Chapter 5
Pattern Separation: A Key Processing Deficit Associated with Aging?

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Pattern Separation and the Influence of Dr. Raymond Kesner

In a recent theoretical review entitled "A Tapestry of Memory," Dr. Raymond Kesner describes his Attribute Model of Memory as "a comprehensive view of memory organization based on multiple processes and multiple forms of memory representation and is based on the neurobiology of a multiple attribute, multiple process, tripartite system model of memory" (Kesner 2009, p. 3). Over the last 15 years of his career, Kesner focused on specific mnemonic processes associated with the event-based memory system with a particular emphasis on the hippocampus. In particular, he became interested in a process referred to as pattern separation. Pattern separation is hypothesized to serve as a mechanism for separating partially overlapping patterns of activation so that one pattern may be retrieved as separate from other similar patterns. A pattern separation mechanism may be critical for reducing potential interference among similar memory representations to enhance memory accuracy. A

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number of early theoretical and computational models suggested that the hippocampus supports pattern separation (Marr 1971; McNaughton and Nadel 1990; O'Reilly and McClelland 1994; Rolls 1996; Shapiro and Olton 1994; Treves and Rolls 1992). Kesner developed one of the first behavioral tasks used to demonstrate that lesions of the hippocampus impair spatial pattern separation (Gilbert et al. 1998). These theoretical and computational models also hypothesized that the dentate gyrus (DG) and CA3 subregions of the hippocampus may be particularly important for pattern separation (O'Reilly and McClelland 1994; Rolls 1996; Shapiro and Olton 1994). To test the predictions of these models, Kesner tested rats with neurotoxin-induced lesions of the DG or CA3 subregions on his spatial pattern separation task previously shown to be dependent on the hippocampus. The results provided support for the hypothesis that the DG (Gilbert et al. 2001) and CA3 (Gilbert and Kesner 2006) hippocampal subregions play a key role in spatial pattern separation. Over the last 15 years, Kesner and his colleagues have published numerous studies examining pattern separation for spatial information (Gilbert and Kesner 2006; Gilbert et al. 1998, 2001; Goodrich-Hunsaker et al. 2005; Hunsaker and Kesner 2008; Morris et al. 2012), temporal order of stimuli (Gilbert et al. 2001; Hunsaker et al. 2008; Kesner et al. 2002; Kesner and Hunsaker 2010; Kesner et al. 2010), olfactory stimuli (Kesner et al. 2011; Weeden et al. 2012), motor responses (Kesner and Gilbert 2006), scenes of visual objects (Gilbert and Kesner 2003), and reward magnitude (Gilbert and Kesner 2002). He has also published numerous theoretical models and review articles on pattern separation (Hunsaker and Kesner 2013; Kesner 2007, 2013a, b; Kesner et al. 2000; Kesner and Hopkins 2006; Rolls and Kesner 2006). The innovative behavioral studies conducted in the Kesner laboratory examining pattern separation have contributed greatly to our understanding of this process. In addition, his work has set the foundation for the recent behavioral investigations of age-related changes in pattern separation that will be reviewed in the present chapter.

In recent years, pattern separation has drawn considerable attention in the literature as an important mechanism for accurate memory formation and subsequent retrieval. Additional computational and theoretical models have been published detailing the role of the hippocampus in pattern separation (Kesner 2007; Myers and Scharfman 2009; Rolls 2010; Rolls and Kesner 2006). In addition, numerous researchers have shown that the DG and CA3 subregions of the hippocampus play a critical role in pattern separation in animal models using electrophysiological recordings (Leutgeb et al. 2007; McNaughton et al. 1989; Tanila 1999), neurotoxin-induced lesions and inactivations (Butterly et al. 2012; Gilbert and Kesner 2006; Gilbert et al. 2001; Goodrich-Hunsaker et al. 2008; Lee et al. 2005; McTighe et al. 2009; Morris et al. 2012), and genetic manipulations (Kubik et al. 2007; McHugh et al. 2007). Furthermore, studies using high-resolution functional magnetic resonance imaging (fMRI) have shown that the human hippocampus (Kirwan and Stark 2007; LaRocque et al. 2013; Motley and Kirwan 2012), and specifically the DG/CA3 subregions (Bakker et al. 2008; Lacy et al. 2011), are active during pattern separation tasks (see also reviews by Carr et al. 2010; Yassa and Stark 2011). Most recently, neuropsychological studies have shown that patients with hippocampal damage have deficits in pattern separation (Duff et al. 2012; Kirwan et al. 2012).

