Chapter 7
Resolving Interference: The Role of the Human Hippocampus in Pattern Separation

C. Brock Kirwan and Michelle I. Nash

Interference in Memory

The medial temporal lobe (MTL) is critically involved in memory for facts and events (Kesner 2009; Squire et al. 2004). Damage to MTL structures, including the hippocampus and surrounding cortex (perirhinal, entorhinal, and parahippocampal), results in profound anterograde amnesia and temporally graded retrograde amnesia (Scoville and Milner 1957; Squire et al. 1989). Computational models of MTL function commonly posit that the MTL cortex establishes representations of statistical regularities in the environment through repeated exposures whereas the hippocampus is capable of establishing rapid, distinct, and nonoverlapping representations (O'Reilly and Rudy 2000, 2001). Several computational models of hippocampal function posit that sparse connections within the hippocampus allow for the establishment of distinct memory representations through a process known as pattern separation (McClelland et al. 1995; Norman and O'Reilly 2003; O'Reilly and Rudy 2001; Rolls and Treves 1998). This ability to establish nonoverlapping representations is essential for effective episodic memory (Tulving 2002) and allows the system to avoid "catastrophic interference" where retrieving one memory representation cues the retrieval of many unrelated memory representations (McClelland et al. 1995; McCloskey and Cohen 1989).

Pattern completion is the complementary computational process to pattern separation whereby previously stored representations are retrieved when given a noisy or degraded cue. Pattern separation and pattern completion are not mutually exclu-

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C. B. Kirwan (✉) · M. I. Nash
Department of Psychology and Neuroscience Center, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA
e-mail: kirwan@byu.edu

M. I. Nash
e-mail: michelle.nash13@gmail.com

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sive processes that occur in distinct neuroanatomical locations. Indeed, computational principles predict that they necessarily must occur in the same brain region to be useful. However, different brain regions are differentially biased toward either pattern separation or pattern completion. The hippocampus, and the dentate gyrus (DG) in particular, is proposed to be biased toward pattern separation whereas later stages of the hippocampus, including the CA3 and CA1 in addition to the MTL cortex, are proposed to be biased toward pattern completion.

Effective pattern separation allows one to resolve interference between potentially overlapping memories. Day-to-day events have a great deal of overlapping information (such as location, people present, or time of day), but an effective episodic memory system must be able to resolve this interference in establishing unique representations for each new event that are later able to be retrieved individually. For example, the episode of eating breakfast on any particular morning is encoded separately from other similar episodes despite the potential overlap in location, time of day, and actors present. Interference between information acquired at different times is thought to be a major source of forgetting (Crowder 1976; Keppel 1984). Consequently, there is a long tradition of studying the effects of interference on memory. An early account of interference rested on the evidence for consolidation of memories over time, and has thus been termed consolidation theory. Müller and Pilzecker (1900) observed that a list of items was better remembered if learning was followed by a quiescent period before testing than if followed by another period of mental activity, such as learning another list. This phenomenon, when new information interferes with the retrieval of older information, is termed retroactive interference (RI). A classic source of evidence for consolidation theory comes from the studies by Jenkins and Dallenbach (1924), in which participants learned a list of words either early in the day or late in the evening. Testing occurred 8 h later, after either a full night's sleep or 8 h of normal daily activity. Retention was better for the list following sleep, indicating that the intervening activity during the day interfered with the material learned in the morning.

It seems intuitive that greater RI would be achieved when the intervening material is more similar to the original material. However, when the intervening material is exactly similar (i.e., identical) to the original material, there is no RI (performance improves instead). Thus, there should be a U-shaped pattern of performance, as performance is unaffected (or even benefited) by dissimilar or identical material, but is harmed by similar material. This theory, known as the Skaggs–Robinson law (Robinson, 1927; Skaggs 1925), lost appeal because of failure to demonstrate the full theoretical curve in a single experiment (Slamecka and Ceraso 1977).

Interference theory was heavily influenced by Underwood's (1957) review of proactive interference (PI). In the case of PI, previously learned material is detrimental to the memory performance on a subsequently learned list. Underwood demonstrated by a review of the literature that over a 24-h period, participants showed a 75 % reduction in memory for a verbal list, and that most of this reduction could be accounted for by previous, massed learning in the laboratory setting. He went so far as to observe that RI probably had little to do with this forgetting. Thus, it seemed plausible that forgetting would be explained in terms of PI. However, criti-

cal for the phenomenon of PI is the spontaneous recovery of the previously learned material, and PI offers no mechanism for this spontaneous recovery other than the simple passage of time. McGeoch's (1932) famous objection to decay theory, that time per se does not cause memories to fade any more than it causes rust to form, also applies to spontaneous recovery (Crowder 1976). Furthermore, PI could not account for the findings of Jenkins and Dallenbach (1924) and others (e.g., Ekstrand 1967) regarding the protective nature of sleep on memory. Proactive interference, and interference theory in general, has since fallen out of favor as a research topic, (for review, see Wixted 2004), but interference is nevertheless, still regarded as "a primary source of forgetting in explicit memory" (Lustig and Hasher 2001, p. 618).

Although interference theory today is not as heavily researched as it was for the first three quarters of the last century, it has not disappeared completely. Recent theoretical and empirical work (Blank 2005) has continued to test the predictions of interference theory. Of particular interest are neuropsychological and neuroimaging studies that bear on the question of how the brain deals with interference. Neuropsychological studies have indicated that damage to the frontal lobe increases the susceptibility to PI (e.g., Shimamura et al. 1995). Consistent with this, a number of neuroimaging studies that investigated the effects of interference in a number of different interference paradigms have reliably shown frontal activity during encoding (Henson et al. 2002) and retrieval (Badre and Wagner 2005; Henson et al. 2002; Herrmann et al. 2001; King et al. 2005; LePage et al. 2005) of high-interference materials. This is consistent with an interpretation that PI is caused by failures in source monitoring, a process known to depend on the frontal lobes (Johnson et al. 1993). Interestingly, many of these studies of PI fail to demonstrate a modulation of MTL activity as a function of interference (however, see LePage et al. 2005), although neuropsychological studies of patients with MTL damage suggest that amnesic patients are more susceptible to interference. Traditional tests of PI contrast two conditions that both require explicit or declarative memory. For example, in the AB–AD paradigm participants learn a list of paired-associates, the AB list, followed after a variable delay by learning a second list with the same stimulus terms paired with new response terms, the AD list. Recalling the AB list and recalling the AD list are both likely to engage the hippocampus strongly. The lack of neuroimaging evidence for activity modulation in the MTL as a function of interference, therefore, may be due in part to the fact that the critical comparison between two conditions is known to activate the MTL. In support of this view, Henson et al. (2002) show a main effect of retrieval in the MTL when collapsing across conditions of high and low interference as compared to a control condition.

