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Integrating new findings and examining clinical applications of pattern separation

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Abstract

Pattern separation, the ability to independently represent and store similar experiences, is a crucial facet of episodic memory. Growing evidence suggests that the hippocampus possesses unique circuitry that is computationally capable of resolving mnemonic interference by using pattern separation. In this Review, we discuss recent advances in the understanding of this process and evaluate the caveats and limitations of linking across animal and human studies. We summarize clinical and translational studies using methods that are sensitive to pattern separation impairments, an approach that stems from the fact that the hippocampus is a major site of disruption in many brain disorders. We critically evaluate the assumptions that guide fundamental and translational studies in this area. Finally, we suggest guidelines for future research and offer ways to overcome potential interpretational challenges to increase the utility of pattern separation as a construct that can further understanding of both memory processes and brain disease.

Episodic memories—records of unique experiences and events in our lives—guide adaptive future behavior. The hippocampus is known to play a crucial role in the formation and storage of episodic memories[1,2]. In doing so, it is constantly faced with the challenge of resolving interference that arises from overlapping day-to-day experiences. In other words, events in people's lives share many similar features (for example, parking a car in the same parking lot every day). Despite this overlap, humans are able to recall specific memories (for example, today's versus yesterday's parking spot). Thus, a key facet of episodic memory is being able to distinguish among these similar experiences. Pattern separation is one potential neurocomputational mechanism that is capable of reducing this interference by using nonoverlapping representations[3–6]. Although the term "pattern separation" may be used to describe any number of processes that reduce the similarity of input patterns, even in low-level sensory cortex, our use of it here is limited to its application to episodic memory.

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Competing interests

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Hippocampal features that support pattern separation

The hippocampus receives and combines information from sensory and associational cortical areas with modulatory inputs from limbic and subcortical regions. It is thought to process this multidimensional input, forming a coherent representation of the experience that is then projected back onto the cortex[7] (Fig. 1a). The hippocampus consists of several subfields, each of which has unique properties and connectivity[8]. Input from cortical regions enters the hippocampus via the entorhinal cortex (EC), which projects to the dentate gyrus (DG) and CA3 subregions via the perforant path (PP). The EC–DG–CA3 circuit is often implicated in pattern separation, although the exact mechanisms by which this occurs remain subject to debate. Several putative mechanisms have been proposed[3–6,9–15], but more empirical studies that test these alternatives are needed.

Empirical evidence for pattern separation in the hippocampus

A number of empirical reports across species and approaches have provided convergent evidence for the hippocampus's involvement in pattern separation. In these experiments, subjects were exposed to experiences that systematically varied in similarity, and neural responses in hippocampal subfields were recorded. A set of three studies in 2004 provided a suitable parametric framework for the examination of pattern separation and pattern completion[16–18]. Results from these studies were summarized as data points along input/output transformations that described the computational bias in each subfield[19] (Fig. 1b). Overall, convergent data have suggested that CA3 is capable of exhibiting pattern completion or pattern separation, depending on the magnitude of the change in sensory input. The CA1 subfield generally appears to respond linearly to incremental changes in sensory input; however, under some conditions it may respond with an abrupt nonlinear change, perhaps reflecting a switch in its dominant input from the entorhinal cortex to CA3[18–20] (but see Stokes et al.[21]). This could be a result of explicit task influences or the requirement for a mnemonic judgment instead of free exploration[19,22]. Consistent with this account, the CA1 region has also been characterized as a match/mismatch detector[23,24], which has been proposed as a core hippocampal com- putation[25–27]. The CA1 receives convergent input from CA3 and EC and may be able to shift between encoding and retrieval modes based on comparison of the inputs[24,28,29].

The DG is more likely than CA3 to show decorrelated patterns, even with minor distortions in the input; that is, its output is consistent with pattern separation[30] and occurs when the output layer shows more distinct firing patterns than the input layer[31]. To determine whether this pattern was a function of subfield-specific computations or simply a reflection of upstream processing, the authors of a recent study recorded activity from EC, CA3 and DG of behaving rats as the testing environment was distorted to varying degrees[31]. They observed rapid decorrelation of the neural signal after any distortion of the testing enclosure in the DG, but not in the EC. The same analyses showed that in CA3, the signal remained relatively coherent over the varying levels of distortion[31]. Similarly, CA3 coherence was weakly represented in upstream areas, which indicated that CA3 is able to pattern-complete a previously learned neural representation given noisy inputs. This work provided additional strong evidence that DG and CA3 computational signals are transformations of upstream

signals and, together with prior work showing these dissociated subfield computations[30], offered crucial support for the long-standing hypotheses regarding the functional properties of these areas[3,4,32].

Hippocampal pattern separation and episodic memory

The study of pattern separation and its role in episodic memory has dramatically increased in recent years. A PubMed search for "pattern separation" yielded about 400 articles on pattern separation published since the 1970s, with an exponential increase in the number of publications since 1974 ($r^2 = 0.708$, $F_{126} = 63.01$, $P < 0.001$; Fig. 2). The development of suitable behavioral models in which to assess this computation has provided a tractable approach to assessing the computation's mechanisms and implications. Performance in these models is typically characterized in terms of a 'discrimination index' that quantifies the subject's ability to overcome interference across similar experiences. Importantly, in discussing this work, we here use the term "discrimination" to refer to the behavioral measures, and reserve the use of "pattern separation" for neural data. For example, a number of studies have used an object-based mnemonic discrimination task[33–38] in which subjects are shown everyday objects during encoding and are then given a recognition test, where they are shown repeated images (targets), novel objects (foils), and similar, but not identical, objects (lures). Behavioral results from this task typically show a linear relationship, with lure-discrimination performance increasing with decreasing similarity of lure items[39–42].