Age-related Changes in the Brain

Aging has been shown to result in both white matter and gray matter changes in various regions throughout the brain (Allen et al. 2005; Driscoll et al. 2009; Kennedy and Raz 2009; Ziegler et al. 2010); however, there has been particular focus in the literature on detrimental age-related changes in regions of the brain that support memory, including the hippocampus and surrounding medial temporal lobe structures (Allen et al. 2005; Driscoll and Sutherland 2005; Good et al. 2001; Raz et al. 2005; Walhovd et al. 2010). In aged rodents, a number of studies have reported preserved numbers of neurons in the hippocampus (Rapp and Gallagher 1996; Rapp et al. 1999; Rasmussen et al. 1996); however, others have reported decreased neuronal density (Driscoll et al. 2006). In addition, some studies have reported a lack of a relationship between hippocampal cell numbers and spatial learning deficits (Driscoll et al. 2006; Rapp and Gallagher 1996); however, hippocampal volume measured by MRI has been shown to correlate with water maze performance in aged rats (Driscoll et al. 2006). Since neuronal loss in the hippocampus alone is unlikely to account for the memory deficits observed in aged animals, it has been postulated that age-related memory decline may stem from functional changes in the hippocampus (Barnes 1994; Driscoll et al. 2006; Gallagher et al. 2010), localized synaptic loss (Wilson et al. 2006), and subregion-specific epigenetic and transcriptional changes in the hippocampus (Penner et al. 2011). In addition, age-related structural and functional changes have been reported in perforant path inputs to the DG from the entorhinal cortex (EC). The total number of contacts per neuron in the middle molecular layer of the DG (afferent EC fibers) was found to be significantly reduced in old rats (Geinisman et al. 1992; see also Smith et al. 2000). Perforant path connections to the DG in old rats were also found to be less excitable and required greater stimulation to achieve long-term potentiation compared to young rats (Burke and Barnes 2006).

Results of longitudinal studies in humans demonstrate that hippocampal and parahippocampal cortices exhibit decreased volumes as a function of increased age in non-demented older adults (Driscoll et al. 2009). The hippocampus has been reported to be particularly susceptible to age-related changes and this structure decreases in volume at a faster rate relative to other structures in the medial temporal lobe (Raz et al. 2004). In addition, the observed hippocampal volume loss has been reported to be a primary predictor of memory deficits in older adults (Kramer et al. 2007; Mungas et al. 2005). A recent longitudinal imaging study revealed that declines in episodic memory were associated with decreased hippocampal volume, as well as decreased activation in the left hippocampus, suggesting that structural and functional changes in the hippocampal formation are linked to memory decline (Persson et al. 2012). Small et al. (2002) reported that 60 % of an older adult sample had diminished MRI signal in at least one hippocampal subregion and this hippocampal dysfunction was associated with declines in memory ability. In addition, the authors demonstrated that DG dysfunction is associated with normal aging, whereas signal decline in the EC is indicative of a pathological process (see also Mueller et al. 2010). Although some studies have reported that the volume of the

EC is relatively resistant to aging (Mueller and Weiner 2009), other studies have reported that shrinkage of the EC is associated with poorer memory performance in older adults (Rodrigue and Raz 2004). Using ultrahigh-resolution microstructural diffusion tensor imaging, the perforant pathway has also been found to undergo significant structural changes with advanced age that related to memory function (Yassa et al. 2011b). As reviewed by Small et al. (2011), the DG has been reported to be particularly susceptible to age-related changes in both human (Small et al. 2002; Wu et al. 2008) and animal models (Patrylo and Williamson 2007; Small et al. 2004). In contrast, the pyramidal cells of the CA subregions are relatively less affected in aging (Small et al. 2004).