Thus, there is a long tradition in psychology of studying the effects of interference on memory, although the failure of interference theory to tell a cohesive story about the characteristics and limitations of long-term declarative memory has caused it to fall out of favor in current theories of cognitive psychology and cognitive neuroscience. Recently, however, there has been a resurgence of interest in interference as a driving factor of hippocampal activity due in part to the suggestion that one of the main functions of the hippocampus is to perform pattern separation for similar or overlapping stimuli (Yassa and Stark 2011).

Testing Predictions of Computational Models

Various computational models propose that the hippocampus uses sparse representations to reduce representational overlap (Burgess and O'Keefe 1996; Hasselmo and Wyble 1997; McNaughton and Morris 1987; Norman ad O'Reilly 2003; Rolls 1989; Rolls and Treves 1998). Using a sparse representation rather than extracting statistical regularities from the environment allows the hippocampus to better represent overlapping stimuli without interference, compared with the cortex. Thus, damage limited to the hippocampus should result in an increased susceptibility to interference. Furthermore, due to the dual demands of encoding and retrieval, as stimulus similarity increases pattern separation processes will give way to pattern completion, and previously stored representations will be activated.

Computational models commonly posit that pattern separation is accomplished as the DG relays a sparse, orthogonalized representation to the CA3 via mossy fiber projections. This representation can be retrieved by reactivating a subset of the original pattern through pattern completion. The CA3 may therefore, show evidence of both pattern separation and pattern completion depending on the task demands and the active afferents to the area (Guzowski et al. 2004). Pattern separation would be evidenced by distinct representations and low representational overlap, while high representational overlap would be consistent with pattern completion.

A number of studies have tested the predictions of computational models using rodent models, particularly in the spatial and temporal domains. For example, Gilbert and colleagues (Gilbert et al. 1998) have demonstrated that lesions to the DG in rats disrupted discrimination of near spatial locations while leaving discrimination performance intact for distant locations. Leutgeb and colleagues (S. Leutgeb et al. 2004) also examined the changes in firing characteristics of CA3 and CA1 in response to changes in the environment and showed that place fields in CA1 showed a great deal of overlap between similar environments. When tested in the same environment in different rooms, the active set of neurons overlapped almost as much as on repeat tests in the same environment in the same room. Place cells in CA3, however, showed distinct firing patterns in different rooms, even in the similar environments, with the overlap between the two rooms being no more than would be expected for independent firing. In this case, the CA3 neurons show a large amount of pattern separation (Guzowski et al. 2004), while CA1 neurons show evidence of pattern completion.

There are also limited electrophysiological data from human patients supporting a role of the hippocampus in pattern separation. These data come from studies of patients with pharmacologically intractable epilepsy who have been implanted with depth electrodes in the MTL to localize the focus of seizure onset (Fried et al. 2002; Fried et al. 1997). Quiroga and colleagues (Quiroga et al. 2005) reported evidence for neurons in the MTL that showed view invariant responses to familiar stimuli. These cells demonstrate the sparse representation that is predicted by the computational models outlined above; however, neurons throughout the MTL demonstrated this sparse representation. Further, this study did not explicitly manipulate inter-

stimulus similarity or interference, so it is difficult to draw conclusions regarding pattern separation processes.

To date, the majority of studies investigating pattern separation processes in the human hippocampus have used functional neuroimaging and behavioral tests of healthy young adults, healthy older adults, and patients with limited hippocampal damage. The results of these studies, reviewed below, are largely consistent with the predictions of computational models. Specifically, they show that the DG is involved in pattern separation in a number of modalities.

Functional MRI and Pattern Separation

A number of descriptive models of MTL function suggest a functional distinction between the hippocampus and the adjacent MTL cortical areas. According to the various descriptive models, the hippocampal region underlies conjunctive (O'Reilly and Rudy 2000; Sutherland and Rudy 1989), associative (Brown and Aggleton 2001), or recollective (Yonelinas 2002) processing, while the adjacent cortex supports memory for single items (Brown and Aggleton 2001) or familiarity processes (Yonelinas 2002). Within this class of models, the distinction between hippocampal and cortical processing is qualitative rather than quantitative, although the proposed processes often can be couched in terms of computational processes. For example, configural representations may be established in the hippocampus through setting up distinct, pattern-separated representations of external stimuli (O'Reilly and Rudy 2000, 2001). Pattern separation is also necessary for episodic and source memory (e.g., remembering where one parked one's car from day to day), while pattern completion is necessary for recollective processing. In spite of this apparent mapping, computational and descriptive models of MTL function make different predictions. For example, according to the descriptive models, lesions restricted to the hippocampus should disproportionately affect relational memory, while not adversely affecting memory for single items. However, computational models (e.g., Norman and O'Reilly 2003) predict that in some cases (e.g., when inter-stimulus similarity or pattern separation demands are increased) selective hippocampal lesions will also impair item memory (see Holdstock et al. 2002a). We suggest that the results of many experiments meant to test the predictions of descriptive models of MTL function (e.g., the distinction between hippocampus-dependent recollection and cortex-dependent familiarity) can be better understood in terms of the underlying computational principles rather than qualitative psychological phenomena.

