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Review

The operation of pattern separation and pattern completion processes associated with different attributes or domains of memory

Michael R. Hunsaker[a], Raymond P. Kesner[b,*]

[a] Department of Psychiatry and Behavioral Sciences, MIND Institute, University of California, Davis Medical Center, 2805 50th Street, Room 1415, Sacramento, CA 95817, USA
[b] Department of Psychology, University of Utah, 380 South 1530 East, Room 502, Salt Lake City, UT 84112, USA

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ABSTRACT

Pattern separation and pattern completion processes are central to how the brain processes information in an efficient manner. Research into these processes is escalating and deficient pattern separation is being implicated in a wide array of genetic disorders as well as in neurocognitive aging. Despite the quantity of research, there remains a controversy as to precisely which behavioral paradigms should be used to best tap into pattern separation and pattern completion processes, as well as to what constitute legitimate outcome measures reflecting impairments in pattern separation and pattern completion. This review will discuss a theory based on multiple memory systems that provides a framework upon which behavioral tasks can be designed and their results interpreted. Furthermore, this review will discuss the nature of pattern separation and pattern completion and extend these processes outside the hippocampus and across all domains of information processing. After these discussions, an optimal strategy for designing behavioral paradigms to evaluate pattern separation and pattern completion processes will be provided.

Contents

* Corresponding author. Tel.: +1 801 581 7430; fax: +1 801 581 5841.
E-mail addresses: ryanhunsaker@me.com (M.R. Hunsaker), rpkesner@behsci.utah.edu (R.P. Kesner).

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1. Introduction

It has been demonstrated on numerous occasions that the hippocampus facilitates learning and recall of information through processes called *pattern separation* and *pattern completion*. Since this idea was formalized into a mathematical model by Marr (1971), it has been evaluated computationally (McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; Rolls and Treves, 1994; Rolls, 1996) and experimentally using behavioral (Kesner et al., 2004; Kirwan et al., 2012; Rolls and Kesner, 2006), neurophysiological (Leutgeb and Leutgeb, 2007; Leutgeb et al., 2007), and functional magnetic resonance imaging techniques (fMRI; Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011). As such, a critical role for the hippocampus can be stated quite simply: In addition to the rapid storage of similar patterns without undue interference, the hippocampus must be capable of using degraded or noisy recall cues to retrieve previously stored activity patterns, so that memories may be later accessed. Thus, the hippocampus must perform pattern separation at the time of encoding and storage, which makes the the stored patterns more distinct from each other, and must perform pattern completion at the time of recall and retrieval in order to recover the full stored pattern from a partial or degraded retrieval cue.

Functionally, it has been proposed the hippocampus serves two primary functions to subserve memory: (1) To serve as a competitive learning network that reduces the degree of overlap among activity patterns to facilitate storage with minimal interference with other activity patterns, and (2) to serve as an autoassociation network that is capable of recalling stored activity patterns from partial cues (Kesner et al., 1987; Marr, 1971; McClelland, 1994; Olton and Papas, 1979; O'Keefe and Nadel, 1978; Rolls and Treves, 1994; Rolls, 1991). In other words, memory retrieval in the hippocampus amounts to performing pattern completion to reinstate the content of the original, unique stored activity pattern. To perform this function efficiently and to prevent false, noisy, or erroneous recall; representations in the hippocampus must be kept distinct, since very similar activity patterns need to be distinguished during retrieval.

Importantly, by definition, pattern separation and pattern completion are separate processes that are dynamically at odds with each other. To the extent that the system takes similar input patterns and separates them into orthogonal representations, unique memories will be formed that do not overlap with previous or subsequent memories. However, this orthogonalization interferes with the pattern completion process which requires that a partial or overlapping input pattern trigger the recall of an existing memory instead of the creation of a distinct, new one. Because there is such a fine balance between pattern separation and pattern completion processes in the hippocampus, it has been proposed that any unbalance to these processes may underlie a wide array of diseased states (*e.g.*, autism and schizophrenia; Cohen, 1994; Femia and Hasselmo, 2002; Hanson and Madison, 2010; Tamminga et al., 2010), as well as neurocognitive aging (Burke et al., 2010, 2011; Gallagher et al., 2010; Yassa et al., 2010, 2011).

The theoretical and computational models describing imbalanced pattern separation and pattern completion in psychiatric disease and cognitive aging are, unfortunately, often frustrated by the prevalence of fundamental misconceptions in the pattern separation and pattern completion literature. The most common misconception in the behavioral neuroscience literature is that pattern separation and pattern completion are not in fact separate processes, but rather comprise two ends of a unitary process: in other words, impaired pattern separation is the same thing as improved pattern completion and *vice versa* (for an introduction to the difficulties that arise from this interpretation *cf.*, Aimone et al., 2011; Sahay et al., 2011a).

This proposal (that of pattern separation and pattern completion occupying two ends of a single continuum) is inaccurate as pattern separation and completion processes are performed by different neuroanatomical structures using distinct coding mechanisms (*cf.*, McClelland, 1994; Treves and Rolls, 1992, 1994), and the two processes are temporally constrained to occur during different phases of memory processing (*e.g.*, pattern separation during encoding and pattern completion during recall). To help overcome these misconceptions, this review will describe pattern separation and pattern completion from both a computational as well as a psychological

perspective. This emphasis will be extended to evaluate pattern separation for perceptual information during encoding as well as more mnemonic processes requiring pattern separation to perform memory tasks (*cf.*, Aimone et al., 2011; Sahay et al., 2011a). Afterward, functional and behavioral dissociations of these processes will be provided. Pattern separation and pattern completion processes will be described across all domains or attributes of memory processing and a comprehensive framework upon which future studies into pattern separation and pattern completion may be designed will be provided and discussed.

Important to this review is the focus on a behavioral analysis for teasing apart the relative contributions of pattern completion and pattern separation for learning and memory. Inherent in using behavior to describe neural processes is the choice of methodology and models used for these studies. For rodent research described in this review, a focus has been placed on the role of excitotoxic lesion studies over other research methodologies. It is clear that ablative research techniques are a relatively blunt tool now that molecular tools to directly modify the genome and cellular activity have been developed. However, at the present time, there are only a handful of studies evaluating pattern separation and pattern completion that are not lesion studies. These studies are included whenever possible, but cannot be used as the primary focus as there are too few overall to characterize the behavioral profiles associated with pattern separation and pattern completion. Optimally, to overcome the experimental difficulties associated with using only a single research method to study a problem, future studies must include combinations of lesion studies with cell class-specific transgenic or knock-out/knock-in mice, optogenetic activation or inactivation of cell populations, as well as correlative measures of cellular activity such as immediate early gene or neurophysiological measures such as single unit recording.

2. Models of pattern separation

2.1. Computational models of pattern separation

The present description of pattern separation processes limit the focus primarily on spatial pattern separation in rats and mice (Chen et al., 2012; Hunsaker et al., 2012; Leutgeb and Leutgeb, 2007; Leutgeb et al., 2005, 2007; Leutgeb, 2008; McHugh and Tonegawa, 2007; McHugh et al., 2007; Nakashiba et al., 2009) and on temporal–linguistic–sensory/perceptual visual pattern separation in humans as these processes are those most commonly tested experimentally. Historically, pattern separation has been defined as a process that can be carried out upon any incoming information across any sensory/perceptual domain (Marr, 1971; O'Reilly and Frank, 2006; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000, 2001; O'Reilly et al., 2011).

Computational models of pattern separation derive from David Marr's mathematical model for the archicortex (*i.e.*, hippocampus) in simple memory (Marr, 1971). These models emphasize the divergence of synaptic projections from ~200,000 cells in the entorhinal cortex *via* the perforant path to ~1,000,000 granule neurons in the dentate gyrus, and the convergent projections from the dentate gyrus granule neurons to the ~160,000 CA3 pyramidal neurons in the rat *via* the mossy fiber pathway (*cf.*, Amaral and Witter, 1989).