Similar results have also been observed in other domains of episodic memory. For spatial tasks, the placement of objects is typically varied during retrieval across a range of spatial locations that vary in proximity from original positions during encoding. Across three different studies[40,42,43], discrimination performance increased as the metric distance from the original location increased. Similar tasks have been designed for rodents, using a dry-land version of the Morris water maze[44] or a touchscreen version of the tasks typically used in human studies[45,46]. For temporal tasks, the lag between events is typically varied, and subjects are asked to make an order judgment during retrieval[47–49]. Results consistently show a linear increase in performance with longer lags[47,48]. Thus, increasing interference in mnemonic discrimination tasks, defined as the parametric similarity along one or more domains, including visual appearance or proximity in space and/or time, poses a demand for pattern separation. Manipulation of interference along other dimensions is also possible, such as reward[50] and valence[51,52].

Evidence for signals consistent with pattern separation in the human hippocampus have been reported in several high-resolution functional magnetic resonance imaging (fMRI) studies in which activity during the presentation of similar items was compared with activity for novel and repeated items. The first study found that activity for lure items was on par with that for novel items rather than that for repeated items, and this was true only in the DG/CA3 subregion of the hippocampus[53]. This work leveraged the well-documented phenomenon of fMRI adaptation or repetition suppression (decreased response to repeated stimuli[54]) to establish benchmarks for novel and repeated items and assess the extent to which lures were treated as either novel or repeated. Importantly, this study could not rule out the possibility that the signals observed were reflections of match/mismatch signaling[55], as similarity was

not parametrically manipulated. Follow-up work examined input/output transfer functions through continuous variation of the similarity of presented items, and found a relatively more discontinuous response (step-function) in the DG and CA3 (DG/CA3) compared with that in CA1, consistent with the computational framework shown in Fig. 1b. Recent neuroimaging studies using multivariate classification approaches have also demonstrated that neural patterns are largely uncorrelated in the DG/CA3 subregion[56]. Recently, ultrahigh-resolution 7T fMRI was used to demonstrate that the DG, but not other hippocampal subfields or medial temporal cortices, exhibits distinct neural patterns for similar items, thus suggesting that the human DG is perhaps selectively engaged in pattern separation[57]. Interestingly, patient B.L., a 54-year-old man with selective bilateral ischemic lesions to the DG subregion of the hippocampus, was found to have impaired performance on a mnemonic discrimination task, which further suggests that the DG is required for pattern separation[58].

Cortical contributions to pattern separation

Cortical input to the hippocampus is largely segregated into two information-processing streams, which can be thought of as ‘what/content’ and ‘where/context’ pathways[59–61]. The lateral entorhinal (LEC)–perirhinal cortex (PrC) pathway primarily transmits sensory cues (content) that are required for object recognition and discrimination, whereas the medial entorhinal cortex (MEC)–parahippocampal cortex (PhC) pathway primarily transmits internally guided cues (context) that are required for navigation and spatial discrimination[59–61]. It is becoming increasingly clear that these streams make distinct computational contributions to domain-specific pattern separation. A double dissociation was recently identified with spatial discrimination engaging the MEC–PhC pathway and object discrimination engaging the LEC–PrC pathway. This domain selectivity was not observed in the DG/CA3 region[39]. These findings are consistent with the representational–hierarchical perspective, which suggests that lower-level representations (cortical) are more ambiguous, whereas higher-level representations (hippocampal) are unique[62]. At the sensory level, interference among individual stimulus features (for example, lines and colors) may be resolved in sensory cortex. When more perceptually complex features are introduced (for example, objects and contexts), interference is resolved at the next level of processing (for example, LEC and MEC pathways). Finally, combinatorial codes (for example, conjunctive representations of objects in context) are resolved in the hippocampus. One important implication of this view is that in investigations of signals consistent with pattern separation, especially those using fMRI in humans, several levels of cortical–hippocampal processing (for example, along the ventral visual stream and into the medial temporal lobes) should be examined in order for the specificity of the computation to be accurately assessed.

In addition to medial temporal cortices, other brain networks appear to be involved in the use of pattern-separated representations in explicit memory tasks. For example, increased blood-oxygen-level-dependent (BOLD) fMRI activity during correct discrimination of similar items is observed in regions such as the bilateral occipitotemporal cortex[63] and the retrosplenial cortex[64], whereas activity related to recognition of similar items is seen in prefrontal cortical regions[63] and thalamic nucleus reuniens[64]. These results suggest that cortical influences are involved in creating and using unique episodic memory traces. Future studies using multi-site neurophysiological recording or calcium imaging could potentially

inform on the temporal order of hippocampal–cortical interactions that may support the use of pattern-separated representations.

Caveats in linking across human and rodent studies

It is important to note that human and rodent studies use different measures of neural activity to capture signals consistent with pattern separation, which is one of the challenges in linking results across species. Rodent studies have used firing rate in varying environments and require the measurement of inputs and outputs to the hippocampus to ensure that signals do not simply reflect downstream processes. Human studies typically measure neural signals that are thought to be consistent with pattern separation by measuring increases in hemodynamic signals (an indirect proxy for neural activity that tends to correlate with local field potentials[65], although this is not always the case[66–68]) during viewing and/or discrimination of lure stimuli. One major difference between animal and human studies is that increased hemodynamic activity, manifesting as either reduced fMRI adaptation in incidental designs or increased contrast between lure rejections and false alarms in explicit designs, is not typically observed in neurophysiological studies of the DG region, where sparseness is thought to support pattern separation. It is worth noting that increases in hemodynamic signals may be a reflection of enhanced inhibition in the region, which is also consistent with sparse signaling. However, without direct pairing of neurophysiological recording and high-resolution fMRI, this account remains speculative. Studies using multivariate approaches such as representational similarity analyses may come closer to examining the correlated structure of activity across the region, which could allow for inferences to be made as to the degree to which similarity of the input (for example, in the EC) differs from similarity of the output (for example, in the DG and CA3). In general, although caution is warranted when generalizing across animal and human studies of pattern separation, these research approaches do appear to converge on similar findings, which can be summarized at the level of representation or input/output transformation processes regardless of the recording method.