For example, Kirwan and Stark (unpublished observations) used functional MRI (fMRI) to examine the processes of encoding and later recalling stimulus pairings within the MTL. Fifteen participants performed an encoding and then a cued-recall task while undergoing fMRI scanning. Participants were first familiarized to a set of card-like stimuli that varied on three dimensions: the shape of the marking on the card, the color of the marking, and the background pattern of the card (Fig. 7.1a). Following stimulus familiarization, participants performed a series of

study/test blocks in which they were first shown a series of card pairs and instructed to memorize the pair for a later memory test. Each study phase consisted of three pairs presented twice in a random order. Following the study phase, participants performed a cued-recall task in which they were shown one card from a pair and asked to recall one dimension of the paired card (shape, color, or background). Each dimension of each pair was tested on different trials in the test phase. Pairs that were well learned were dropped from subsequent study/test blocks while pairs that were not learned were retained thus maintaining a constant level of performance across study/test blocks. For the fMRI analysis, study trials were sorted into four "memory strength" bins according to subsequent performance on the test block with the lowest memory strength reflecting near-chance performance and the highest memory strength reflecting perfect performance. During encoding, fMRI data analysis revealed activity changes associated with subsequent memory strength in bilateral hippocampus (Fig. 7.1b–c). Activity in this region was highest while studying pairs that were subsequently categorized as low memory strength. Activity decreased in a linear fashion as subsequent memory performance increased (Fig. 7.1d). FMRI activity during cued recall test trials on which participants were correct (hits) increased with increasing memory strength, not only in the hippocampus but also in

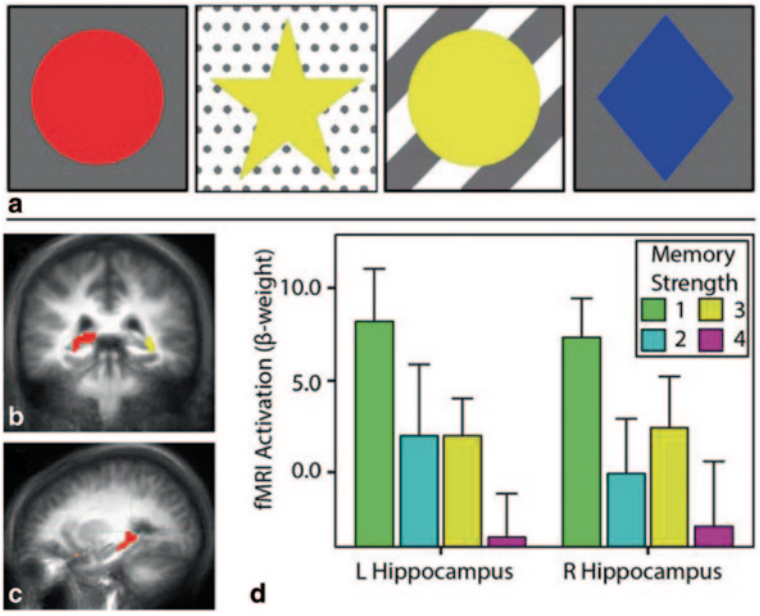

Fig. 7.1 Stimuli and fMRI results from a cued-recall paradigm. **a** Stimuli consisted of card-like stimuli that could vary in foreground shape, color, and background pattern. Subjects studied pairs of cards at encoding. At test, one card from the pair was presented and subjects were prompted to retrieve one aspect (shape, color, background) of the paired card. Pairs of stimuli were binned according to the number of features correctly retrieved into memory strength bins 1 (low) to 4 (high) (**b–c**), A contrast of encoding trials in memory strength bins 1 vs. 4 revealed activation in the left (red) and right (yellow) hippocampus where activity decreased in a linear fashion (**d**)

the adjacent cortical structures of the MTL. This pattern of results was also found in a distinct region of perirhinal cortex when just the miss trials were analyzed. While the pattern of results during the cued-recall trials is consistent with either a memory strength or recollection interpretation of MTL function (i.e., greater activity associated with the retrieval of more information or higher confidence responses), the pattern of results during encoding is more difficult to interpret. Subsequent analyses ruled out a novelty-detection response or a response as a function of the amount learned on each trial. One possible explanation is that pairs in the lowest memory strength bins were those with the highest pattern separation demands. Although the factorial combination of a limited number of stimulus features allowed us to test a relatively large stimulus set with limited behavioral responses, it also presented a unique challenge to participants. While overlap between pairs was intentionally limited, it could not be altogether eliminated. Interstimulus interference increased as more stimulus pairs with overlapping features were introduced into the experiment. Therefore, the pattern separation demands of encoding the stimulus pairs are potentially quite high. Here, we are operationally defining high pattern separation demands as any time the mnemonic demands of the task are high due to increased interstimulus overlap. This occurred in the current paradigm because the task demands required participants to attend to the three stimulus features (color, shape, background) and these features repeated in different combinations across stimulus pairs. This interpretation is supported by examination of a representative participant's behavioral performance (Fig. 7.2). Some pairs were learned quickly and the estimate for the probability for a subsequent correct response to that stimulus (our estimate of memory strength; see Law et al. 2005) increased rapidly. However, other stimulus pairs were not learned at all despite repeated testing. Further, these unlearned pairs seem to come later in the experiment as the potential for interference has built up with newer stimuli. Although the computational models of hippocampal function outlined above predict a high level of hippocampal activity due to pattern separation demands during the encoding phase of both preliminary experiments, the observed increases in hippocampal activity at time of encoding in this experiment cannot be attributed unequivocally to pattern separation mechanisms.