Pattern Separation and Aging

Wilson et al. (2006) proposed a model of neurocognitive aging, which suggests that age-related changes in the hippocampal processing circuit may account for some of the common episodic memory deficits experienced by many older adults. Based on a review of neurobiological and neurophysiological evidence, the authors suggest that subtle changes in each of the hippocampal subregions may lead to a functional reorganization of information processing in the aged hippocampus. Specifically, the DG receives less input and excitation from the EC via the perforant path, which may result in decreased pattern separation efficiency. The CA3 subregion also undergoes specific age-related changes, including decreased input from the EC and reduced ACh modulation. Reduced ACh input releases the CA3 auto-associative network from inhibition, causing this subregion to become entrenched in pattern completion—a mechanism that allows for completion of stored, familiar patterns given only partial cues (Kesner and Hopkins 2006). Collectively, the changes in the CA3 subregion may result in a strong bias toward retrieval of previously stored representations. The authors propose that the combination of a hypoactive DG and hyperactive CA3 in the aged hippocampus alters the balance of information processing, such that encoding of novel information (pattern separation) is attenuated due to interference from previously stored information (pattern completion). This functional reorganization may explain why older adults often have difficulty remembering new events whereas prior memories are relatively well preserved. In support of this model, Yassa et al. (2011) reported that age-related changes in perforant path integrity and changes in functional activity in the DG/CA3 network are associated with decreased pattern separation activity in older humans. These changes are suggested to increase reliance on retrieval of stored information at the expense of processing novel information (Yassa et al. 2011a).

Pattern Separation in Older Animals

Given the critical role of the DG subregion in supporting pattern separation and the susceptibility of this region to age-related neurobiological changes, recent studies have begun to examine a possible link between aging and efficiency of the pattern separation mechanism in rodents. A study published by Marrone et al. (2011) provided some of the first neurobiological insight into how age-related changes in the DG of rodents may affect pattern separation and spatial memory. The study used a marker of cellular activity (zif268/egr1) to examine granule cell activity in young and older animals during exploration of similar and dissimilar environments. The authors found that age-related changes in pattern separation correlated with a decreased ability of older animals to disambiguate similar contexts when performing a sequential spatial recognition task.

Another more recent study provides additional behavioral evidence that spatial pattern separation may be impaired in older rats (Gracian et al. 2013). Young and old rats were tested on a task developed by McDonald and White (1995) that was recently shown to be dependent on the DG hippocampal subregion (Morris et al. 2012). The rats were trained on a radial 8-arm maze to discriminate between a rewarded arm and a non-rewarded arm that were either adjacent to one another (high spatial interference) or separated by a distance of two arm positions (low spatial interference). The authors found that old rats committed significantly more errors compared to young rats on the adjacent condition. However, young and old rats committed similar numbers of errors in the separated condition. The authors concluded that decreased spatial pattern separation in old rats may impair performance in the adjacent condition, which involved greater spatial interference among distal cues. However, in the separated condition, when there was less overlap among distal cues and less need for pattern separation, performance improved in the older rats. Collectively, the aforementioned studies offer evidence that spatial pattern separation may become less efficient in rodents as a result of aging, presumably due to changes in the DG.

Studies have also provided some evidence that the reductions in neurogenesis observed in old animals (Kuhn et al. 1996) may be related to decreased hippocampal volume and impaired performance in hippocampal dependent tasks (Driscoll et al. 2006). Penner et al. (2011) suggest that age-related memory decline may stem from subregion-specific epigenetic and transcriptional changes in the hippocampus. Newborn neurons are reported to be involved in mnemonic processes such as pattern separation that are particularly dependent on the DG subregion (Aimone et al. 2010, 2011; Clelland et al. 2009; Creer et al. 2010; Deng et al. 2010; Luu et al. 2012; Sahay et al. 2011), whereas older DG cells may contribute to pattern completion (Nakashiba et al. 2012). Interventions that increase neurogenesis during adulthood may have clinical implications for reversing age-related impairments in pattern separation and associated DG dysfunction (Sahay et al. 2011). The development of such interventions may be particularly important given recent evidence in animals suggesting that pattern separation deficits may begin in middle age (Huxter et al. 2012). Creer et al. (2010) reported that voluntary running improved the ability of adult mice to discriminate between two spatially adjacent locations, suggesting an improvement

in spatial pattern separation. In addition, this improvement was correlated with increased neurogenesis. Therefore, exercise may be a potential intervention to combat pattern separation deficits and decreased neurogenesis in adulthood. Unfortunately, voluntary running did not have similar effects on pattern separation or neurogenesis in very old mice (Creer et al. 2010). Given the aforementioned studies, the development of behavioral tasks sensitive to age-related changes in spatial pattern separation may have implications for future studies of neurogenesis in older animals.