Clinical and translational applications of the pattern-separation framework

In recent years, mnemonic discrimination tasks have become an important component of cognitive testing in clinical populations, with the hope of detecting subtle changes in hippocampal memory function early in the disease process. Figure 3 summarizes alterations in the hippocampus and surrounding medial temporal cortices across various clinical disorders.

Age-related cognitive decline and dementia

There is extensive evidence that declining memory function is present with increasing age[69–71] and is a major symptom of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Convergent data across animal and human studies have suggested that a key neural substrate for this decline is a shift in hippocampal network dynamics away from pattern separation and toward pattern com- pletion[72], which appears to be mediated by CA3 hyperactivity[35,73–76] and representational rigidity[35,72,75,77]—a failure to remap or manifest a

novelty signal when stimuli are similar but not identical. These alterations may be closely linked to changes in the perforant path[78–81] and to disinhibition in the DG and CA3 subregions resulting from the loss of inhibitory tone in GABAergic interneurons[72,82]. These changes in excitation/inhibition balance in hippocampal circuitry may act to strengthen CA3's recurrent collaterals, potentially biasing the network toward reactivation of prior experiences (that is, pattern completion) at the expense of learning new information[71,72]. A recent study found that the LEC contributes to CA3 hyperactivity in aged rats with object-discrimination deficits[76]. However, studies have reported that hippocampal activity is eventually reduced during memory task performance in those with mild AD[83,84]. It is likely that the reduced hippocampal volume typically seen in aging subjects is a result of these small synaptic changes rather than of morphological cell loss[85,86]; however, a meta-analysis has suggested that the relationship between hippocampal volume and memory is weak in healthy older adults[87]. This suggests that the examination of more subtle hippocampal alterations may be a more sensitive method for detecting early memory change compared with examination of gross hippocampal volume.

A number of studies have shown that, compared with young adults, older adults show impairments in the ability to discriminate highly similar items across object[34,35,37], spatial[40,42,43], temporal[48] and emotional[88,89] domains. It is important to recognize that older adults and even amnesic patients can still recognize repeated stimuli[90], but they have difficulty discriminating among highly similar items[43], which highlights the importance of dissociating between general recognition memory and mnemonic discrimination. When object and spatial memory were directly compared, older adults showed greater impairment of object discrimination than spatial discrimination relative to that in young adults[91]. This is taken as evidence of impaired processing in the LEC–PrC pathway, which forms one of the earliest sites of tau pathology in aging[92] and AD[93,94].

A high-resolution fMRI study tested patients with amnestic MCI on an object-discrimination task and found that patients showed impaired performance on trials that taxed their pattern-separation abilities. In addition, the authors observed hyperactive BOLD signals in the DG/CA3 and hypoactive signals in the EC during discrimination[36]. Additional evidence suggests that lure-discrimination performance may be linked to ApoE4 status as well as cerebrospinal fluid β-amyloid burden[95]. A recent study found that cognitively normal older adults showed increased amyloid and tau as measured by in vivo positron emission tomography imaging and that this was associated with aberrant activity in the medial temporal lobes during an object-discrimination task[96].

Overall, although these studies have demonstrated clear age- related deficits in these tasks (Fig. 3a), even after accounting for age-related deficits in perceptual and working memory processing, cognitive aging remains a complex condition that is not easily deconstructed. Tasks are rarely, if ever, process-pure and will therefore undoubtedly be contaminated by additional components such as impairments in pattern completion[97], which may also be subject to the effect of aging and AD. An important future direction will be to validate the neural basis of each behavioral deficit and manipulate task conditions such that other variables can be systematically eliminated (perceptual or attentional influences, overt instructions during encoding, continuous recognition versus study/test blocks, etc.)[98].

Neuropsychiatric disease

A role for hippocampal pattern separation has been suggested in psychiatric disorders such as depression, anxiety, schizophrenia, autism and post-traumatic stress disorder[99–102]. Depression is characterized by anhedonia, fatigue, changes in sleep and eating behavior, and alterations in memory and mood[103,104], with impairment in episodic memory as well as a negativity memory bias. Postmortem human studies of depression have found that synaptic loss, rather than morphological cell loss, occurs mostly in the DG and CA3 subregions of the hippocampus[105]. Chronic stress manipulations have been used in animal models of depression to examine many of the core features of depression such as anhedonia, despair, appetite changes and anxious behavior[106], and these models typically result in reduced hippocampal volume, which has been attributed to CA3 dendritic retraction and suppressed DG neurogenesis[107–109]. Recent work has shown that individuals with depressive symptoms have a diminished capacity to discriminate highly similar neutral objects[110–112] and scene stimuli[52]. Furthermore, discrimination of negative scenes is enhanced in individuals with depressive symptoms in a manner that corresponds to the severity of the depressive phenotype[52]. This behavioral difference is accompanied by increased amygdala activity and decreased DG/CA3 activity in high-resolution fMRI. Furthermore, the level of DG/CA3 activity is negatively correlated with depressive symptom severity, which indicates that reduced DG/CA3 activity may be a pathological condition[51,113]. Older adults experiencing late-life depression also show enhanced discrimination of negative scenes, in addition to alterations in their amygdala–entorhinal–hippocampal network[114] (Fig. 3b). Thus, overall results from studies of patients with depressive symptoms suggest the presence of impairments in pattern separation for neutral information and enhanced pattern separation for negatively valenced information, which is consistent with the negative rumination common to depression.