To explicitly test pattern separation processes in the MTL, Kirwan and Stark (2007) developed a continuous recognition paradigm that directly manipulated the similarity between stimuli in order to drive pattern separation demands. We hypothesized that a task that placed high demands on pattern separation processes would drive hippocampal activation. We further hypothesized that other MTL cortical regions would fail to show a distinction among stimulus types based on pattern separation demands. Rather than a standard study/test recognition memory paradigm, this study used a continuous recognition paradigm in which participants were required on each trial to encode stimuli to a sufficient threshold that they would be able to quickly and accurately recall the encoded information, compare it with current information, and determine whether or not they had previously encountered the information. Participants were shown either a series of objects (experiment 1) or a series of faces (experiment 2) while undergoing fMRI scanning. They were asked to determine whether each picture was new

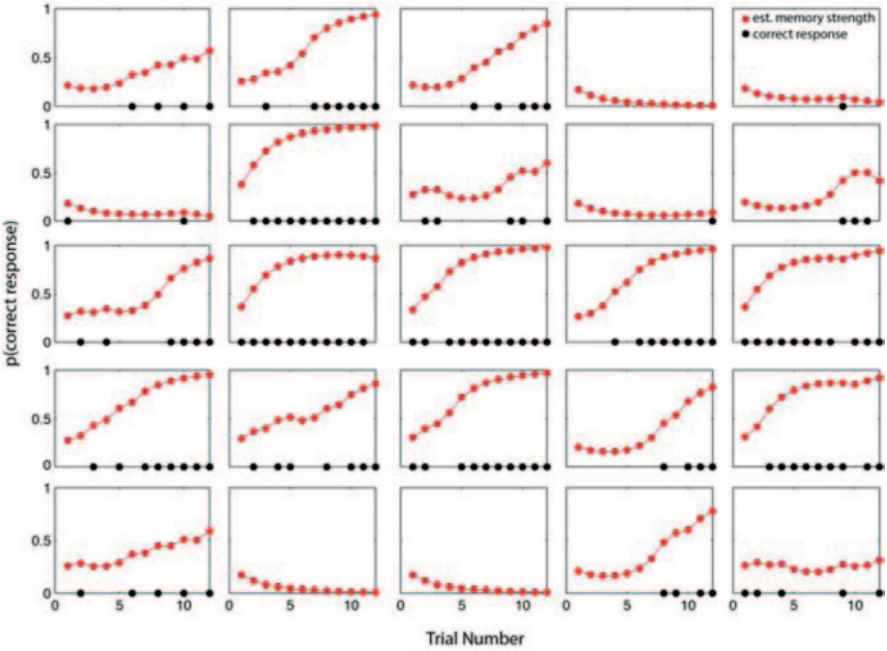

Fig. 7.2 Example performance on the paired-associates learning task. Subjects learned a series of pairs of cards, three pairs at a time. Each plot represents performance for one pair. Pairs were tested 12 times (four trials for each dimension of the test card). *Black dots* indicate correct trials (hits). *Red dots* indicate estimated memory strength for each pair. While some pairs were learned almost immediately, others were never learned

(never seen before), old (exact image as previously seen or "repeat"), or similar (similar to a previously seen image, but not exact or "lure"; Fig. 7.3). Repeated and lure items were separated from their first presentations by 10–40 items (or 25–100 s). This particular task places high demands on the participant and their ability to resolve memory interference and accurately perform pattern separation. The "recall to reject" strategy needed to successfully complete this task was supported by reaction time (RT) data; participants took longer to accurately identify a stimulus as "similar", presumably due to the process of recalling previously encoded information, comparing the current stimulus to the recalled stimuli, and then correctly identifying the stimulus as "similar". Furthermore, fMRI data from both experiments showed that the hippocampus was the only MTL structure to provide differentiated activation that distinguished the various trial types. Specifically, pattern of fMRI activity in the hippocampus was different for hits (correctly identifying a repeat stimulus as "old"), lure correct rejections (correctly identifying a similar stimulus as "similar"), and lure false alarms (incorrectly identifying a similar stimulus as "old"). This pattern of differentiation was not displayed in the parahippocampal gyrus.

Fig. 7.3 Example target-lure stimulus pairs from the continuous recognition paradigm

Bakker and colleagues (Bakker et al. 2008) sought to differentially determine which subregions of the hippocampus are involved in pattern separation and which are involved in pattern completion. These authors again used a continuous recognition fMRI task consisting of new, repeated, and lure objects. However, instead of requiring participants to make an overt memory decision about each stimulus, they asked participants to identify whether an object was typically found indoors or outdoors. This incidental encoding task was used to remove any explicit memory confounds from the study and test the default hippocampal bias toward pattern separation or pattern completion. In addition, this methodology more closely resembled pattern separation and pattern completion tasks previously utilized in free exploration rodent studies. Using this indirect task, the authors hypothesized that lure stimuli would generate one of two types of activity within hippocampal subregions which could then be used to infer pattern separation or pattern completion processes. If lures generated a similar level of activity as new objects for a given subregion, it would be involved in pattern separation. In contrast, if lures generated a similar activity level as repeated objects a given subregion would be involved in pattern completion. Although high-resolution fMRI scans were performed in this study, resolution is still not sufficient enough to distinguish between CA3 and DG subregions of the hippocampus; therefore, these two regions were combined in the analyses. However, given that the DG projects predominantly to the CA3 region it is unproblematic to pair these regions together. Hippocampal activity inclined toward pattern separation in the CA3/DG subregions and activity favoring pattern completion was observed in the CA1 subregion as well as several other MTL regions. These results are in alignment with the prediction from computational models that the DG is primarily involved in pattern separation processes. DG activity has been observed to be elevated in amnestic mild cognitive impairment (aMCI), a putative precursor to Alzheimer's disease. This elevated activity may reflect either compensatory recruitment of additional neurocognitive resources or, alternately, aberrant activity that directly contributes to the behavioral memory impairment observed

in aMCI. Bakker and colleagues (Bakker et al. 2012) administered a low dose of levetiracetam, an antiepileptic drug known to reduce hippocampal hyperactivity (Koh et al. 2010), to a group of aMCI patients. Drug treatment led to significant behavioral improvements in the explicit version of the continuous recognition task as well as reductions in activity in the CA3/DG of the treatment group. The authors interpreted these results as consistent with a drug-dependent shift from pattern completion processes to pattern separation processes in the hippocampus.