Based on patterns of neural connectivity, Marr (1971) suggested that the hippocampus contains an autoassociative network, that is, a network of interconnected neurons in which a simple representation of an input is formed. Subsequent models of hippocampal function (Kesner and Rolls, 2001; Kesner et al., 1987, 2000; Kesner, 1991; Levy, 1990; Stringer et al., 2002, 2004, 2005) have also proposed that the hippocampus is able to quickly store memories using an autoassociative network (*cf.*, Grossberg, 1973; Hopfield and Tank, 1986; Hopfield, 1982, 1984; Rolls and Treves, 1994; Rolls, 1996).

This proposed mechanism underlying pattern separation was analyzed further and extended in a number of theoretical and computational models (McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000, 2001; Rolls and Treves, 1994; Rolls, 1991, 1996; Treves and Rolls, 1992, 1994). Pattern separation, or *orthogonalization*, was proposed to occur by an increase in sparseness of neural activity as patterns spread from the entorhinal cortex into dentate gyrus and then subsequently to CA3 (*i.e.*, the probability of different activity patterns in the entorhinal cortex activating identical dentate gyrus networks is exceedingly low). The separation of patterns can also benefit from competitive modification of inputs to dentate gyrus generating distinct, random representations, thus reducing the probability of patterns overlapping to an even greater extent (Myers and Scharfman, 2009, 2011; Treves and Rolls, 1992, 1994).

Pattern separation has traditionally been computationally defined by evaluating the effect of parametric alterations to input pattern overlap on output pattern overlap. To put it simply, if there are a two inputs that share a specified degree of overlap (*e.g.*, 50% overlap within a given feature domain), then pattern separation is the process by which the brain reduces the degree by which these output patterns overlap upon storage (*e.g.*, 50% incoming signal pattern overlap reduced to 25% pattern overlap in that feature for storage). It has been proposed that the dentate gyrus produces these orthogonal representations that are used by CA3 neurons during associative learning (Treves and Rolls, 1992, 1994). The first step to pattern separation is that the perforant path – dentate granule neuron system acts as a competitive learning system to eliminate redundant features from the inputs, producing more orthogonal, more easily categorized outputs (Marr, 1971; Rolls, 1996; Treves and Rolls, 1994). This process allows overlapping inputs to the hippocampus to be separated at the level of the dentate gyrus by increasing the sparseness by which information is encoded prior to transfer to CA3 *via* the mossy fiber pathway. Furthermore, the mossy fiber projections from the dentate gyrus to CA3 are sufficiently sparse that the probability of two different input patterns from the DG *via* the mossy fiber pathway activating the same set of CA3 neurons *via* the mossy fibers is extremely remote.

As a specific example from Rolls (1996), consider three patterns A, B and AB where AB is a linear combination of A and B. (To make the example concrete, consider binary patterns where A = 010, B = 001 and AB = 011). The hippocampal memory system is required to associate A with reward (010+), B with reward (001+), but AB with punishment (011−). Notice that A and B both share an element with AB (*i.e.*, share 50% similarity). This redundancy across cues needs to be reduced to prevent erroneous recall of A or B when specific recall of AB is required. This is one of the configural learning tasks emphasized by Sutherland and Rudy (1991) as a defining characteristic of the memory functions performed by the hippocampus. Without the hippocampus, rats have difficulty in solving such problems due to the overwhelming levels of interference among stimulus sets (*cf.*, Kumaran and McClelland, 2012; Kumaran, 2012).

As suggested by Sutherland and Rudy (1991) and explicitly modeled by O'Reilly and McClelland (1994), it is a property of competitive neuronal networks such as that found in the dentate gyrus to separate such overlapping patterns with high resolution. From these and other data, it can be inferred that one critical feature of the hippocampal neuronal network architecture relies on a competitive network in the dentate gyrus that precedes the CA3 autoassociation system. Without the dentate gyrus providing orthogonal inputs of A and B *via* pattern separation (*i.e.*, separating pattern overlap of 001 compared to 010, and subsequently separating both from 011 – a process also referred to as structural learning:

cf., Aggleton et al., 2007; Sanderson et al., 2006), an autoassociation network presented with the mixture AB could produce a mixed output state combining A (010+) and B (001+) into 010+, 001+, 000+, or 011+, the latter of which would catastrophically interfere with AB (011−) as all elements other than reward state are shared. The network would therefore be incapable of storing separate memories for A, B, and AB due to insurmountable levels of interference among stimuli, and rodents would fail at learning the task (referred to as *catastrophic interference* in the computational literature).

2.2. Psychological models of pattern separation

Recently, more mnemonic models of pattern separation have been developed based on the psychological concept of *discrimination*. These theories are supported by observed changes in pyramidal cell activity to different spatial environments in rats (Chawla et al., 2005; Guzowski et al., 2004, 2005; Kubik et al., 2007; Vazdarjanova and Guzowski, 2004; Vazdarjanova et al., 2006). Importantly for this theory, it was shown that place fields in the dentate gyrus showed reduced firing rates or remapped to even very small changes in the environment, whereas place fields in CA3 required larger environmental alterations to reduce firing rates or remap, and CA1 showed a tendency to require even greater changes still to remap (Lee and Knierim, 2007; Lee et al., 2004a,b; Leutgeb et al., 2005, 2007). When a similarity index for these cellular responses across experiments and across brain regions was plotted, a sigmoid-like function was observed, suggesting pattern separation sat at one end of a continuum with pattern completion on the other end (*cf.*, Guzowski et al., 2004). It must be emphasized, however, that more recent descriptions of these data do not support strong conclusions on whether such remapping is a direct readout of pattern separation or if it is a different measure altogether of some higher-level mnemonic process that relies on pattern separation to function (Aimone et al., 2011; Yassa and Stark, 2011).

In human research, it has been shown using continuous recognition paradigms that activation patterns in the hippocampus show a similar pattern, with dentate gyrus/CA3, but not CA1/Subiculum, activation corresponding to discriminating or reporting whether a foil that is very similar to the sample, was in fact different. Activity in CA1/Subiculum was more reflective of pattern completion processes, or generalizing across the sample and the foil (Bakker et al., 2008; Lacy et al., 2011; Yassa and Stark, 2011; Yassa et al., 2010, 2011). Importantly, this kind of behavioral discrimination is impaired in individuals with well characterized brain damage limited to the hippocampus (Kirwan et al., 2012).

3. Models of pattern completion

3.1. Computational model of pattern separation

Similarly to pattern separation, the present conceptualization of pattern completion processes focus primarily on spatial pattern completion in rats and mice and on temporal–linguistic–sensory/perceptual visual pattern completion in humans (*i.e., generalization*). Historically, pattern completion was defined as a process that can be carried out upon any incoming information across any cognitive domain to guide recall of a learned pattern using a degraded or partial version of the original stimulus pattern as a recall cue.

One mechanism through which the hippocampus facilitates memory retrieval is pattern completion (Marr, 1971; Willshaw and Buckingham, 1990), which is the ability to retrieve a stored memory trace based on an incomplete or degraded set of sensory cues as input. Based on neural connectivity, Marr (1971) suggested that the hippocampus contains an autoassociative network, that is, a network of interconnected neurons in which a simple representation of an input is formed (*cf.*, Hopfield, 1982, 1984). Subsequent models of hippocampal function (Levy, 1990, 1996; Levy et al., 2005; Rodriguez and Levy, 2001, 2004; Wu et al., 1998) have also proposed that the hippocampus is able to quickly store memories using an autoassociative network, and that such a network allows the rapid completion of previously acquired activity patterns using inputs that have been degraded from the original (*i.e.*, partial cues; O'Reilly and McClelland, 1994; Rudy and O'Reilly, 1999).

On the basis of the evidence summarized above, Rolls and co-workers (Rolls and Kesner, 2006; Rolls, 1996, 2007, 2010; Rolls et al., 2002; Rolls and Treves, 1994; Treves and Rolls, 1992, 1994), Levy and co-workers (Levy, 1990, 1996; Rodriguez and Levy, 2001, 2004; Wu et al., 1996, 1998), and O'Reilly and co-workers, (Frank et al., 2003; McClelland et al., 1995; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000, 2001; O'Reilly et al., 2011; Rudy and O'Reilly, 1999, 2001; Rudy et al., 2002; Van der Jeugd et al., 2009; Van Elzakker et al., 2003), among many others posited that CA3 enables episodic memories to be formed and stored on a brief timescale (seconds) within the CA3 network, and the extensive recurrent collateral connectivity allows for the retrieval of a whole representation by the activation of some small part of the previously activated representation (the cue) *via* recurrent collateral circuitry (but *cf.*, de Almeida et al., 2009, 2012).