Recent studies investigating age-related changes in visual object recognition have also provided evidence that pattern separation for visual object information may be impaired in aged rats (Burke et al. 2010, 2011) and monkeys (Burke et al. 2011). In a study by Burke et al. (2011), young and old rats were tested on a variant of the spontaneous object recognition task hypothesized to measure pattern separation. When the rats were tested on the task with objects that did not share any common features, both old and young rats showed an exploratory preference for the novel object. However, when the animals were tested using objects with overlapping features (presumably increasing the need for pattern separation); only young rats showed a preference for the novel object. In a second experiment, young and old monkeys were tested on an object discrimination task. When the objects were dissimilar, both young and old monkeys learned to choose the rewarded objects. However, when objects with overlapping features were used in the discriminations, old monkeys required more trials than young monkeys to learn the discriminations between the rewarded and non-rewarded objects. Given that the performance of the older animals was similar to that of animals with perirhinal cortex lesions (e.g. Bartko et al. 2007a; Bussey et al. 2003), the authors conclude that age-related changes in the perirhinal cortex may lessen the ability of aged animals to support visual object pattern separation (Burke et al. 2010, 2011, 2012). Continued efforts to investigate pattern separation in older animal models may provide a better understanding of the relationship between age-related changes in various brain regions and impaired pattern separation associated with aging.

Pattern Separation in Older Humans

Recent studies have also begun to examine the relationship between aging and decreased pattern separation efficiency in humans. Age-related changes in pattern separation ability have been demonstrated on tasks involving visual objects (Stark et al. 2013; Toner et al. 2009; Yassa et al. 2011), temporal order of items in a sequence (Tolentino et al. 2012), spatial locations (Holden et al. 2012; Stark et al. 2010), and perceptually related verbal stimuli (Ly et al. 2013). Toner et al. (2009) examined the performance of young and cognitively normal older adults on a continuous recognition paradigm developed by Kirwan and Stark (2007). Participants viewed pictures of everyday objects on a computer screen and were asked to make a judgment about whether or not they had seen each object previously in the task. Some of the objects were repeated across trials and some objects, referred to as lures, were similar but not identical to objects presented previously in the task. For each object,

participants were asked to press a button to indicate whether the stimulus was: (1) new—the object had never been presented during the task, (2) old—the exact same object had been presented previously, or (3) similar—the object was similar, but not identical to one that had been presented previously during the task. This task was hypothesized to require pattern separation due to the highly overlapping object features of the lure items. Young adults significantly outperformed older adults in correct identification of lure items as similar, but there were no group differences in correct responses to new or repeated stimuli, suggesting that visual object pattern separation was less efficient in older adults (Toner et al. 2009).

In a more recent study, Yassa et al. (2011) used high-resolution fMRI to examine age-related neural changes in the human hippocampus whereas subjects performed the same task used by Toner et al. (2009). Behaviorally, the authors found a similar pattern of age-related impairment in the visual object pattern separation task. The study also included an additional experiment, which demonstrated that the behavioral pattern of activity maps onto the predictions of the model by Wilson et al. (2006). Specifically, older adults were found to require a larger degree of input dissimilarity before separation could occur. The results from the fMRI analyses revealed increased activity in the DG/CA3 subregions on trials that taxed pattern separation. On trials in which older adults were able to correctly identify lure stimuli as "similar," greater activation was observed in the DG/CA3 regions compared to when lure stimuli were incorrectly identified as "old." A subsequent study involving a similar incidental encoding behavioral task used high-resolution fMRI to reveal that representational rigidity (defined as the requirement for increased dissimilarity before stimuli can be orthogonalized) in the DG/CA3 regions of older adults was linked to deficits on the pattern separation task (Yassa et al. 2011). Using ultrahigh-resolution microstructural diffusion tensor imaging, the authors also found age-related changes in perforant path integrity that were inversely correlated with DG-CA3 representational rigidity in older adults. In addition, perforant path integrity was found to correlate with performance in the pattern separation task. The results provide further evidence for a reduction in pattern separation in DG/CA3 subregions of older adults. The findings reveal structural and functional deficits in the perforant path and the DG/CA3 subregions as potential contributors to pattern separation deficits associated with aging. The changes may result in a shift toward increased reliance on retrieval of stored information at the expense of processing novel information in older adults (Yassa et al. 2011).