Recently, work in this area has shifted to examining the transfer function (Guzowski et al. 2004; Kumaran and Maguire 2009; Leutgeb et al. 2007; Leutgeb, 2008) in subregions of the hippocampus (i.e., CA3/DG vs. CA1) and other cortical areas. The hallmark of pattern separation is a step-like change in activity in response to gradual changes in stimulus input. This kind of pattern separation response has been demonstrated in place cell responses in the CA3 of rats in response to gradual changes across similar environments (Leutgeb et al. 2004). Pattern completion, on the other hand, should be evidenced by more gradual changes in output in response to gradual changes in input (Yassa and Stark 2011).

Lacy and colleagues (Lacy et al. 2011) used an incidental continuous recognition paradigm similar to Bakker et al. (2008). Based on normative similarity ratings, target-lure pairs were split into high- and low-similarity categories. Consistent with the findings of Bakker et al. (2008), activity in the CA3/DG was consistent with pattern separation processes whereas activity in the CA1 was more consistent with pattern completion processes. When examined separately, the difference between CA3/DG and CA1 was most pronounced for the high-similarity stimuli. Considering fMRI activation likely reflects input into an area (Logothetis et al. 2001), this finding is consistent with a differential transfer function between these regions where early stages of the hippocampus are more sensitive than later stages to small changes in input.

Rather than using a "mnemonic similarity" index, Motley and Kirwan (2012) explicitly manipulated target-lure similarity by rotating objects between study and test trials in a continuous recognition paradigm. These authors hypothesized that pattern-separation regions would have large differences in fMRI activity in response to small changes in stimulus similarity (i.e., small degree of rotation) and pattern-completion regions would have large differences only when stimulus similarity exceeded a threshold. They further hypothesized that intentional encoding would enhance the distinction between "old" and "similar" (i.e., rotated) stimuli and that top–down processing of task demands (dependent upon whether the task involved intentional encoding or incidental encoding) would enhance ventral stream inputs, both of which would aid hippocampal pattern separation. Individuals participated in either an intentional or incidental encoding pattern separation task. Individuals in the intentional paradigm were shown a series of objects and asked to identify them as either "new" (novel stimuli), "old" (previous seen stimuli), or "rotated" (previously seen stimuli from another angle). Independent behavioral testing indicated that rotations of 15°, 25°, 35° and 55° lead to a roughly linear change in behavioral performance from mostly false alarms (calling rotated stimuli "old") to mostly correct rejections (calling rotated stimuli "rotated"). Participants in the incidental paradigm were shown the same stimuli as in the intentional paradigm, but were

asked to identify objects as either "toy" or "not toy". The authors found that for the intentional encoding task, behavioral accuracy increased as the objects became more dissimilar in a linear fashion (i.e., as the rotation angle increased); however, activity in the hippocampus and posterior parahippocampal cortex was curvilinear, with a sharp change in fMRI activation from exact repeats to 15° rotations but a smaller change in activity between larger rotation differences. This pattern of large changes in fMRI activity in response to small changes in the input was taken as evidence of pattern separation processes. Task demands determined laterality in left and right medial temporal lobe. The authors found activity in the left hippocampus and posterior parahippocampal cortex consistent with pattern separation (i.e., large activity differences for small changes in the input) during the incidental encoding condition. In contrast, activity in the right hippocampus and parahippocampal cortex was consistent with pattern separation during the intentional encoding task. The finding of pattern-separation-like signals in the parahippocampal gyrus is consistent with rodent work that has shown a deficit in pattern separation for objects following perirhinal cortex damage (Kesner et al. 1993; 2001). The finding of lateral differences between the two tasks was interpreted in terms of semantic vs. spatial task demands in the incidental ("toy" or "not toy") and intentional ("old", "new", or "rotated") conditions. Furthermore, ventral stream activity depended upon the task encoding condition (i.e., whether the task involved intentional or incidental encoding). Specifically, there was decreased activation in the ventral stream during the incidental encoding task compared to intentional encoding, providing evidence for a top–down influence on hippocampal activity during the intentional condition. The authors speculated that the ventral stream inputs modulate information processing and are subsequently amplified by the hippocampus, which then conducts pattern separation processes.

Interference Following Hippocampal Damage

The computational models of hippocampal function outlined above predict a specific pattern of impairments when damage is limited to the hippocampus, namely a disproportionate impairment in pattern separation, behaviorally demonstrated as increased susceptibility to interstimulus interference. However, neuropsychological damage is rarely so selective as to affect only the hippocampus. Nevertheless, it is instructive to consider cases of amnesia caused by damage to structures including, or related to the hippocampus, as they demonstrate instances of hippocampal dysfunction. When considering cases of amnesia with a wide range of etiologies, it is apparent that amnesic patients are indeed more susceptible to interference than matched controls (for review, see Lustig and Hasher 2001).

The data supporting this claim come from a number of studies, each of which demonstrate significant PI (Kinsbourne and Winocur 1980; Mayes et al. 1987; Warrington and Weiskrantz 1974, 1976, 1978; Winocur and Moscovitch 1996) and RI (Winocur and Weiskrantz 1976) in amnesic patients. In each of these studies, patients and matched controls learned semantically related paired associates in the

AB–AD paradigm. Patient's performance, however, shows improvement relative to controls when the amount of interference is reduced, for example, when the AD list is not semantically related to the AB list (Winocur and Weiskrantz 1976), or the number of possible responses is limited (Kinsbourne and Winocur 1980; Warrington and Weiskrantz 1974, 1978). When the task has implicit memory instructions, i.e., when participants are given free-association instructions, controls' performance falls to the level of amnesics'. These data indicate that amnesic patients do not have the mechanisms available to resolve cases of high overlap (i.e., pattern separation) and must therefore rely on other memory mechanisms (i.e., cortical mechanisms) that are more prone to generalization and thus more susceptible to interference. This is not to say that amnesia per se is responsible for the increased susceptibility to interference (see Mayes and Downes 1997). Rather, the two are symptoms of damage to the MTL memory system.