Anxiety is characterized by feelings of restlessness, alterations in fight-or-flight responses, difficulty concentrating and memory problems. Many patients with anxiety disorders display an overgeneralization of fear responses to emotional stimuli. In post-traumatic stress disorder, there is an overgeneralization of memory for the stimuli associated with the aversive event. Anxiety states have also been tested via mnemonic discrimination procedures in rodents and humans. In rodents, a contextual fear discrimination task has been used in which mice are trained to fear an aversive context and then to discriminate between the aversive context and a highly similar safe (no shock) environment. Mice freeze when exposed to the similar context, and thus generalize across the two contexts[101]. When humans are placed in an induced anxious state (that is, when subjected to the threat of unpredictable shock) during encoding, mnemonic discrimination improves when retrieval occurs in a safe context. However, when retrieval occurs in an unsafe environment, the benefit of improved pattern separation is lost, and this provides a putative mechanism for overgeneralization[115]. Thus, it appears that impaired pattern separation underlies the overgeneralization that is often seen in anxiety disorders.

Schizophrenia has been associated with impairments in cognitive functioning such as poor executive functioning, inability to sustain attention, and episodic memory deficits[116]. Postmortem studies have demonstrated a selective reduction in glutamate transmission in the

DG and in its efferent mossy fiber pathway[117,118], as well as increased neuronal activity in CA3[119] and CA1[120] (Fig. 3c). Individuals with schizophrenia have impaired object discrimination but not impaired general recognition memory compared with healthy controls[121,122]. Similar deficits have been shown in a ketamine-administration model of schizophrenia, which suggests that NMDA-receptor-mediated mechanisms might underlie the deficit[122]. Overall, these studies suggest that pattern separation may be impaired in schizophrenia, although neural recording studies (for example, using fMRI) would be needed to draw this conclusion. In addition, the behavioral deficits observed in schizophrenia may be partially explained by visual and perceptual deficits[123].

Individuals with autism spectrum disorder (ASD) exhibit cognitive dysfunction and impaired emotion regulation[124]. They tend to overidentify objects as more different from previously viewed objects in object mnemonic discrimination tasks[125]. Discrimination accuracy also correlates with multiple measures of negative emotionality in those with ASD. Although it is still very early to say for certain, it is possible that the hyperdiscrimination observed in ASD is related to the negativity-related hyperdiscrimination observed in depression[52] and may stem from limbic imbalance. However, neural studies are needed to formally test these hypotheses.

Across clinical conditions that involve hippocampal impairment, it appears that the computational capacity of the DG is compromised in largely nonspecific ways and, as a result, deficits in mnemonic discrimination are characteristic of a number of these conditions. Although the use of tasks sensitive to pattern-separation deficits is informative with regard to the pathophysiological mechanisms of different diseases, the phenotype does not have the specificity for differential diagnosis and seems to be generally sensitive to hippocampal impairment, but not specific to condition. Notable exceptions are the behavioral enhancements observed in ASD and depression (for negative stimuli), and it is possible that these enhancements stem from nonhippocampal modulations such as the amygdala or prefrontal cortex that may shift attention toward differences or bias the hippocampus toward a more discriminative encoding procedure. We caution, however, against simple interpretations in clinical disorders that tend to be quite complex, affecting not only memory but also a swath of other cognitive functions. Other factors, such as perception, attention and executive functioning, must be examined and/or controlled to determine whether impairments or enhancements in discrimination are a result of memory or other non-mnemonic effects.

Physical activity and exercise

Voluntary running has been shown to enhance the ability of adult mice to discriminate between the locations of two adjacent identical stimuli. More recent work has shown that running increases hippocampal neurogenesis and significantly improves memory for similar objects, whereas different objects can be distinguished by both running and sedentary mice[126] (Fig. 3d). Age-related impairments in contextual discrimination are also reversed by running, which may be supported by mechanisms other than neurogenesis[127]. In humans, long-term aerobic exercise has been associated with improved discrimination of similar lures in an object mnemonic discrimination task[111]. A brief (10-min) bout of moderate exercise

(50% of VO_2 max) was shown to improve mnemonic discrimination of similar lures, but did not alter performance with either identical targets or novel foils[128]. Recent work has examined the effect of aerobic exercise in healthy older adults on vascular plasticity in the hippocampus. Changes in fitness and in hippocampal perfusion and volume were positively associated with changes in recognition memory and early recall for complex spatial objects, which requires discrimination among similar complex objects[129]. Overall, it appears that the benefits of both acute and long-term exercise for memory may be mediated in part by effects on hippocampal pattern separation, which enhances performance on discrimination tasks[130]. Understanding the neural mechanisms for these effects remains a significant challenge, especially because exercise is multifaceted and probably targets several mechanisms to enhance cognition.

Environmental enrichment

The exploration of visually stimulating virtual environments in video games can be used as a model of environmental enrichment, which has been associated with increased hippocampal neurogenesis, synaptogenesis, neurotrophic factors and dramatic improvement on hippocampus-dependent learning and memory tasks[131,132] (Fig. 3d). A recent study showed that video gamers who specifically favor complex 3D video games performed better in object discrimination. In addition, after 2 weeks of training on the 3D video game (Super Mario 3D World), naive video gamers showed improved discrimination ability. Training on a comparable 2D video game (Angry Birds) showed no such improvements. Furthermore, individual performance in both hippocampal-associated behaviors correlated with performance in the 3D game, but not in the 2D game, which suggests that how individuals explore a virtual environment may influence hippocampal computational abilities[133], although this account remains speculative in the absence of neural data.