In a recent study, Stark et al. (2013) used an incidental encoding version of the task described above to examine visual object pattern separation ability across lifespan. The study included cognitively normal adults divided into four age groups, ranging from 20 to 89 years of age. In the encoding phase of the task, participants were asked to make an indoor/outdoor judgment about pictures of everyday objects. In the subsequent recognition memory phase, participants were again presented with pictures of everyday objects and were asked to determine whether each object was new, old, or similar, using the same guidelines outlined for the continuous recognition task (Kirwan and Stark 2007). Recognition memory, measured by correct responses to repeated presentations of objects, did not differ across the four age groups. In contrast, as age increased, the ability to correctly identify lure objects as

similar (pattern separation) declined in a linear fashion and leveled off around age 60. Performance was also examined as a function of the degree of mnemonic similarity among lure objects. The data revealed a systematic trend in which increased age was associated with a need for greater dissimilarity of lure objects to achieve accurate identification of the objects as similar. These results further support the hypothesis that visual object pattern separation efficiency declines with age.

Tolentino et al. (2012) examined the effects of temporal interference on sequence memory in young and nondemented older adults. Participants were presented with a sequence of eight circles at the end of each of the arms on a computerized version of a radial 8-arm maze. After the participant viewed the sequence, the radial 8-arm maze was presented with a circle at the end of two of the study phase arms. There were four possible temporal separations of 0, 2, 4, and 6 lags, which represented the number of circles in the original sequence that came between the two circles presented in the choice phase. The researchers hypothesized that circles closer together in the study phase sequence would result in increased interference and a greater need to temporally separate the items. This study involved two experiments, one with a new random sequence for each trial and one with a fixed sequence across trials. In the random sequence experiment, performance for both groups improved as the temporal lag increased and young adults outperformed older adults across all temporal lags. In the fixed sequence experiment, young adults performed significantly better than older adults on all temporal lags with the exception of the 6 lag, which involved the least amount of temporal interference. Both experiments demonstrated age-related deficits in temporal order memory as a function of increased interference. The authors postulated that temporal order memory is less efficient and more susceptible to interference in older adults, possibly due to impaired temporal pattern separation.

Age-related pattern separation deficits have also been demonstrated in memory for spatial location (Holden et al. 2012). Young adults and cognitively normal older adults performed a delayed match-to-sample task that involved manipulations of the degree of spatial interference. Participants were presented with a gray circle along a nonvisible horizontal line on a computer screen. After a short delay, two circles were presented simultaneously and the participant was asked to decide which circle was in the same location as the original gray circle. Distances of 0, 0.5, 1.0, and 1.5 cm separated the two choice circles. It was hypothesized that choice circles that were closer together would result in heightened interference and thus an increased need for pattern separation. Performance increased in both young and older adults as the distance between the two choice circles increased. However, young adults outperformed older adults, suggesting that spatial pattern separation was less efficient in aged individuals (see also Holden and Gilbert 2012).

In a recent study, Ly et al. (2013) sought to further elucidate the nature of age-related deficits in pattern separation by manipulating the type of interference. The authors were interested in understanding whether inefficient pattern separation in older adults is due to conceptual or perceptual interference and suggested that prior studies were unable to disentangle the two, due to the nature of the pictorial stimuli utilized. For this study, the researchers used verbal stimuli that were either phonologically similar (perceptual interference) or semantically similar (conceptual

interference). The data revealed age-related deficits in pattern separation ability for perceptually related words, but no performance differences for conceptually related words. The authors proposed that perceptual recollection may be more sensitive to pattern separation deficits because it relies on item-specific information (e.g., item features and details), whereas conceptual recollection relies more on gist information. The results of this study suggest that not all types of memory are equally susceptible to interference and, more specifically, that age-related impairment in pattern separation may be specific to perceptual interference.