An important caveat to this theory are the reports that CA3a,b (the major bend in CA3 that is not surrounded by the blades of the dentate gyrus) matches the criteria proposed in the majority of models of CA3, whereas CA3c (also called CA4 historically; *cf.*, Amaral and Witter, 1989) does not contain recurrent collateral circuitry and may function independent to the rest of CA3 (*cf.*, Hunsaker et al., 2008a). Since CA3c pyramidal cells do not have recurrent collateral connectivity but do send Schaffer collateral projections to CA1, we treat them as a separate cell population than the CA3a,b pyramids. As such, we will refer to CA3 as CA3a,b when referring that portion of CA3 and CA3c when referring to the CA3c region adjacent to the hilus and surrounded by the granule neurons of the dentate gyrus. The primary assumption of this hypothesis is that CA3a,b operates effectively as a single, large network that can freely allow arbitrary associations between many different inputs from any number of domains to be formed across all sensory modalities (*i.e.*, like CA3 in other models), and CA3c operates in networks more closely related to dentate gurus function than CA3a,b function (*cf.*, Kesner et al., 2008; Rolls and Kesner, 2006).

Autoassociation networks such as the recurrent collaterals in CA3a,b have the ability to store the number of different memories, each one expressed as a stable, reverberatory activity pattern, referred to as a stable attractor. However, the hippocampal CA3a,b cells do not necessarily have to operate as a set of permanently fixed, stable attractors: instead, it would be sufficient if CA3a,b cells could retrieve stored information in response to a partial cue initiating retrieval. The partial cue would remain present during recall, so that the attractor network would be operating directly upon incoming cues and not solely upon its own reverberatory activity *via* the recurrent collaterals (Rolls, 1996; Rolls and Treves, 1994; Treves and Rolls, 1992, 1994).

Critically for the computational models, there is a direct perforant path input into CA3a,b from the entorhinal cortex from the same axons that send the axon collaterals that synapse in the dentate gyrus that activate CA3a,b pyramidal neurons on average 2–3 ms prior to dentate granule neurons (*cf.*, Breindl et al., 1994) – thus providing a mechanism by which a non-orthogonalized input direct from the entorhinal cortex can serve as a retrieval

cue. Essentially, the recall cue would initiate reverberatory activity patterns within the CA3a,b recurrent collaterals that are capable of competing with the mossy fiber inputs carrying orthogonalized information. If the perforant path input is capable of reactivating a subset of a previously learned activity pattern, the completion of this pattern would then provide more information than the incomplete cue that entered the hippocampus, and the extra information retrieved would be sent to CA1 *via* the Schaffer collaterals and subsequently on to the neocortex to be acted upon (Hasselmo and Schnell, 1994; Hasselmo et al., 1995, 1996; Rolls and Kesner, 2006).

A critical element to the ability of the hippocampus to complete patterns based on a degraded cue was described by O'Reilly and McClelland (1994). There are effectively two different forms of recall cue that can be provided to the network, partial cues and noisy cues. A partial cue is simply a subset of the original activity pattern – similar to cues used to guide spatial recall – whereas a noisy cue is a subset of the original activity pattern with the addition of some extra noise that could come from outside the original activity pattern. Noisy cues, such as those used in human studies, have a tendency to preferentially engage the pattern separation properties of the hippocampal circuit. In fact, O'Reilly and McClelland (1994) demonstrated that a noisy cue input sharing 90% of the original activity pattern and 10% noise added to the input pattern would result in under 50% output overlap with the original pattern. In other words, if the pattern of activity from the entorhinal cortex into CA3a,b *via* the direct perforant path and dentate gyrus during recall were to be just a subset of the original learned pattern, there is a high probability that pattern completion process in the CA3a,b recurrent collateral system would be engaged in a manner directly proportional to the degree of cue similarity (Treves and Rolls, 1992). However, if the activity pattern entering the dentate gyrus were a subset of the original pattern interleaved with signal unrelated to the original activity pattern, the dentate gyrus may pattern separate, sending outputs to CA3a,b orthogonal to the learned pattern, and the direct inputs from the entorhinal cortex would be insufficient to elicit pattern completion processes, primarily due to the fact that the noise would be encoded as a novel feature that requires orthogonalization to be learned (Treves and Rolls, 1992, 1994).

3.2. Psychological models of pattern completion

Recently, more mnemonic models of pattern completion have been developed based on the psychological phenomenon termed *generalization* (*cf.* discussion of generalization as a process both separate and independent from pattern completion in Kumaran and McClelland, 2012; Kumaran, 2012). In the majority of behavioral reports, pattern completion is operationally defined as a lack of pattern separation (Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011; Lever and Burgess, 2012; Nakashiba et al., 2012; Yassa and Stark, 2011; Yassa et al., 2010), or generalizing across the sample and the foil or lure. This operational definition may or may not be true, depending upon task parameters and whether task performance requires pattern separation. Unfortunately, in many cases it is impossible to discriminate poor memory and lack of pattern separation in behavioral tasks since all the cues used for testing are degraded, rather than partial, in nature. It is impossible to determine or quantify the competition between pattern completion and pattern separation under these conditions. What has not been rigorously performed, however, is the experiment wherein a subset of the original cue is provided and responses collected – a condition that would unarguably require pattern completion processes independent to pattern separation processes since all incoming stimuli share features with a previously learned pattern.

4. Perceptual and mnemonic pattern separation and completion

As has been pointed out recently, there are at times differences between the role of a brain region for pattern separation of incoming sensory stimuli and a role for the same brain region for pattern separation when a memory component is added to the task (*cf.*, Aimone et al., 2011). As we shall cover later, the mnemonic requirements placed upon the individual or animal fundamentally change the nature of encoding – and thus change the manner by which the brain processes individual stimuli and relationships among stimuli.

An important issue involving the extension of pattern separation and pattern completion from theoretical models into behavioral testing is that of timescale. While pattern separation and pattern completion processes are clearly delineated by the computational models at the level of single cells and small scale neural networks, it is important to note that the behavioral readout of these processes can be very difficult, if not impossible, to isolate. Whereas the time scale of a theoretical/computational model is at the level of a theta cycle (*i.e.*, ~140 ms), one might be able to isolate encoding and retrieval, animal and all human studies operate on behavioral output that operates in a much longer time scales (seconds to minutes or years in some studies; as a concrete example of this issue human reaction time is often defined as >150 ms in cognitive tasks). For example, if one is training an animal to learn a completely novel task, then one can be reasonably comfortable that this acquisition phase involves primarily, though not exclusively, encoding (*cf.*, Hunsaker et al., 2008b). However, if one is teaching a human a list of words, retrieval will be an automatic partner process to encoding as the meaning of the words are automatically retrieved when read during the encoding phase.

A common example of this is the delayed recognition memory task in which a list of related words is encoded and later the related, but lures that had previously not been presented are later "incorrectly" recalled. Likewise, many fMRI studies have leveraged the fact that encoding occurs automatically, whether one has seen the stimulus previously or not. This encoding activity then infiltrates the "retrieval" task (and *vice versa*), making it difficult to isolate specific encoding and retrieval related activity. Additionally, an explicit retrieval task often induces a "recall to reject" strategy when participants are presented with a related lure item. In this case, pattern separation occurs once the pattern completion match has failed. While pattern separation or completion is certainly biasing the behavioral output, it is important to note that one cannot simply rely on the stage of the task (the encoding phase or the retrieval phase) to define which process is involved unless the task conditions are very carefully parameterized. When this is the case, it is important to consider an encoding task is one during which encoding is the more efficient strategy to perform the task correctly. Conversely, a "retrieval" task is one during which retrieval is the more efficient strategy to perform the task correctly. In our view and throughout this review we make the assumption that pattern separation predominates during encoding epochs, whereas retrieval is more predominant during retrieval epochs. We do not include examples of tasks where this assumption is clearly violated as examples of either pattern separation or pattern completion.