Psychostimulants and pharmacological agents

Post-training caffeine administration (compared with placebo) was shown to improve consolidation on a 24-h object-discrimination test in caffeine-naive individuals[134]. Although the mechanism for this effect is not clear, it is possible that it is mediated at least partly by noradrenergic modulation, or possibly through action on adenosine receptors in the hippocampus. In patients with MCI, low doses of an anti-epileptic drug (levetiracetam) have been shown to reduce dysfunctional DG/CA3 hyperactivity and EC hypoactivity and rescue memory deficits on a mnemonic discrimination task[74,135]. Notably, the same therapy may also reduce hippocampal hyperactivity and rescue memory deficits in aged rodents[136] and in mouse models of schizophrenia[137] and AD[138]. This suggests that this interventional route may restore the excitation–inhibition balance in a host of conditions that involve hippocampal pathology.

Recent data have suggested that one mechanism by which selective serotonin-reuptake inhibitors (SSRIs) may reduce memory symptoms in those with depression is by improving DG neurogenesis[139,140] (Fig. 3d). A recent review suggests that an improvement in pattern separation, particularly for situations that are emotionally arousing, may affect mood and anxiety symptoms as well[141]. The effect of DG neurogenesis on pattern-separation

computations in healthy and disease- affected populations is an important avenue of future investigation, particularly as rodent studies have identified a role for adult-born neurons in population-based coding in DG[14] and CA3[142]. Recent studies using nuclear-bomb-test-derived ^{14}C suggest high levels of turnover in the human DG[143], indicative of a continuous role for adult neurogenesis. However, assessing neurogenesis in humans is far from trivial. Some attempts have been made, but the applicability and specificity of these techniques has yet to be determined[144].

Cautionary notes for clinical applications of pattern separation

The application of knowledge about the computational properties of the hippocampus in order to better characterize memory impairment and clinical populations can be a fruitful avenue of investigation. However, caution is warranted when making claims about the links between hippocampal computations and cognitive deficits. Absent neurobiological data, it is very difficult to make strong claims about hippocampal pattern separation or contributing mechanisms such as DG neurogenesis. For example, there are numerous other neurobiological processes outside of pattern separation that can contribute to discrimination-task performance. Thus, inferences about underlying neurobiology made purely on the basis of task performance and in the absence of neurobiological evidence may be premature. We suggest that, to avoid confusion and potentially misleading inferences, the term “pattern separation” should specifically refer to neurobiological processes, whereas the term “mnemonic discrimination” should be used to refer to the behavioral correlate of pattern separation. Translation from basic neurobiology and computational principles to clinical disorders is a crucial avenue of research and should be encouraged. Box 1 contains suggested guidelines for experimental design. Below, we also outline conditions for behavioral and neurobiological validation, intended to improve the quality of clinical and translational science in this arena.

Behavioral validation

Mnemonic discrimination tasks are largely similar to traditional object-recognition tasks, with the exception of the use of similar lure stimuli. The lures (in particular, the parametric manipulation of lure similarity) offer a unique opportunity to test the individual’s ability to resolve mnemonic interference. Thus, characterization of performance on just one level of similarity is not sufficient to draw conclusions about underlying mechanisms. Rather, performance should be considered as a function of interference. Figure 4 illustrates this approach and the types of patterns that can be detected both behaviorally (Fig. 4a) and neurally (Fig. 4b).

Effective behavioral tests of pattern separation require multiple levels of stimulus similarity in order for inferences to be made about the computation. Performance should be evaluated as a function of these different levels of stimulus similarity, which range from maximum interference (essentially no discernable difference) to no interference (very different stimuli). Along this continuum are stimuli that possess intermediate levels of similarity and interference, which can be broadly categorized as high and low interference. The resolution and range of the *x* axis will vary across experiments and designs, but a minimum of two

intermediate levels of interference are recommended to characterize the input/output function. Figure 4a describes several stereotypical patterns of behavior that have been observed in past studies in healthy and clinical populations.

In healthy adults, the expected pattern of discrimination performance as a function of decreasing interference is largely linear (pattern 1). In clinical conditions, one might expect to see variations in this pattern such that for certain interference conditions, discrimination performance is lower or higher than expected compared with controls. Thus, an important first step in developing a task would be to show a linear relationship between interference level and task performance in a healthy sample. Deviations from this linear pattern may be suggestive of impairments in pattern separation, but the exact pattern of deviation will dictate whether certain conclusions can be drawn.

For example, a clinical sample may show worse discrimination than healthy controls at high or low interference, but may not differ from controls in the discrimination of targets or foils (pattern 2). This would suggest an impairment that is selective to items with interference and perhaps some specificity to pattern separation. This type of behavioral deficit has been characterized as a form of 'mnemonic rigidity'[71]. A selective deficit on the high, but not the low, interference stimuli could be stronger evidence in favor of this argument. In contrast, a more generalized impairment that includes even the items that induce little or no interference cannot be interpreted as selective to pattern separation (pattern 3).

It is interesting to note that in some cases, it is possible to observe an enhanced discrimination profile that is selective to items with interference (pattern 4). This tuning would be suggestive of more effective processing and resolution of interference and can be thought of as a form of 'mnemonic flexibility'. We suggest that this is possible under conditions that enhance pattern separation, such as emotional arousal, caffeine use, or physical or cognitive exercise. Only one report thus far has observed this phenomenon[130], which is associated with higher levels of physical fitness.

Neurobiological validation

Although behavioral tasks that appropriately parametrically manipulate interference are necessary for the examination of pattern separation, behavioral results are not a sufficient basis for claims about altered neural computations. Neurobiological validation is still required for such claims. We suggest that the most robust neurobiological validation uses a procedure analogous to that recommended for behavioral analyses, namely, the examination of data in terms of input/output transformations.