Variability in Pattern Separation Efficiency in Older Humans

Although the research reviewed thus far suggests that cognitive aging is associated with deficits in pattern separation, growing evidence also suggests that there may be individual differences among older adults in pattern separation efficiency. Stark et al. (2010) were the first to assess potential age-related variability in a task designed to measure spatial pattern separation. In this task, participants viewed pairs of pictures and were asked later to decide whether the pictures were in the same location or whether one of the pictures in the pair was in a different location. There were four possible conditions on the choice trial, one *same* condition (both pictures were in the same location) and three *different* conditions (one of the pictures in the pair had been moved). The *different* conditions were designated as *close, medium, and far*, representing the distance and angle from the original location. In the initial comparison of young and older adults, no group differences were found. However, when the older adult group was divided into an aged–impaired and aged–unimpaired group based on performance on a standardized auditory learning task, the young adults and aged–unimpaired groups performed significantly better than the aged–impaired group in the *different* trials that taxed spatial pattern separation. In an attempt to replicate these findings using a different paradigm to assess spatial pattern separation (described above), Holden et al. (2012) also divided older adults into impaired and unimpaired groups based on performance on standardized assessment of word learning. The pattern of deficits was remarkably similar to those of Stark et al. (2010). The group labeled older–impaired showed spatial pattern separation deficits relative to the young adults and older–unimpaired adults (Holden et al. 2012). The results of these two studies suggest that there may be individual differences in pattern separation deficits in the domain of spatial memory.

Evidence also suggests that there may be variability among older adults in visual object pattern separation. As discussed previously, Stark et al. (2013) utilized an incidental encoding task to examine pattern separation for visual object information. As part of this investigation, cognitively normal participants over 60 years of age were divided into aged–unimpaired and aged–impaired groups based on standardized list-learning task performance. These two groups of healthy older adults were compared to a group of individuals diagnosed with amnestic mild cognitive impairment (aMCI). The aged–unimpaired group outperformed both the aged–impaired

group and aMCI group on trials that taxed visual object pattern separation, but there were no significant differences between the aged–impaired group and the aMCI group on these trials. In contrast, individuals with aMCI were impaired relative to both of the other groups on a measure of recognition memory, but there were no recognition memory differences between the aged–unimpaired and aged–impaired groups. In addition, when performance was examined as a function of the mnemonic similarity of lure objects, the correct identification of lures required greater object dissimilarity for aMCI individuals relative to the two older adult groups, as well as for the aged–impaired group relative to aged–unimpaired group. A previous study reported that when compared to cognitively normal older adults, individuals with aMCI were impaired in a continuous recognition task that taxed visual object pattern separation abilities and that the observed deficits were associated with structural and functional changes in the DG/CA3 region of the hippocampus (Yassa et al. 2010). The results of the recent study by Stark et al. (2013) suggest that it may be possible to further characterize impairment in mnemonic processes in older adults through specific patterns of impairment in individuals with aMCI (impaired recognition and pattern separation), cognitively normal individuals with subtle cognitive decline (intact recognition and impaired pattern separation), and those who are aging successfully (intact recognition and intact pattern separation).

Holden et al. (2013) also examined age-related variability in visual object pattern separation efficiency utilizing a task that involved intentional encoding (Toner et al. 2009; Yassa et al. 2011). Similar to previous studies that divided older adults into impaired and unimpaired groups (Holden et al. 2012; Stark et al. 2010, 2013), older adults were divided into two groups based on standardized verbal learning task performance. The data revealed that young adults and older–unimpaired adults outperformed older–impaired individuals when correctly identifying lure items as similar, suggesting that visual object pattern separation was less efficient only in this subset of older adults. All groups performed similarly in the correct identification of new and repeated stimuli, suggesting that the deficits were not due to general recognition memory impairment. The results of this study further support the idea that there may be individual variability in pattern separation ability among cognitively normal older adults and that this variability occurs across multiple domains, including memory for visual objects and spatial memory. In addition, the findings discussed above by Stark et al. (2013) and Yassa et al. (2010) provide evidence for a link between impaired pattern separation and a diagnosis of aMCI, which is a risk factor for the development of Alzheimer's disease (AD).

Is Memory Decline in Aging and Alzheimer's Disease Linked to Pattern Separation?