4.1. Pattern separation and completion at the sensory/perceptual level

An example of pattern separation processes being performed directly upon incoming sensory stimuli is the recent work in the olfactory system. Wilson and co-workers (Barnes et al., 2008; Sahay et al., 2011a; Wilson and Sullivan, 2011; Wilson, 2009) have

demonstrated that in mixtures of odorants, there is a clear pattern separation effect when a single odorant is replaced with another. This effect takes place at the level of the olfactory bulb, suggesting that at this earliest stage of processing stimuli are already processed in an orthogonal manner so far as possible. This is compared with behaviors observed when the odorant mixture is missing an odor from the mixture – resulting in a partial cue condition. In the piriform cortex of rodents, a clear pattern completion effect is observed in that the cellular firing as well as behavioral outputs associated with the original mixture is recalled from the degraded cue. Importantly for pattern completion, the piriform cortex has been shown to have a recurrent collateral system sufficient to perform an autoassociative function (Barkai and Hasselmo, 1997).

Another example of pattern separation at a perceptual level occurs within the hippocampus is the role of the dentate gyrus for the generation of orthogonal spatial and contextual representations. The hippocampus receives information from multiple sensory modalities, and one role proposed for the hippocampus is the generation of a spatial context using these inputs (O'Keefe and Nadel, 1978; Redish, 1999; Rolls, 1996). Since the incoming stimuli contain idiothetic cues as well as visual and other sensory information, it is critical that the hippocampus be able to form orthogonal representations of each spatial location to prevent erroneous recall of previously learned contexts. Rolls and co-workers (Rolls, 1996; Treves and Rolls, 1992, 1994) have proposed a specific role for the dentate gyrus in creating spatial representations with a very high resolution that can guide very specific behaviors. Importantly, Rolls further asserted that the CA3a,b subregion contributes to the generation of spatial representations independent of the dentate gyros as well, but that these representations, referred to as charts, are at a lower resolution and are more apt for discriminating large scale spatial geometry than for guiding specific behaviors (*cf.*, Hunsaker et al., 2008a; Rolls and Kesner, 2006). The model for fine dentate gyrus spatial pattern separation being involved in the generation of spatial context has also been reported in the context of place field formation in the firing patterns of principal cells of the hippocampus (Cerasti and Treves, 2010; Si and Treves, 2009; Stella et al., 2011; Treves, 2004; Treves et al., 2008). Furthermore, these models have been extended to explicitly account for empirical data derived from behavioral and physiological studies that were designed to explicitly challenge and extend upon computational models of hippocampal function (de Almeida et al., 2009, 2012; Hunsaker et al., 2008a; Myers and Scharfman, 2009, 2011).

4.2. Pattern separation and completion at the mnemonic level

In parallel with the example given for perceptual pattern separation using olfactory cues, it can be shown that the hippocampus is critical for pattern separation for olfactory cues when a mnemonic component is included. A recent report from Kesner et al. (2011) demonstrated that for a series of straight carbon chain alcohols that form an aliphatic series (*i.e.*, the differences among chemicals is a linear series of carbons; Cleland et al., 2002), the ventral, but not dorsal, hippocampus is critical for solving a task requiring the rat choose which of two odors was previously encountered during a working memory paradigm. Importantly, rodents performed increasingly poorly on this task as the number of carbons separating the odors was reduced, suggesting increased interference among the olfactory cues – presumably along the domain of carbon chain length. To verify there was not a deficit at the sensory/perceptual level, rats trained to discriminate odors separated by as little as one carbon were able to make the discrimination, so long as the mnemonic contribution to task performance was minimized (*i.e.*, no delay or memory demand was present that required flexible use of olfactory information).

To specifically assess pattern separation during this task, and more specifically the role of the dentate gyrus for this processing, working memory and pattern separation for odor information was assessed in rats using a matching-to-sample for odors paradigm. Odor separations of 1, 2, 3 or 4 were selected for each choice phase and represented the carbon chain difference between the study phase odor and the test phase odor. Once an animal reached a criterion of 80–90% correct across all carbon chain separations over 16 trials, rats received a control or ventral dentate gyrus lesion and were retested on the task after a 7 day recovery period. On postoperative trials, there were no deficits at 15 s delay for either the controls or the ventral dentate gyrus lesioned rats. However, when the delay was increased to 60 s rats with ventral dentate gyrus lesions were significantly impaired at short carbon chain separations, but their performance improved linearly as the difference in carbon chain length increased. The performance of rats with ventral dentate gyrus lesions matched control rats at the largest odor based separation. The graded nature of the impairment and the significant linear improvement in performance as a function of increased separation illustrate a deficit in odor pattern separation. Based on these results, it was concluded that lesions of the ventral dentate gyrus decreased the efficiency of odor based pattern separation, which results in impairments on trials with increased odor similarity among working memory representations (Weeden et al., 2012). The data suggest that the ventral hippocampus, especially the ventral dentate gyrus, but not the dorsal hippocampus, support pattern separation for odor information along the domain of carbon length in aliphatic series.

The addition of this mnemonic component to a task was sufficient to completely change the nature of pattern separation performed on the stimuli. If the rats used by Kesner et al. (2011) and Weeden et al. (2012) showed deficits for the perceptual pattern separation similar to those reported by Barnes et al. (2008), the rats would have been unable to perform the control task – as the interference among the stimuli would have been insurmountable. Similarly, deficits for the type of olfactory pattern separation being measured by Kesner et al. (2011) and Weeden et al. (2012) would be irrelevant for performance of the tasks reported by Barnes et al. (2008) as these experiments did not require flexible use of the orthogonal representations to guide task performance.

4.3. Dissociations of mnemonic and perceptual pattern separation/completion

Similar to Aimone et al. (2011), we propose that it is not only important to functionally dissociate pattern separation across the perceptual and mnemonic levels of processing, but also essential to a more complete understanding of how pattern separation and pattern completion processes influence behavior. As described above, one can see a clear dissociation of mnemonic and sensory/perceptual pattern separation as well as mnemonic and sensory/perceptual pattern completion so long as tasks are designed to emphasize one process over the other. These examples illustrate the importance of accounting for task design in studies into pattern separation and pattern completion. What may appear to be a paradigm requiring intact pattern separation at a mnemonic level may actually be subserved by pattern separation processes at a more basic level. Importantly, such data further emphasize that pattern separation exists across all sensory modalities to facilitate orthogonal coding of behaviorally relevant stimuli even at the level of primary sensory cortex – without the assistance of the hippocampus. However, when a mnemonic load is required such as the requirement that orthogonal representations be held in memory between sample and test phases, the hippocampus may be recruited to assist in pattern separation across multiple attributes or domains, and not just for spatial processing (Aimone et al., 2011;

Gilbert and Kesner, 2002b, 2003b; Kesner et al., 2002; Kesner and Rogers, 2004).

5. Independence of pattern separation and pattern completion

5.1. Evidence from human research

In experiments where lures are degraded versions of the original stimulus sets, then it follows that activation of firing patterns associated with a previously learned stimulus from the degraded input as a retrieval cue would depend upon pattern separation. However, in cases where the lures have been altered beyond degrading the cue by the addition of noise, it becomes more difficult to interpret the activation of previously learned patterns using an altered lure as a retrieval cue as purely a pattern completion process, as opposed to an impaired pattern separation process. In other words, at the level of behavioral output, it is often impossible to elucidate the neural processes underlying behaviors. As such, generalization processes have, in many cases, become thought of as synonymous with pattern completion – which is not necessarily the case (for a thorough description as well as solution to this apparent discrepancy the reader is referred to models of effective generalization in cases of perfect pattern separation; *cf.*, Kumaran and McClelland, 2012; Kumaran, 2012). Another critical point with pattern completion is the fact that if a cue elicits the activation of cell assemblies not at all activated by the original cue, then by definition the cellular response does not reflect pattern completion. Pattern completion works to complete/retrieve previously learned patterns, not to generalize across familiar patterns and patterns never previously encountered (*cf.*, Marr, 1971). Erroneous activation is more likely the result of a general memory deficit, generalization across stimuli, or deficiencies in pattern separation processes rather than pattern completion (*cf.*, Kumaran, 2012).