For example, given the same four levels of interference we used for behavioral analyses, the *y* axis can be switched from discrimination performance to 'difference in neural signals' (Fig. 4b). This can be BOLD fMRI contrast, decorrelated immediate early gene (IEG) population activity or single-unit firing, or any other indicator of neural change (Δ) in output. These measures reflect different scales of pattern-separation measurement, but their expected input/output transformations are similar (that is, linear versus curvilinear patterns as interference decreases). Unlike behavior, however, neural signals are more sharply tuned

such that normative samples typically show a curvilinear pattern (pattern 1). In this case, an impairment profile could appear to be linear (pattern 2). A linear 'flattening' of the neural tuning function can be interpreted as impairment in pattern separation. A more generalized impairment even on the items without interference (pattern 3) would be more suggestive of a general memory impairment that is not specific to pattern separation.

Finally, an enhanced tuning of the input/output neural transformation function is also possible (pattern 4) and would be expected under conditions that enhance memory, although evidence reporting this type of tuning remains lacking.

It is important to note that with any neural recording technique, including fMRI, IEG and unit recordings, it is still difficult to directly measure hippocampal pattern separation, as most studies do not have the capability to measure the inputs and outputs simultaneously and with sufficient resolution to evaluate the input/output transformation directly. Some studies have come close to this[31], but the assessment requires recording from multiple different regions and different types of cells simultaneously, which is challenging even with the most modern techniques. Instead, we rely on convergent data across studies and species to make inferences about the role of different brain regions in pattern separation and the linking of behavioral discrimination impairments to regionally specific pattern separation impairments.

Summary and conclusions

Over the past decade, there has been renewed interest in investigations of hippocampal pattern separation. We argue that although this has certainly been a healthy expansion of the field and has substantially informed efforts to understand memory computations, it has also led to some growing pains that are typical of the early stages of expansion of any young enterprise. As we reflect on the 13 years of empirical studies since the seminal demonstrations of hippocampal pattern separation in 2004, it behooves us to critically evaluate our approaches thus far to chart the path forward. In this Review, we not only summarized the current literature on the topic, but also put forth guidelines for future research, as well as some boundary conditions for making claims about pattern separation. We hope that this provides some guidance to improve the quality of the collective science and allow for careful fundamental investigation and even more careful clinical and translational application.

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Box 1

Guidelines for designing clinical research studies on pattern separation

Although making direct claims about pattern-separation deficits solely on the basis of performance in mnemonic discrimination tasks is not recommended, it is important to note that it is critical to demonstrate a deficit in discrimination before asking neurobiological questions about the underlying mechanisms. We suggest that this might be considered a first step in the line of inquiry, and further delineate the conditions necessary to demonstrate relative specificity to hippocampal computations.

Condition 1: A parametric manipulation of similarity (at least two levels, but preferably more) is needed in which performance is impaired in conditions that have elevated interference (for example, high similarity), but improves when this interference is minimized. This type of behavior is suggestive of impairment in pattern separation.

Condition 2: Control conditions in which there is no interference (such as traditional recognition in human tasks or simple object recognition in the absence of similarity in animal tasks) are required to dissociate deficits in pattern separation from general memory deficits. These tasks should show minimal or no difference between groups.

Condition 3: Control conditions in which there is interference but no mnemonic load (for example, no-delay or short-delay discrimination tasks with no buildup of proactive interference—that is, each trial is tested immediately after encoding) are also necessary to demonstrate the specificity of the deficit to mnemonic rather than sensory, perceptual or attentional confounds.

Condition 4: If task-performance profiles satisfy all three of the conditions listed above, a tentative argument can be made that the mnemonic deficit may stem from an impairment in hippocampal computations and, in particular, pattern separation. However, in order for definitive conclusions about this to be drawn, the task results must be coupled with neurobiological data. Neurobiological data from in vivo recording (for example, electrophysiology, optical imaging, IEG imaging and fMRI) in the same subjects or the same population can be used to discover brain–behavior relationships that provide mechanistic support for the deficit. Several types of neurobiological evidence can be considered here, but the most powerful demonstrations will involve observations of deficits in coding properties as a function of interference.

As research in this field has flourished in recent years, meeting these conditions has become an important focus. However, it may be difficult to meet all of these conditions in any single study. There are numerous examples of studies that meet either condition 1[34,37,38,49,52,53] or condition 2[34–36,38,43,52,123,146]. A smaller number of studies have met condition 3[35,52,123], and we find that this condition is often overlooked in clinical samples where performance could be altered on a number of untested conditions. Condition 4 has often been met[20,31,35,36,51,57,114], but perhaps not in the same studies

that satisfy conditions 1-3. One reason that concurrently satisfying all four conditions may be difficult is that imposition of an explicit task will sometimes lead to a diminished ability to record subfield-specific evidence of pattern separation[33]. We suggest that convergent data across more than one study may be used to make the case that a particular clinical deficit can be ascribed to pattern separation. In the absence of neurobiological evidence in a particular clinical population, however, it is difficult to justify the claim that pattern separation is specifically impaired and to rule out the alternative that the observed behavioral deficit is a result of another type of neural dysfunction.