In the USA, AD is the most common cause of dementia in older adults and accounts for 60–80% of dementia cases (Alzheimer's Association 2012). In the year 2012, an estimated 5.4 million Americans were diagnosed with AD; however, this number

is projected to increase to 11–16 million by 2050 (Alzheimer's Association 2012). As a result of the aging "baby boom" generation and increasing longevity in the US population, the disease is a growing public health concern with costs estimated to reach $ 200 billion in 2012. Although a number of risk factors for AD have been discussed (e.g., diagnosis of mild cognitive impairment, family history of AD, genetics), one of the most well-documented risk factors for the disease is increasing age (Kamboh 2004). Therefore, a major aim of recent research has been to identify early indicators of cognitive dysfunction in older adults.

Age-related cognitive impairment has been documented in a variety of domains. However, one of the most commonly reported neurocognitive deficits associated with aging is memory decline. Although not all aspects of memory are equally affected by aging (e.g., source vs. item memory), some domains such as episodic memory appear to be particularly sensitive to age-related change. Episodic memory deficits have been well documented in older adults (Rand-Giovannetti et al. 2006) and are a prominent symptom of AD that may be detectable many years prior to disease onset (Bondi et al. 1999). Episodic memory impairment has also been documented in cognitively normal older adults who are at risk of AD by virtue of a diagnosis of mild cognitive impairment (Hodges et al. 2006) or genetic factors (Saunders et al. 1993). Episodic memory may rely on the functioning of the temporal and frontal lobes; however, the functional contributions of each cortical region can be dissociated (Kramer et al. 2005). The hippocampus may be important for memory accuracy, whereas the frontal lobes may be more important for decision-making and strategic aspects of episodic memory (Kramer et al. 2005). As discussed above, the hippocampus may support specific mnemonic processes, such as pattern separation, that may facilitate the encoding and subsequent retrieval of episodic memories to enhance memory accuracy. A key feature of episodic memory that differentiates it from other types of memory is that the elements of an episodic memory must be associated with a context to demarcate the episode in space and time. In addition, a pattern separation mechanism may be necessary to separate the elements of different episodic memories to avoid interference (Gilbert et al. 2001). The studies reviewed above provide evidence that less efficient pattern separation in older adults may contribute to age-related memory deficits, particularly in situations when interference is high. The identification of a key mnemonic processing deficit in pattern separation may result in behavioral interventions that structure daily living tasks to mitigate interference and potentially improve episodic memory in older adults.

Normal and pathological aging may have differential effects on subregions of the hippocampus. The DG subregion may be particularly susceptible to age-related changes in humans; however, there may be less impact on pyramidal cells in the CA subregions (Small et al. 2002). In contrast, the CA subregions may be more vulnerable to pathological changes associated with AD (Apostolova et al. 2010; Braak and Braak 1996; Price et al. 2001; Small et al. 2011; West et al. 2000). As mentioned previously, a primary goal in AD research is to identify risk factors and preclinical markers of the disease in older adults. Given the differential effects of normal aging and AD on the various subregions of the hippocampus, tasks that are sensitive to dysfunction in particular subregions, such as measures of pattern separation, may

help to differentiate between cognitive impairment associated with normal aging and pathological changes associated with AD. In support of this idea, Stark et al. (2013) found unique patterns of performance in a visual object pattern separation task in individuals with aMCI, cognitively normal older individuals with subtle cognitive impairment, and cognitively normal older adults. In addition, another recent study utilized the continuous recognition memory task for visual objects (Kirwan and Stark 2007) used in previously mentioned aging studies (e.g. Toner et al. 2009; Yassa et al. 2011) to behaviorally examine pattern separation in individuals diagnosed with aMCI or mild AD (Ally et al. 2013). The authors also examined how performance changed as a function of the lag between the study and test objects. The data revealed that behavioral pattern separation rates decreased as a function of increasing lag between interfering objects in individuals diagnosed with aMCI. Performance of the aMCI group matched controls at the shortest lag of four interfering objects; however, the group performed comparably to the AD group at the largest lag of 40 interfering objects. The AD group was significantly impaired relative to controls across all lags. The data provide additional evidence for impaired visual object pattern separation associated with aMCI and offered some of the first behavioral evidence that pattern separation may be further impaired in those diagnosed with mild AD (Ally et al. 2013). Recent studies have begun to examine the relationship between standardized memory test performance and specific hippocampal subregion function (Brickman et al. 2011). Behavioral tasks that measure specific mnemonic processes, such as the previously reviewed pattern separation tasks, may be highly sensitive to subtle age-related changes. These tests may be used one day in conjunction with standardized neuropsychological measures to help differentiate normal aging and AD.