Hippocampal amnesics are able to overcome this increased susceptibility to interference if their memory is probed in an appropriate way. Holdstock and colleagues (Holdstock et al. 2002b) describe the case of patient YR, who suffered selective adult-onset hippocampal damage. In tests of recognition memory, YR is unimpaired relative to matched controls for single items when tested in both forced choice and yes/no recognition formats (Holdstock et al. 2000; Mayes et al. 2002; Mayes et al. 2001). However, when target and lures were made more similar (i.e., interference was increased), YR's yes/no item recognition was impaired relative to controls (Holdstock et al. 2002b), indicating a pattern separation deficit (but see Bayley et al. 2008). Duff and associates (Duff et al. 2012) also demonstrated that when interstimulus similarity increased, patients with hippocampal damage were differentially impaired in a memory task relative to matched controls.

In a recent study, Kirwan and colleagues (Kirwan et al. 2012) hypothesized that memory-impaired patients with hippocampal damage would have pattern separation impairments which would present as an inability to correctly identify lure stimuli as similar compared to previously presented target stimuli; instead they speculated that these individuals would identify similar objects as "old". Three memory-impaired individuals with damage thought to be limited to the hippocampus and 11 controls performed baseline recognition memory tests for faces and objects. During the study phase, participants were shown a series of stimuli and asked to rate them as either "pleasant" or "unpleasant" and were told their memory of the stimuli would be tested later. After a brief delay, participants were shown a series of target (previously presented) and novel stimuli and were asked to identify which stimuli were "old" (i.e., targets) and which were "new". Following the baseline task, participants also completed a series of experimental tasks where interstimulus similarity was explicitly manipulated. The study phase of the experimental task also consisted of a series of stimuli (faces or objects), which the participants rated as either "pleasant" or "unpleasant". During the testing phase, participants were shown either repeat, similar, or novel stimuli and were asked to identify them as "old", "similar", or "new" respectively. In the face condition, similar stimuli consisted of the same individual as previously shown, but a different photograph of them in which some characteristic(s) differed (such as gaze direction, expression, hairstyle, clothes,

etc.). In the object condition, similar stimuli consisted of the same type of object as previously shown, but a different specific example. Memory-impaired patients with hippocampal damage did not differ from controls in baseline memory recognition. However, patients were impaired compared to controls in the pattern separation conditions with significantly reduced "similar" responses to lure stimuli (corrected for overall "similar" response rates). Contrary to what was predicted, patients were not biased toward identifying similar objects as "old", rather they were more likely than controls to respond to similar objects as either "old" or "new" verses the correct response of "similar". The authors speculated that this response pattern indicates a pattern separation deficiency at the time of encoding for memory-impaired patients with hippocampal damage.

The preceding studies examined visual pattern separation abilities following damage to the hippocampus. According to Kesner's Attribute Model (Kesner 1991), the DG is involved in pattern separation of spatial locations. This conclusion is supported by a number of rodent lesion studies (e.g., Gilbert et al. 1998). Hopkins and Kesner (Hopkins and Kesner 1993; Kesner and Hopkins 2006) sought to extend these findings to spatial pattern separation in humans in a real world task. Patients with hippocampal atrophy due to hypoxia and matched controls performed a geographic distance task using cities on a map. In the study phase, participants were shown a series of cities on a map of New Brunswick and instructed to remember their locations. In the test phase, participants were given a pair of city names and asked which was further in a given direction (north, south, east, or west). The city pairs differed in the number of other cities in between, with separations of 0, 2, 4, and 6 intervening cities. Hypoxic patients were impaired relative to controls for all spatial distances. Taken together, these results indicate that damage to the hippocampus does result in pattern separation deficits for both objects and locations, as manifest by greater susceptibility to interstimulus interference.

Pattern Separation and the Aging Hippocampus

Memory impairments are one of the most common age-related cognitive complaints. One possible mechanism underlying age-related memory decline is a decrease in hippocampal integrity (Small et al. 2002). A number of studies have examined the effects of aging on pattern separation processes (see Holden and Gilbert 2012; Gilbert this volume). An emerging theme of these studies is that, similar to overall memory performance, there is a large degree of inter-subject variability in pattern separation performance among the aging population, even in the absence of any neurodegenerative disease.

Toner and colleagues (Toner et al. 2009) explored age-related changes in pattern separation utilizing a visual object continuous recognition task. They examined differences between young adults and nondemented older adults utilizing the previously discussed paradigm developed by Kirwan and Stark (2007). Since the lure items used are very similar but not identical to previously seen objects in

this task, it was hypothesized that lures would produce increased interference and thus an increased demand on pattern separation. Older adults and younger adults performed similarly in their ability to distinguish new and old stimuli. However, younger adults significantly outperformed older adults in their ability to correctly identify lures as similar, with older adults more likely to identify lures as "old". The authors suggested that these results may come about due to age-related changes in hippocampal subregions resulting in less efficient pattern separation processes. Based on previous findings, they proposed the DG may be particularly vulnerable to age-related changes. The age-related differences in identifying lure objects may result from decreased integrity of the DG (Small et al. 2002), resulting in less DG dependent pattern separation. The authors speculate these age-related differences may result in a dominant pattern completion bias with lure stimuli incorrectly identified as old stimuli. In addition, they found the performance of older adults was significantly correlated with several neuropsychological tests involving the MTL. For example, number sequencing, a basic element involved in executive function tasks, was correlated with older adults correctly identifying lures as "similar". Thus pattern separation tasks which can discriminate performance in hippocampal subregions may be useful in identifying age-related changes in these areas. In a follow-up analysis, Holden and colleagues (Holden et al. 2013) split older adults into impaired and unimpaired groups based on their performance on a separate neuropsychological memory test (the Hopkins Verbal Learning Test-Revised, HVLT-R). Older adults in the unimpaired group performed as well as younger controls on the pattern separation task while those in the impaired group tended toward pattern completion (i.e., were more likely to call the lures "old" than "similar").