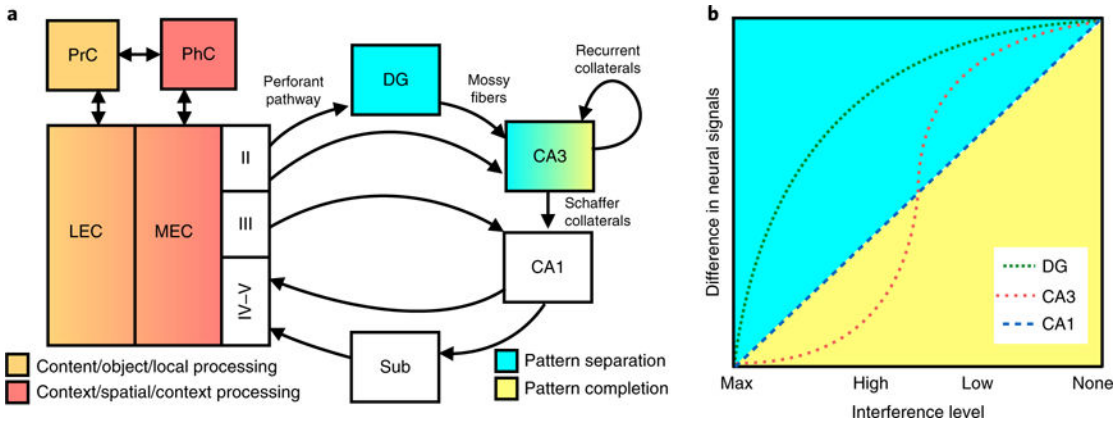

Fig. 1. Circuitry and computational properties of the hippocampus

a, This simplified circuitry of the hippocampus consists of the DG, CA3, CA1 and subiculum (Sub). The EC is the major input into the hippocampus and consists of the LEC and MEC. Layer II of the EC is the main input to DG and CA3 subregions (via the perforant pathway), whereas layers IV-V are the main output from the CA1 and Sub of the hippocampus to other cortical regions. The DG projects to the CA3 via mossy fibers. The CA3's largest projection is onto itself via recurrent collaterals[145]. The CA3 projects to the CA1 via Schaffer collaterals. The LEC mainly receives input from PrC (postrhinal in rodents), and the MEC mainly receives input from the PhC, although there is crosstalk between PrC and PhC, as well as between LEC and MEC. The PrC-LEC pathway is largely involved in content, object and local processing (orange), whereas the PhC-MEC pathway is largely involved in context, spatial and global processing (red). The DG is capable of performing pattern separation (blue), whereas the CA3 can perform pattern separation and pattern completion, depending on the input. **b**, The *x* axis shows interference levels (maximum, high, low and no interference), and the *y* axis shows the difference in neural signals (for example, BOLD fMRI contrast, decorrelation in IEG population activity or single-unit firing, or any other indicator of neural change in output). The DG shows a sharp increase in signal even with high levels of interference (pattern separation), whereas the CA3 shows lower neural signals at higher levels of interference and higher neural signals at lower levels of interference and is capable of performing pattern completion and separation. The CA1 shows a linear response function, with greater neural signals with lower levels of interference.

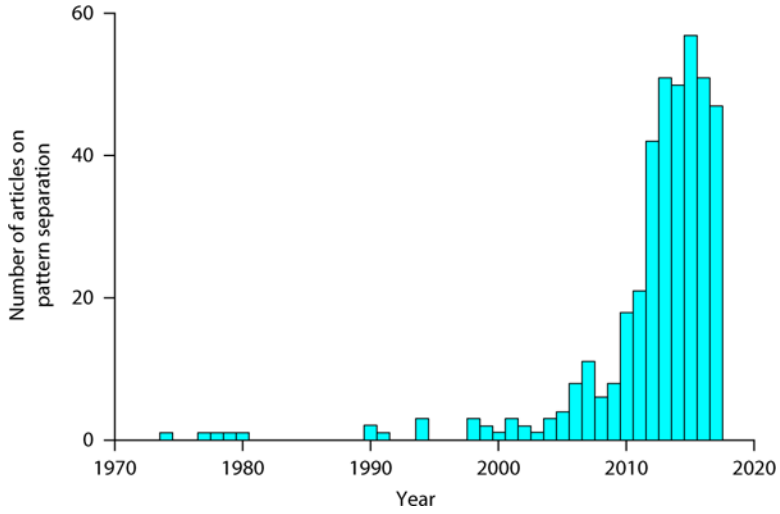

Fig. 2. Exponential increase in articles on pattern separation

The first articles on pattern separation were published in the 1970s, but it wasn't until ~2010 that a marked increase in pattern separation publications occurred.