Pattern Separation Beyond the Hippocampus

Although most of the studies examining the neural substrates of pattern separation have focused on the DG/CA3 subregions, there is growing evidence that other regions of the brain may also support pattern separation (reviewed by Hunsaker and Kesner 2013; Yassa and Stark 2011). For example, researchers have reported that pattern separation may be facilitated by the CA1 hippocampal subregion for temporal order information (Gilbert et al. 2001; Hunsaker et al. 2008; Kesner and Hunsaker 2010; Kesner et al. 2010, 2011), the perirhinal cortex for visual object information (Barense et al. 2010; Bartko et al. 2007a, b; Burke et al. 2011; Gilbert and Kesner 2003), the piriform cortex for olfactory information (Barnes et al. 2008; Sahay et al. 2011; Wilson 2009; Wilson and Sullivan 2011), and the amygdala for reward value (Gilbert and Kesner 2002). Many of these regions of the brain undergo age-related change. For example, age-related functional changes have been observed in perirhinal cortex in rodents (Moyer and Brown 2006) and humans (Ryan et al. 2012). However, aging studies have reported that total neuron numbers in rodents (Rapp et al. 2002) and cortical volumes in humans (Insausti et al. 1998) are largely preserved in the perirhinal cortex. Although there is growing evidence to

suggest that the human hippocampal subregions support pattern separation based on overlapping object features (Bakker et al. 2008; Kirwan and Stark 2007), there are data to suggest that perirhinal cortex may also play a role in pattern separation for visual objects. Rodent studies have shown that the perirhinal cortex may distinguish between visual objects with overlapping features to reduce feature ambiguity (Bartko et al. 2007a, b; Bussey et al. 2003, 2006; Gilbert and Kesner 2003; Norman and Eacott 2004). As discussed previously, data from the laboratory of Carol Barnes (Burke et al. 2010, 2011, 2012) provide evidence that age-related changes in the perirhinal cortex of rodents may impair pattern separation for visual objects. Therefore, functional changes in the perirhinal cortex of older animals and possibly humans may affect pattern separation for visual objects. As proposed by Burke et al. (2011), future studies should investigate whether the connections between the hippocampus and perirhinal cortex are necessary to support pattern separation. It is clear that additional research is needed to examine the relationship between age-related changes in brain regions outside of the hippocampus and pattern separation for various types of information. These studies are needed in animal models and also in humans using functional neuroimaging techniques. Although numerous computational and theoretical models have been published to describe potential neural mechanisms that may support pattern separation in the hippocampus, very little is known about pattern separation mechanisms in other brain regions. Therefore, future studies are needed to explore potential neural mechanisms for pattern separation beyond the hippocampus.

Conclusions

In conclusion, memory deficits have been well documented in older adults and may serve as an early indicator of MCI or AD in some individuals. Pattern separation may be a key mechanism for reducing interference among similar memory representations to enhance memory accuracy. Growing evidence suggests that brain regions critical to pattern separation, including the DG and CA3 hippocampal subregions and the perforant path input, may be particularly susceptible to adverse age-related changes. A growing literature indicates that pattern separation becomes less efficient as a result of normal aging in both humans and animal models. It is possible that this decreased pattern separation efficiency contributes to memory deficits, including episodic memory impairment, associated with aging. Given the evidence reviewed in the present chapter, it is clear that additional research is needed to examine the relationship between pattern separation and brain changes associated with aging and neurodegenerative disease. In addition, there is a need for additional research to examine this relationship in animal models. Through continued research we hope that new and innovative behavioral approaches and methodologies will be developed for future aging studies investigating: (1) episodic memory impairment, (2) hippocampal subregion specific epigenetic and transcriptional changes, (3) structural and functional changes in the hippocampus using neuroimaging techniques, and (4) the differentiation of preclinical markers of AD from those of

normal aging. The findings may have important implications for studies in humans and translational studies in animal models to shed new light on processes that may contribute to hallmark age-related episodic memory deficits. Finally, we would like to acknowledge the work of Dr. Raymond Kesner and his significant contributions to our understanding of processes supported by the hippocampus such as pattern separation. The innovative behavioral tasks developed in his laboratory for use in rodents have set the foundation for many of the studies discussed in this review.

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