In another study, Holden and associates (Holden et al. 2012) used a delayed match-to-sample varying spatial location task to study pattern separation differences between young and older adults. During the first phase of this task a circle appeared in one of 18 possible locations on a screen. This was followed by a brief delay during which participants looked away from the screen and read a random letter sequence. Afterwards, two circles appeared on the screen and the participants had to identify which circle matched the location of the previously displayed circle. The authors found that young adults had significantly greater performance scores than older adults. Furthermore there was a significant linear effect of spatial separation; performance for both young and older adults increased as the spatial distance between the circles increased. To rule out the possibility of general memory deficits related to normal aging as the contributing factor to the performance differences, older adults were split into impaired and unimpaired groups based on their HVLT-R delayed recall scores. Results showed the original findings between young and older adults remained after accounting for verbal memory impairment. The authors concluded that although general memory decline cannot be ruled out, it is more likely that the differences between young and older adults is likely due to less efficient spatial pattern separation as a result of normal aging processes. They further elaborated that this inefficiency is likely due to age-related changes in the DG and CA3 subregions of the hippocampus.

Other studies have also explored spatial pattern separation abilities in older adults. For example, Stark and colleagues (Stark et al. 2010) modified a rodent

spatial pattern separation task (Gilbert et al. 1998) for use within the human population. However, rather than only varying the spatial separation of stimuli on one dimension (e.g., distance) they varied it on two dimensions, changing both the distance and the angle of two stimuli. They hypothesized that the extent of movement between the stimuli would tax the spatial pattern separation demands in humans in a manner similar to that observed within rodent research. Furthermore, they sought to explore potential variability in task performance among healthy aged adults. They had young and older adults complete a series of standardized neuropsychological tests, which included the Rey Auditory-Verbal Learning Task (RAVLT), and participate a spatial pattern separation task. During the study phase, participants were briefly shown pairs of pictures and asked to remember the location of these stimuli. During the test phase, participants were asked to identify whether the pictures were in the same or a different location. For the different location trials, only one of the pictures from the pair changed locations and this change occurred in either a small (close), moderate (medium), or large (far) amount in both x- and y-coordinates. The results showed no overall differences between young and older adults with a positive linear trend across the conditions (i.e., same, close, medium, and far). The authors divided the older adult participants into impaired and unimpaired groups based on their RAVLT delayed word learning performance scores. While all of the older participants scored within the normal range for their age those that scored more than one standard deviation below the young adult norms were placed in the impaired group. Impaired participants performed worse on the different location trails compared to the unimpaired participants in the spatial pattern separation task. The authors found that as RAVLT delayed recall scores increased, participants' performance on the different location trails increased. The authors concluded that spatial pattern separation processing is diminished in mildly impaired older adults and that the spatial pattern separation task utilized in this study may be a sensitive marker of memory variability in aged individuals.

In a high-resolution fMRI paradigm, Yassa and associates (Yassa et al. 2011a) assessed changes in hippocampal subregion activity in older adults. They hypothesized that older adults would exhibit a bias toward pattern completion rather than pattern separation; that older adults would show increased activity in CA3 and/or DG subregions of the hippocampus; and that older adults would need greater dissimilarities between stimuli in order to correctly identify previously experienced stimuli from novel stimuli. Experiment 1 consisted of the continuous recognition task previously used by Kirwan and Stark (2007). The authors compared the contrast of lure trials correctly identified as "similar" against lure trials incorrectly identified as "old" to examine young adult and old adult MTL activity. Consistent with their hypothesis, the authors found that older adults were more likely to identify lure items as "old" (false alarm) rather than "similar" (correct rejection), indicating a bias toward pattern completion. Furthermore, older adults only successfully identified 33 % of the lure trials as "similar" compared with young adults correctly identifying 59 % of the lure trials. They also found a significant increase in signal (the difference between correct rejections and false alarms) in the right CA3/DG region of the hippocampus during the first and second presentations. Experiment 2 involved a mnemonic similarity task similar to that used in experiment 1; however,

these stimuli had been previously normed to generate mnemonic similarity ratings for each pair of similar stimuli. The lure items were then sorted based on the degree of mnemonic similarity. They found that larger degrees of differences between similar stimuli were necessary for older adults to engage in successful pattern separation and correctly identify lure stimuli as "similar" rather than "old", confirming the last portion of their hypothesis.

In a separate study, to test whether CA3/DG pattern separation signals would diminish with age as stimuli increased in similarity, Yassa and colleagues (Yassa et al. 2011b) examined high-resolution fMRI hippocampal activity profiles in young and older adults during pattern separation tasks with varied stimuli similarity. The authors predicted that changes in the CA3/DG functional network would be correlated with structural indicators as measured by ultrahigh-resolution microstructural diffusion tensor imaging (msDTI). Furthermore, they hypothesized that degraded perforant pathway input to the DG and CA3 subregions would be linked to age-related pattern separation impairments. They had young and older adults participate in an explicit recognition task out of the scanner and in an implicit fMRI recognition task. In addition, ultrahigh-resolution msDTI scans were performed on each participant. Just like many of the other continuous recognition pattern separation tasks used in other studies, during the explicit recognition task, participants were shown a series of novel, repeat, and lure stimuli and asked to identify each as "new", "old", or "similar". During the implicit recognition task, participants were scanned while shown a different series of novel, repeat, and lure stimuli; however, in this task they were asked to identify whether each item was an "indoor" or "outdoor" object. Based on previous mnemonic similarity ratings (Yassa et al. 2011a), the lure stimuli were analyzed according to their degree of similarity. When lure stimuli were very different they found no differences in CA3/DG activity between young and older adults. Alternatively, as stimuli became more similar, CA3/DG responses diminished in older adults, but remained high in young adults. The authors report that this pattern indicates a weakened pattern separation response to lure stimuli in older adults' CA3/DG hippocampal region and refer to this change as "representational rigidity" or the "requirement for increased dissimilarity before stimuli can be orthogonalized" (Yassa et al. 2011b, p. 8873). The extent of the representational rigidity predicted behavioral deficits in the discrimination task. There was also a correlation between the left CA3/DG gray matter functional rigidity and fractional anisotropy in this same region. The authors suggest that these results indicate that structural dendritic changes in the CA3/DG region may influence the functional impairments observed in older adults. Finally, they found correlations between the perforant path integrity and the amount of left CA3/DG rigidity. In addition, perforant pathway integrity was predictive of older adult performance on the behavioral discrimination task. They further found that CA3 rigidity was correlated with the functional pairing of the CA3/DG region with the entorhinal cortex. The authors speculated that signal reduction between the entorhinal cortex and the hippocampus may be related to the level of CA3/DG rigidity resulting in greater resistance to change. The authors conclude that age-related degradation in the perforant path

and CA3/DG network bias this system toward pattern completion and may impact mnemonic deficits often observed in older adults.