To overcome these difficulties, it is necessary to generate stimulus sets and lures that have been extensively tested and carefully manipulated to control the degree of interference between the test lure and the study stimulus. If one can generate a clear gradient in behavioral output that scales with the degree of interference in a carefully controlled experiment, then differences in performance can be more easily inferred based on the overall pattern of deficits within that individual (Lacy et al., 2011). An important point emphasized by computational models is that researchers must take care to carefully parameterize lures because partial cues that are simply degraded version of the original sample scale linearly (*i.e.*, partial cues with 50% cue degradation = 50% overlap with the original sample), whereas noisy cues have a tendency to engage the pattern separation properties of the hippocampal feedforward circuit (*i.e.*, noisy cues with 10% degradation replaced with 10% noise = under 50% overlap with the original sample). This point is not trivial as most experiments used in human research use noisy, as opposed to partial, cues (Bakker et al., 2008; Kirwan and Stark, 2007; Kirwan et al., 2012; Toner et al., 2009; *cf.* Lacy et al., 2011 for an analysis of careful cue parameterization).

Despite these difficulties, it has clearly been demonstrated that pattern separation processes and pattern completion processes result in differential, non-overlapping activation of hippocampus subregions. In short, research using fMRI has demonstrated that, as has been proposed in rodents, the dentate gyrus (and CA3 as CA3 is largely surrounded by the dentate gyrus in the human hippocampus) activated when a participant is demonstrating behavior congruent with pattern separation, and CA1/Subiculum activation occurs when participants demonstrated behavioral pattern completion (Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011).

5.2. Evidence from rodent research

Similarly, in rodent research, it can be extremely difficult to differentiate the role for general memory impairments, pattern separation deficits, and pattern completion deficits. It is quite common to use behavioral experiments such as contextual fear conditioning and water maze performance as an index of pattern separation and pattern completion. Unfortunately, at present these tasks have not been adequately parameterized such that performance and spatial/contextual interference show meaningful relationships (Nakashiba et al., 2008, 2012; Nakazawa et al., 2003). Most problematically, when rats are being tested on the water maze, deficits for recall of the previously learned platform location during the probe test session are interpreted as spatial pattern separation deficits. The interpretation of such data are inappropriate and unsupported by the data as retrieval or recall tests are not appropriate tests to evaluate pattern separation – as pattern separation is a process associated with encoding of stimuli, not retrieval. One experiment has evaluated the precision of spatial encoding in mice using the water maze, and the degree of imprecision was used as an index of impaired pattern separation (Garthe et al., 2009). This process provides a fairly robust quantification of the resolution of spatial processing, but cannot be attributed to pattern separation *per se* as there is no measure or metric of spatial interference that can underlie the inefficiencies reported in the behaviors (*cf.*, Nakashiba et al., 2009, 2012; Nakazawa et al., 2003). However, similar measures in conditions wherein the interference is modulated would reflect pattern separation processes.

Despite these difficulties, there have been efforts to develop apparatus appropriate for experiments into pattern separation and completion in rodents (Leutgeb and Leutgeb, 2007; Leutgeb et al., 2005, 2007; McHugh et al., 2007; Nakashiba et al., 2012). One such modification has been to make parametric changes to the environment or context that the rodents use to guide behavior. Leutgeb et al. (2007) recently showed that when rats experienced a completely different environment, CA3c place cells developed orthogonal representations of those different environments by changing their firing rates between the two environments, whereas CA1 place cells maintained similar responses.

To further test the role of CA3a,b in mediating pattern separation, an experiment was conducted to determine whether the the dentate gyrus or CA3a,b regions cooperate to perform spatial pattern separation operations for specific spatial locations as well as the spatial geometry of the environment or whether the dentate gyrus performs spatial pattern separation on the basis of specific locations in space and the CA3a,b performs spatial pattern separation on the basis of the geometry of the environment (Hunsaker et al., 2008a). Rats with lesions of dentate gyrus and CA3a,b were given the opportunity to explore a white or black circular or square box of the same size as reported by Leutgeb et al. (2007) and, in addition, in the box there were two objects spaced 68 cm apart. After habituation to the box and the objects, the rats received one of two transfer tests. In the first test the objects were changed to a 38 cm distance, but the box shape (geometry of the environment) remained the same.

In the second test the box shape (geometric environment) was changed, but the distance between the objects remained the same. The efficacy of the transfer test in terms of re-exploration of the metric change is based on a comparison between the level of object exploration during the transfer session *versus* object exploration during the last session of habituation. Similarly, the efficacy of the transfer test in terms of re-exploration of the geometry of the environment is based on the number of grid crossings (activity level) and rearing behaviors during the transfer session *versus* the number of grid crossings and rearing bouts during the last session of habituation. The results indicate that lesions of the dentate gyrus, but not

CA3a,b, disrupt both the detection of metric changes in the spatial location of objects and changes in a geometrical environment.

Thus far, these data are consistent with the prediction of the Rolls computational model that the dentate gyrus is the critical substrate for spatial pattern separation. These data are not consistent with findings of a pattern separation function for geometrical environments (Leutgeb et al., 2005, 2007; Tanila, 1999). It has been shown that the CA3 region can be divided into a CA3a,b, and c subareas (*cf.*, Amaral and Witter, 1989; Li et al., 1994). Most of the recorded CA3 cells that respond to different environments reported by Tanila (1999) and Leutgeb et al. (2007) were based on electrode placements in the CA3c area. The lesion data were based on lesions within CA3a/b, but not CA3c. It has been proposed that mossy cells receive excitatory inputs from granule neurons and CA3c pyramidal neurons and integrate the inputs from granule neurons and CA3c pyramidal neurons, which, in turn, *via* excitatory recurrent axonal projections activate many distal granule neurons (Amaral et al., 2007; Myers and Scharfman, 2009, 2011). This role is in addition to the traditional role for the mossy cells in providing competitive inhibition to the granule neurons *via* influential excitatory connections to GABAergic interneurons in the hilus that synapse onto granule neurons.

Such a circuit could integrate spatial location information and form representations of geometrical environments. Additional experiments with CA3c lesions in contrast to the CA3a/b lesions were carried out (Hunsaker et al., 2008a). The results indicated that dorsal CA3c lesions only disrupted pattern separation processes when the animal was required to detect a metric change in object location (*i.e.*, required fine spatial resolution), but there was no apparent effect during the environmental change task. It must be noted, however, that dorsal CA3c lesions never caused effects as dramatic as those caused by dorsal dentate gyrus lesions. One interpretation may be that the dentate gyrus selectively recruits CA3c to assist in the metric detection and not the detection of the overall environmental change, as CA3a,b were able to form spatial representation of sufficient resolution to discriminate overall geometry of the box (*i.e.*, fine pattern separation *vs.* charts). The present experiment provides behavioral evidence that dorsal CA3c and the dorsal dentate gyrus interact during spatial information processing, perhaps *via* recruitment of CA3c pyramidal cells to facilitate pattern separation in the dentate gurus.

This effect was only seen during the condition in which the animal is required to detect a discrete metric change in object location, a task that has been shown to be particularly sensitive to dentate gyrus damage (Goodrich-Hunsaker et al., 2005, 2008). In a followup experiment based on novelty detection for a change in the color (black, dark grey, light grey and white) of the box (in this case the change in box color reflected and overall change in context), it was possible to show that the dentate gyrus plays an important role in mediating pattern separation for changes in color as a function of contextual interference (identical boxes painted different shades of grey; Kesner and Musso, unpublished observations), suggesting that non spatial contextual cues such as color are also processed by the dentate gurus (*cf.*, Hunsaker et al., 2007a).

