigm could be addressed, particularly the ceiling effects in identifying target and foil micropatterns. These changes could include increasing the passive listening phase to acquire electrophysiological data on the MMN signal. In addition, limiting the number of lures in the behavioral portion of the study (which in the end were combined in our analysis) might make the study more efficient, as would asking participants to identify whether an item was old, new, or similar to better separate lures from foils. A future experiment using more difficult standard and deviant tones to counter the ceiling effects may be worthwhile.

5.6 Conclusion

This work shows that the hippocampus, traditionally viewed as a declarative memory structure, also contributes to the perception and pattern separation of non-visual information. This finding helps to support speculation that the established role of the hippocampus in memory is a by-product of its more fundamental role in fine discrimination of perceptual detail (Moscovitch et al., 2016). Furthermore, I have helped to establish that automatic auditory discrimination is related to behavioral pattern separation in episodic memory. Notably, this mnemonic discrimination can be achieved using abstract auditory stimuli. Together, these findings and three studies broaden our understanding of pattern separation, traditionally confined to research using semantically known visual objects. The testing done over three studies and discussed in this dissertation provides a critical bridge between perception and memory. It provides a path forward to explore pattern separation in previously unexamined domains.

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Appendices

Appendix A: Abbreviations

CP:	categorical perception
DG:	dentate gyrus
EC:	entorhinal cortex
ERP:	event-related potential
FF:	famous faces
MAST:	Mnemonic Auditory Similarity Test
MST:	Mnemonic Similarity Test
MTL:	medial temporal lobe
NF:	nonfamous faces

Appendix B:
BL's Face Discrimination Strategy

The following transcript is of patient BL's response to the question of strategies he used to discriminate faces in Study 2. SB = Stevenson Baker, the experimenter during this session.

SB: What were you doing to tell the faces apart? What sort of strategies, if any?

BL: I was trying to match up the eyes. And the eyebrows. The nose, not so much. And the lips. The position of the lips. And trying to like, see if they had large irises or small irises. Like their eyes, if they were bigger or smaller.

SB: OK.

BL: I didn't notice if anyone had ears. [Laughs]

SB: What about eye colour, or colour of the skin?

BL: Yes, I was looking for that too.

SB: What you are saying to me is that you were looking at the features a lot.

BL: Yeah.

SB: Would you say that is a strategy you used for most of the faces, or were there any faces you just got right away? Sort of like the whole face, rather than the individual features.

BL: Well, yeah, but then I would sort of pick it apart, compared to the one next to it, sort of thing.

SB: So it's really dwelling on the features is what I'm hearing you say.

BL: Comparing. Comparing for, like . . . differences.

[1] Limitations on EEG testing related to the COVID-19 outbreak prevented me from completing this planned testing.