Most of the aging pattern separation studies have used pictures of objects in their paradigms, which are typically both perceptually and conceptually similar to each other. Due to the inability of pictorial pattern separation paradigms to differentiate between conceptual and perceptual interference, Ly et al. (2013) utilized a verbal stimuli paradigm to explore these differences in young and older adults. They expanded upon the Deese-Roediger and McDermott (DRM) paradigm (Roediger and McDermott 1995) and created two recognition conditions, one testing perceptual similarity and the other testing conceptual similarity. Two groups of young and older adults were randomized to either the perceptual or conceptual condition. Words used in the perceptual condition were phonologically similar and shared at least the first phoneme (e.g., cork and corn) while words in the conceptual condition were similar in semantic or categorical meaning (e.g., bell and whistle). During the initial encoding phase of the experiment, participants were shown a list of words and asked to identify whether each word represented an indoor or outdoor object. This phase was followed by the recognition phase (either perceptual or conceptual) during which participants were shown a series of novel, repeat, and lures) words and asked to identify if each was "old" or "new". The authors found no significant differences between young and older adults on the conceptual task; however, there were differences on the perceptual task with increased false alarms in older adults. To address whether perceptual impairments in older adults were influencing the results the authors conducted another experiment utilizing a match-to-sample paradigm on a separate group of young and older adults. In this paradigm, participants were shown the same stimuli used in the perceptual condition except that words were yoked to their similar lures and separated by a visual noise stimulus to remove any sensory trace. Participants were asked to identify whether the second word was the same or different from the first word in each pair. They found no differences between young and older adults and concluded that age-related deficits in perceptual working memory did not account for the previously found older adult impairment on the perceptual task. Instead they suggest that this impairment results from proactive interference and likely is the result of a gist or false familiarity processing bias. They further propose that while conceptually similar stimuli are likely immune from a pattern completion bias, perceptually similar stimuli are susceptible to pattern separation failure.

Improving Pattern Separation

There are many conditions that result in impairments to hippocampal dependent pattern separation, including depression (Déry et al. 2013), aMCI (Bakker et al. 2012), aging (Holden et al. 2013; Stark et al. 2010), and hippocampal damage (Kirwan et al. 2012). Is it possible to improve pattern separation? Rodent studies have demonstrated that increasing neurogenesis in the DG leads to improved per-

formance in spatial pattern separation tasks (Sahay et al. 2011). Déry et al. (2013) administered an exercise intervention to a population of healthy young adults who were previously relatively sedentary. Since exercise has been shown to increase neurogenesis (van Praag et al. 1999), the authors reasoned that the exercise intervention would result in increased neurogenesis in the hippocampus and subsequent improvement in pattern separation performance. A modified version of the object pattern separation task (Kirwan and Stark 2007) was administered prior to and following a 6-week exercise intervention. Pattern separation performance in the exercise group improved as a function of the increase in physical fitness. The authors took this result as evidence that increased neurogenesis leads to improved pattern separation performance. These results are tempered, however, by the inclusion of a clear outlier in the group who responded to the exercise intervention (see Déry et al. 2013 their Fig. 7.2) and will require replication.

Another possible way to improve pattern separation processing in the hippocampus is to increase the amount of norepinephrine (NE) available in the DG. The DG has a high concentration of NE receptors and may be modulated by noradrenergic activity in the locus coeruleus and the basal lateral amygdala (McGaugh 2002; Young and Kuhar 1980). Segal and colleagues (Segal et al. 2012) manipulated NE levels by having participants view a series of high-emotional-valence stimuli prior to encoding a series of objects. Participants performed a recognition memory test with targets, novel foils, and similar lures following a 15-min delay. NE levels were assessed prior to the emotional arousal phase, prior to encoding, and at the beginning and end of the delay period via saliva sample. There was a positive relationship between the change in NE levels and performance on the pattern separation task, indicating that NE may have a direct effect on pattern separation processing in the DG.

Finally, it appears that ongoing behavioral state may also affect pattern separation performance. Duncan et al. (2012) demonstrated that the trial preceding a lure stimulus in the continuous recognition pattern separation task influence performance on the lure trial. Lures preceded by a (correctly identified) novel stimulus were more likely to be correctly identified as “similar” than those preceded by a repeated stimulus. The authors manipulated the inter-trial interval and found that the effect was most pronounced with short intervals (500 ms) and was absent at longer intervals (1500 and 2500 ms). The authors speculate that encoding a new stimulus disposes the hippocampus toward pattern separation processes while the retrieval of a previously stored representation may dispose the hippocampus toward pattern completion processes. Further work is needed to elucidate the mechanisms underlying this effect.

Conclusions

Since event-based memories have a high degree of overlap, the medial temporal lobe memory system must perform pattern separation in order to avoid catastrophic interference at the time of retrieval. Here, we have reviewed evidence from animal

models that support the predictions of neuroanatomically-based computational models, which propose that the sparse connections in the DG are especially suited for performing pattern separation. There is also an increasing amount of supporting evidence from fMRI and behavioral studies with a variety of populations, including healthy young adults, memory-impaired patients with limited hippocampal damage, and healthy older adults. These and other studies offer promising avenues for both describing and improving pattern separation processes.

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