In summary, although the present behavioral data do not show any disruptive effects of dorsal CA3a,b lesions on pattern separation, the dorsal dentate gyrus lesion effect is clear. Additionally, the dorsal CA3c lesion data suggest that there is a circuit involving dorsal CA3c and the dorsal dentate gyrus that is perhaps important for pre-processing spatial information prior to dorsal CA3a,b processing stages. Critically, as mentioned above the task modifications tended to result in cues that were noisy as opposed to partial in nature, thus pushing the hippocampus into a mode favoring pattern separation functions over pattern completion functions.

As an example of how to overcome such difficulties in rats, Gilbert et al. (2001) demonstrated a clear spatial pattern separation deficit in rats with the granule neurons of the dentate gyrus in the hippocampus ablated using a delay match to place task that emphasized spatial interference during recall, but not encoding (Gilbert et al., 1998). However, a clear deficit using the same behavioral task was observed after lesions to the pyramidal neurons in CA3a,b (Gilbert and Kesner, 2006). This latter deficit could also be easily interpreted as a pattern separation deficit; however, when the performance data were plotted against the degree of spatial interference, there was a clear difference between the pattern of effects of CA3a,b and dentate gyrus lesions. The rats with dentate gyrus lesions showed a clear, monotonically increasing function that scaled with the degree of spatial interference, such that the rats were at chance performance at high interference and did not differ from controls in cases of low interference. In contrast, the CA3a,b lesioned rats showed a general spatial memory deficit, such that the performance was not modulated by the degree of spatial interference.

More recently, the paradigm used by Gilbert et al. (1998, 2001) has been adapted for usage with a semi-automated touchscreen apparatus for rats and mice (Clelland et al., 2009; Creer et al., 2010; McTighe et al., 2009; Talpos et al., 2010). This paradigm can be either spatial match or nonmatch to sample for the distance between two bars on the touchscreen. The benefit of this task is that it does not require the constant presence of an experimenter, but it does require extensive pre-training of the rodents to use the touchscreen. The only difficulty with this task is that it evaluates the computation spatial distance by the rat, not the generation of high resolution spatial representations as there are no contextual cues in the apparatus that can be used to generate spatial maps to guide behavior. As such, this task evaluates coordinate or metric processing more than spatial pattern separation *per se*. This being said, metric processing is one of the computations most closely linked to pattern separation in rodents, so as long as the task is performed at various levels of interference (distance) among stimuli, pattern separation is straightforwardly inferred from the behavioral data.

Another behavioral paradigm being modified to evaluate pattern separation are paradigms emphasizing contextual discrimination during contextual fear conditioning (Kheirbek et al., 2012; Nakashiba et al., 2008, 2012; Nakazawa et al., 2003; Sahay et al., 2011b). In these experiments, rats or mice are conditioned to a context by use of aversive foot shock. After an interval, the subject is put into a different environment and the freezing to the new context is measured. When the rodents freeze to a novel context, it is determined they did not discriminate contexts appropriately – measured by generalization of the fear response to a novel context. The only problem with this approach is that, if only two contexts are used, there is no way to know if any deficits are due to poor memory or discrimination, or pattern separation *per se*. Including highly similar as well as different environments for the test cases would parameterize contextual interference, and the resulting data could be interpreted as pattern separation deficits (*cf.*, approach in Kheirbek et al., 2012; Sahay et al., 2011b). Unfortunately, at present evaluating contextual fear retrieval using multiple, graded contexts has not been performed beyond using a very similar *versus* a very different context test, providing a rough measure of pattern separation – and then only across, not within, individual mice/rats.

Using a similar task to Gilbert et al. (1998, 2001), Gold and Kesner (2005) demonstrated pattern completion by parametrically altering the quantity of environmental cues available to guide recall for a spatial location (paradigm from Kirwan et al., 2005) – and saw deficits in CA3a,b lesioned rats, as well as in rats with temporary inactivations to mu-opioidergic plasticity mechanisms in CA3a,b (Kesner and Warthen, 2010). The role of mu-opioidergic dependent plasticity was not a minor point in this study as the lateral perforant path inputs into CA3a,b are mu-opioidergic, suggesting a role

for the perforant path inputs into CA3a,b for pattern completion (mossy fibers use kappa-opioidergic as co-peptides with glutamate, which were not blocked in this study). The requirement for this input is supported by an experiment from Lee and Kesner (2004), who demonstrated that the perforant path input into CA3a,b is critical for retrieval processes – indicative of pattern completion, whereas the dentate gyrus is critical for encoding processes – indicative of pattern separation. These data support the assertions made by Treves and Rolls (1992, 1994) demonstrating that, computationally, such an effect of the perforant path inputs was necessary to drive pattern completion in the hippocampus.

5.3. Biasing CA3 toward pattern separation or pattern completion: A proposal

A circuit between the hippocampus and medial septum/diagonal band of Broca has been characterized, as well as an efferent pathway from the hippocampus to the lateral septum (Gaykema et al., 1991; Raisman et al., 1966; Swanson and Cowan, 1977; Wyss et al., 1980). Briefly, CA3 subcortical efferents in the fimbria terminate in the lateral septum, medial septum, and diagonal band of Broca that result in net medial septum/diagonal band of Broca inhibition. CA1 subcortical efferents in the dorsal fornix also terminate in the lateral septum, medial septum, and diagonal band of Broca that result in net medial septum/diagonal band of Broca excitation. These differential effects occur because the CA3 and CA1 projections synapse onto distinct neuron populations. The medial septum and diagonal band of Broca send cholinergic efferents *via* the fimbria into the hippocampus that have been implicated in the hippocampal theta rhythm and modulation of learning and memory (Hasselmo and Bower, 1993; Hasselmo and Fehlau, 2001; Hasselmo and Giocomo, 2006; Hasselmo and McGaughy, 2004; Hasselmo and Schnell, 1994; Hasselmo, 1999, 2005; Hasselmo et al., 1995, 2002a,b; McLennan and Miller, 1974; McNaughton and Miller, 1986; Rawlins et al., 1979). Critically, these studies also demonstrated that acetylcholine in the hippocampus acts presynaptically by inhibiting glutamate release, presumably through M4 muscarinic acetylcholine receptor activation primarily at synapses in the stratum radiatum. GABAergic inputs are involved in hippocampal function as well, but act too rapidly to modulate encoding and consolidation/retrieval as operationally defined in most studies (*i.e.*, behavioral encoding and retrieval are measured in seconds or minutes as opposed to the millisecond time course of the GABAergic modulation within theta phase precession and similar processes; *cf.*, Wallenstein and Hasselmo, 1997). We suggest these GABAergic projections are potentially involved in biasing pattern separation and pattern completion dynamics at millisecond timescales such as during theta cycles, and acetylcholine regulates these processes at longer timescales, such as the second to minute timescales encountered during cognitive testing. In CA1 and CA3, acetylcholine has a more robust inhibitory effect in stratum radiatum than stratum oriens, stratum lacunosum-moleculare or stratum lucidum in slice preparations. In the dentate gyrus there are dense cholinergic projections into the inner molecular layer as well as the hilus and acetylcholine effects to disinhibit granule neurons in the dentate gyrus by reducing tonic inhibition.

The CA3 recurrent collaterals terminate primarily within the stratum radiatum, whereas the perforant path inputs terminate in the stratum lacunosum-moleculare and the mossy fibers terminate largely in the stratum lucidum with additional synapses onto thorny excrescences in the stratum oriens and stratum radiatum as well. Despite a partial overlap in connectivity among these input pathways, this pattern of connectivity suggests that the mossy fiber pathway (at least synapses in the stratum oriens and stratum lucidum) and perforant pathway inputs (in the stratum lacunosum-moleculare) are not as dramatically affected by acetylcholine influx as the recurrent collateral and Schaffer collateral inputs (which are presynaptically inhibited by acetylcholine *via* M4 receptors) – though they are bound to be affected to some degree, but this could arguably be beneficial and result in a high signal to noise ratio in the hippocampal system (*cf.*, Hasselmo et al., 1995; Hasselmo et al., 1996). These data suggest that acetylcholine modulates the hippocampus primarily by selectively altering the signal to noise ratio within the recurrent collaterals and Schaffer collaterals in the stratum radiatum by reducing synaptic transmission (Hasselmo and Schnell, 1994; Hasselmo et al., 1995, 1996). A diagrammatic model of the trisynaptic hippocampal circuit as well as how the septal nuclei interact with the hippocampus is presented in Fig. 1A.