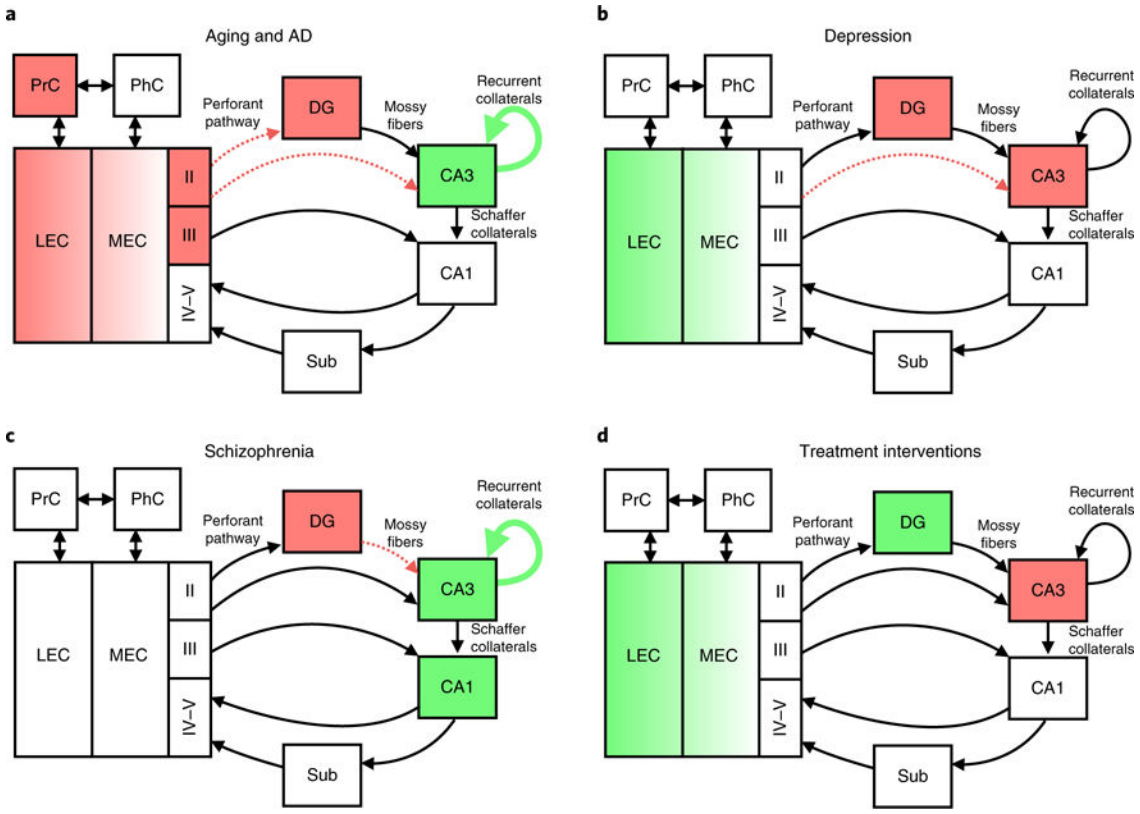

Fig. 3. Medial temporal lobe circuitry alterations in disease

a, In aging and AD, there is a reduction of the perforant path, hyperactivity in CA3, reduced inhibition of CA3, hypoactivity in the EC, reduced reelin and tau deposition in the LEC, decreased EC thickness, and impaired object versus spatial processing depending on PrC. **b**, In depression, there is a retraction of the CA3 dendrites, decreased DG neurogenesis and decreased DG/CA3 BOLD activity. In late-life depression, there is altered DG/CA3 activity and LEC hyperactivity. **c**, In schizophrenia, there is reduced DG and mossy fiber glutamate transmission, as well as increased CA3 and CA1 activity. **d**, DG neurogenesis increases with exercise, environmental enrichment and SSRI treatment. Antiepileptic treatment in MCI patients reduces CA3 activity and increases the level of LEC activity.

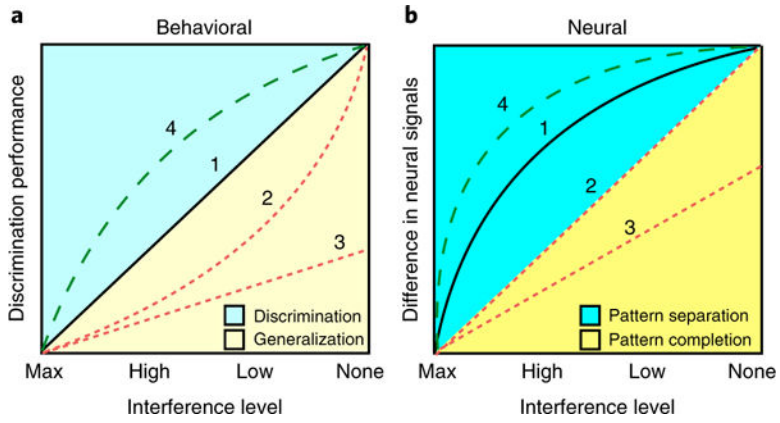

Fig. 4. Behavioral and neural predictions of discrimination performance and pattern separation

a, The *x* axis shows the interference level, from maximum interference to no interference, and the *y* axis shows discrimination performance (typically measured as a lure-discrimination index). The typically observed pattern of discrimination performance as a function of decreasing interference is largely linear (pattern 1). In clinical conditions, one might expect to see variations in this pattern, such that for certain interference conditions discrimination performance is lower or higher than that expected on the basis of control performance. Deviations from this linear pattern may be suggestive of impairments in pattern separation; however, the exact pattern of deviation will dictate whether certain conclusions can be drawn. For example, a clinical sample may show worse discrimination than that in healthy controls at high or low interference, but performance may not differ from that of controls in discrimination of targets or foils (pattern 2). This would suggest an impairment that is selective to items with interference and perhaps some specificity to pattern separation. This type of behavioral deficit has been characterized as a form of mnemonic rigidity. A selective deficit on the high, but not the low, interference stimuli could be stronger evidence in favor of this argument. In contrast, a more generalized impairment that includes even the items that induce little or no interference cannot be interpreted as selective to pattern separation (pattern 3). In some cases, it is possible to observe an enhanced discrimination profile that is selective to items with interference (pattern 4). **b**, Difference in neural signals (on the *y* axis) is more sharply tuned, such that normative samples typically show a curvilinear pattern (pattern 1). In this case, an impairment profile could appear linear (pattern 2). A linear ‘flattening’ of the neural tuning function can be interpreted as impairment in pattern separation. A more generalized impairment even on the items without interference (pattern 3) would be more suggestive of a general memory impairment that is not specific to pattern separation. Finally, enhanced tuning of the input/output neural transformation function is also possible (pattern 4) and would be expected under conditions that enhance memory, although evidence for this type of tuning remains scarce, with exercise studies possibly being an exception. Note the correspondence between numbers 1-4 in **a** and **b**, which indicates that overall curves in **a** are detuned versions of the curves in **b**, probably as a result of nonhippocampal influences, which introduce additional variability that influences the decision-making process. These hypothetical curves are based on a combination of observations from extant data and computational predictions.