An important additional effect of elevated acetylcholine levels in the hippocampus is the net result on dentate gyrus granule neurons. Bilkey and Goddard (1985) demonstrated that activations of septal projections into the hippocampus resulted in dis-inhibition of granule neurons through inhibition of inhibitory interneurons that provide tonic inhibition to the granule neurons (*i.e.*, disinhibition). Medial septal stimulation at magnitudes insufficient to result in evoked responses facilitated population spikes in the dentate gyrus to medial perforant path stimulation *in vivo*. In other words, the tonic inhibition on the granule neurons from the inhibitory neurons in the hilus typically attenuating or shunting the activity levels of granule neurons is reduced by cholinergic influx – thereby increasing the levels of responsiveness to stimuli of the dentate gyrus granule neurons under the same conditions that the influence of the recurrent collaterals in CA3 are minimized, supporting cholinergic models of encoding/retrieval dynamics in the hippocampus (*cf.*, Hasselmo et al., 1996). Alternately, any reduction from the baseline levels of cholinergic influence in the dentate gyrus would result in a net increase in inhibitory tone on granule neurons. This mechanism is important for models of hippocampal encoding and retrieval that require a relatively quiescent mossy fiber input to allow retrieval processes to be initiated *via* the perforant path projections from the entorhinal cortex (*cf.*, Rolls, 1996; Treves and Rolls, 1992, 1994; Fig. 1C).

At first glance it appears counterintuitive that increased dentate gyrus activity *via* acetylcholine influx would facilitate pattern completion given that the dentate gurus is known for being relatively quiescent and having high levels of competitive inhibition. However, this is not counterintuitive at all since the the proposed mechanisms whereby the dentate gurus engages in pattern separation does not actually require low activity levels of granule neurons, but rather requires the sparseness of encoding – that is to say the divergent connections from the entorhinal cortex to the dentate gyrus *via* the perforant path and the subsequent convergence of mossy fiber inputs to CA3 (Rolls, 1996; Treves and Rolls, 1992, 1994). In this case, the reduction of tonic inhibition in the dentate gurus would not result in reduced competitive inhibition, as the disinhibited granule neurons would be more likely to fire action potentials that excite the inhibitory interferons that mediate competitive inhibition than they were when inhibited. What would be facilitated by disinhibition, however, is the responsiveness of the dentate gurus granule cells to perforant path inputs.

In other words, although the dentate gyrus granule cells would be more responsive to entorhinal inputs, the cells would not sacrifice precision in their encoding because the following factors would remain unaltered: (1) the connectivity matrix with the entorhinal cortex would not be changed. (2) The competitive inhibition through local interferons would be intact as the interneurons would still respond to mossy fiber inputs in the normal way. (3) CA3c is recruited in the dentate gurus network with the mossy cells in the hilus for pattern separation (*cf.*, Myers and Scharfman, 2009, 2011) and these cells remain relatively

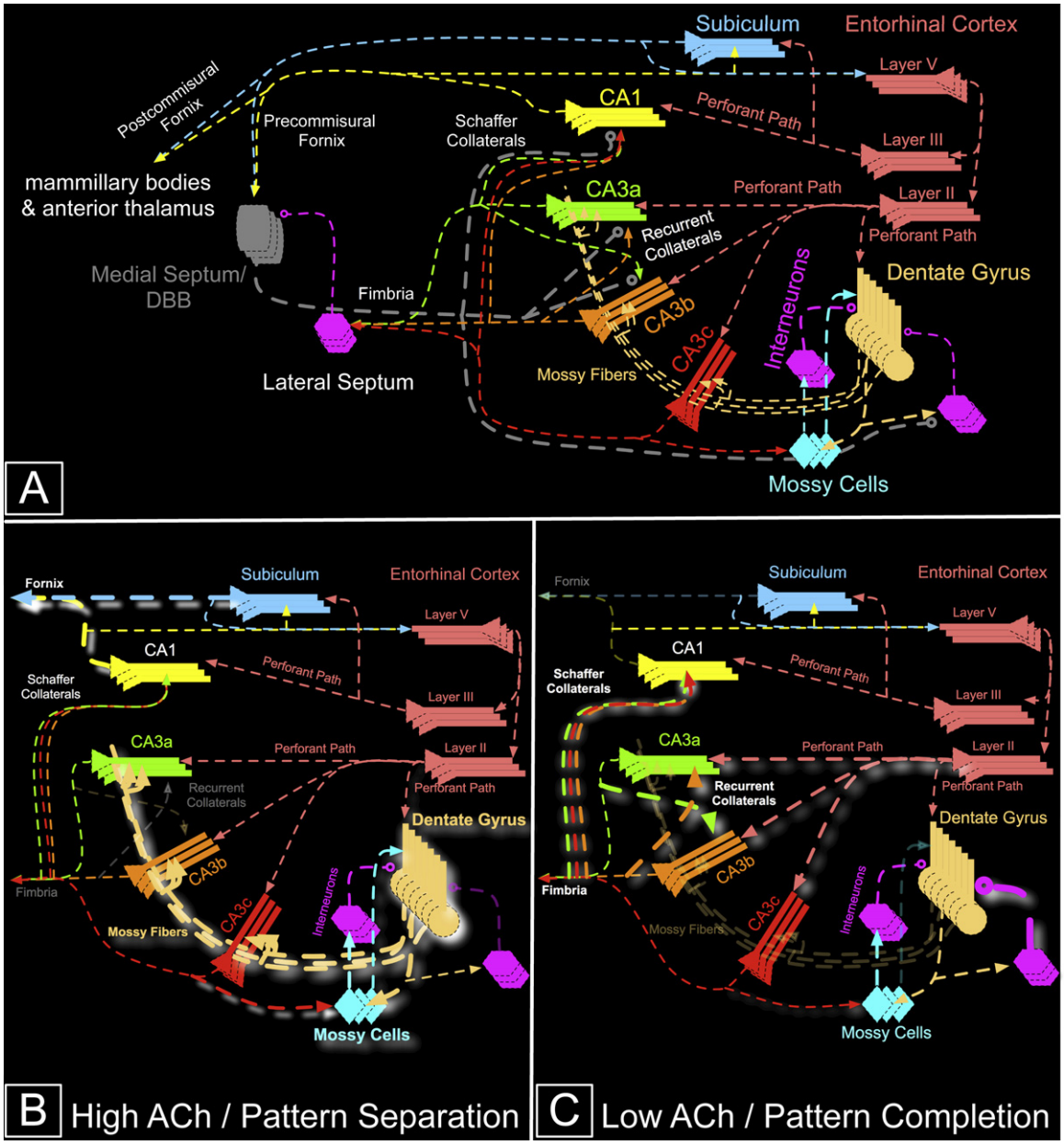

Fig. 1. Hippocampal circuitry. (A) Diagram of the trisynaptic loop and relevant connections within the hippocampus and septal nuclei proposed to subserve pattern separation and pattern completion. The bottom panels diagrams the relative strengthening and weakening of pathways during pattern separation and pattern completion processes. In this model, a mismatch between Schaffer collateral and perforant path inputs into CA1 result in a mismatch signal being sent to the cholinergic projection cells in the medial septum *via* the fornix – biasing the trisynaptic loop toward pattern separation and new encoding. The net result in activation of the medial septum and increased acetylcholine in the hippocampus. If the Schaffer collateral and perforant path inputs match, then projections from CA3 *via* the fimbria to the lateral septum result in medial septum inhibition through inhibitory connections from the lateral to medial septum, and reduced acetylcholine in the hippocampus – biasing the trisynaptic loop toward pattern completion and retrieval of previously encoded activity patterns. (B) Pathways that are lightened are those known to be negatively modulated by increasing acetylcholine levels in the case of pattern separation and thickened connections are those positively modulated by acetylcholine. (C) Pathways that are lightened are those known to be inhibited by reductions to acetylcholine levels in the case of pattern separation and thickened connections are those potentiated by reductions in acetylcholine. Cholinergic pathways shown in A are omitted from B, C for simplicity.

unaffected by acetylcholine efflux (no recurrent collateral synapses in the stratum radiatum). These three factors being unchanged, the net effect on the dentate gurus would actually be an increase in the overall competitive inhibition in the network but now with a lower threshold for initiation of these winner take all processes. This increased responsiveness to stimuli in the granule neurons, in concert with the reduced efficacy of the recurrent collateral synapses to activate CA3 pyramidal cells would facilitate information transfer from the mossy fibers to the CA3 pyramidal cells with no net sacrifice of dentate gyrus dependent pattern separation.

Based on the models proposed by Hasselmo and co-workers, it is suggested that CA1 provides a feedback control over the cholinergic modulation of the hippocampus. It is proposed that CA1 sends a “mismatch” signal to the lateral septum, medial septum, and diagonal band of Broca in response to information that needs to be encoded – a process facilitated by pattern separation. This means that if information from the Schaffer collateral fiber pathway does not match the information in the perforant path projections, then CA1 signals the septum to raise levels of acetylcholine in the hippocampus to facilitate pattern separation processes and attenuate pattern completion processes by reducing recurrent collateral

transmission while disinhibiting the granule neurons in the dentate gyrus. The CA1 projections, importantly, are excitatory on cholinergic projection cells, overriding any effects of CA3 projections in the fimbria that serve a somewhat tonically inhibitory function. Conversely, in the absence of a CA1 mismatch signal, CA3 projections *via* the fimbria to the medial septum and diagonal band of Broca result in reduced acetylcholine levels, which facilitate pattern completion and retrieval of learned patterns. This means that if information from the perforant path matches the information in the Schaffer collaterals, then CA1 does not send excitatory signals the septum, which when combined with CA3 projections that inhibit the medial septum, serves to attenuate levels of acetylcholine in the hippocampus to facilitate pattern completion and retrieval and attenuate pattern separation processes (for a quantitative analysis of the computational models being described *cf.*, Hasselmo and Schnell, 1994; Hasselmo et al., 1995, 1996). The effects on the dentate gyrus of the reduced acetylcholine levels would be that the granule neurons would be inhibited and less responsive to perforant path stimulation from the entorhinal cortex, thus providing the necessary reduction in dentate gyrus activity levels required for retrieval processes to occur per the models posited by Treves and Rolls (1992, 1994; *cf.*, Fig. 1B).

It has been clearly demonstrated that disrupting CA3a,b subcortical efferents in the fimbria disrupts encoding, but not retrieval, of spatial information during learning of a Hebb–Williams maze task (Hunsaker et al., 2008b). During this task, rats were required to traverse a maze from the start to goal box in the most direct possible path. Learning across the final 5 trials of the first day compared to the first 5 trials of the first day of training was used as an index of encoding, and performance on the first 5 days of the second day compared to the last 5 trials of the first day was used as an index of retrieval. These operationally defined encoding and retrieval epochs were on average 10 min in length each Rats with CA3a,b outputs to the septal nuclei *via* the fimbria disrupted were impaired for encoding or within day learning, but showed intact abilities to perform between day retrieval. Rats with CA1 outputs to the septal nuclei *via* the dorsal fornix/alveus disrupted showed intact abilities to perform within day encoding but were impaired for between day retrieval. Importantly, for these tasks the cholinergic inputs to the hippocampus *via* the fimbria were intact.

We propose this effect is due to a critical role for cholinergic inputs to the hippocampus in biasing CA3a,b to pattern separation *via* silencing the recurrent collateral influence relative to the mossy fibers, since a disruption of these cholinergic projections would disrupts the ability of CA3a,b to encode spatial information (Hunsaker and Kesner, 2009; Hunsaker et al., 2007a,b, 2008b, 2009). The consequence of increasing the cholinergic projections to CA3a,b would be a decrease in the synaptic transmission of the recurrent collaterals and thus less recurrent activation relative to the mossy fiber inputs. Also, when acetylcholine levels increase in the dentate gyrus, the inhibitory interneurons in the hilus are inhibited – thus reducing the amount of tonic inhibition on the granule neurons. The effect of this disinhibition is to increase mossy fiber neurotransmission (assuming increased transmission follows from increased responsiveness to stimulation), further biasing CA3a,b toward encoding information from the dentate gyrus over recurrent activity from the recurrent collaterals.

Reducing acetylcholine by attenuating excitation of the medial septum/diagonal band of Broca cholinergic neurons would favor pattern completion and recall over pattern separation and encoding and push CA3a,b into the role of a working memory buffer by reducing the signal to noise level, and thus providing the best environment for the detection and completion of patterns from partial cues (Kesner and Rolls, 2001; Rolls and Kesner, 2006). As mentioned above, concurrent with the effects on CA3, reducing acetylcholine would reduce inhibitory tone on inhibitory interneurons in the hilus – thus increasing inhibition on the dentate gyrus granule neurons, and subsequently reducing mossy fiber inputs to CA3a,b. Further models also support this assertion by demonstrating decreased acetylcholine levels in a septohippocampal classical conditioning learning model result in overall reductions to learning rate (Myers et al., 1996).

The pattern of results for scopolamine (a cholinergic antagonist) and physostigmine (a cholinergic agonist) infusions into CA3a,b is intriguing. Scopolamine infusions into CA3, but not physostigmine infusions, disrupt encoding. In contrast, physostigmine infusions into CA3, but not scopolamine infusions, disrupt recall. This was observed during a spatial exploration paradigm (Hunsaker et al., 2007b), during Hebb–Williams maze learning (Rogers and Kesner, 2003), and during delay fear conditioning (Rogers and Kesner, 2004). These data suggest that cholinergic levels directly influence information processing in the hippocampus, supporting our assertion that acetylcholine levels are perfectly located in time and place to bias CA3a,b toward either pattern separation or pattern completion.

6. Attribute model

In order to evaluate the potential for pattern separation and pattern completion processes both with and without hippocampal contributions, one must have a framework in which to organize the processes underlying memory formation. To meet this need, Kesner (Kesner et al., 1987; Kesner, 1991, 2007a,b), proposed an attribute processing model emphasizing massively parallel processing of all incoming sensory/perceptual stimuli by the brain with an emphasis on identifying and characterizing the specific roles of candidate neuroanatomical loci for information processing. Importantly, a critical assumption of this model is that anatomical loci act independently upon the information received from higher and lower level structures – such that there is no hierarchal or compartmental explanations for information processing as have been proposed at the level of behavioral output (Cohen et al., 1997; Eichenbaum et al., 1989, 1992; Squire, 1992; Squire et al., 2004). The benefit of such a model is that it allows similar processes to occur across cognitive domains without catastrophic interference from unrelated structures or types of information.

The memory systems proposed by Kesner are event-based, knowledge-based, and rule-based memory systems that have access to information comprised of sensory/perceptual, temporal, spatial, linguistic, affect, and response domains (or attributes). These attributes interact in a unique manner within and among each different memory system, and different overlapping and non-overlapping subsets of neuroanatomical substrates contribute to each memory system. This is akin to parallel information processing within the framework of multiple memory systems. It must be emphasized that these proposed memory systems are not to be thought of as compartmental models such as the declarative/nondeclarative or implicit/explicit memory models, since no memory system is assumed to operate independently of the others. The attribute model is better described as a catalog of component processes that facilitates behavioral dissociations of memory systems and memory processes based on the attributes subserved by each anatomical region, as well as the sum total and the nature of interactions with other brain regions within and among these distinct memory systems.

6.1. Event based memory system

The event-based memory system provides a temporary, highly plastic, short-term representation of information concerning the immediate past, the present, and the immediate future. The

event-based memory system rapidly encodes data and events that are personal (or egocentric) in nature and occur within specific external and internal contexts. In other words, the emphasis of the event-based memory system is on processing available information and comparisons with only very short-term representations of the very recent past and immediate future goals. Initial learning on any behavioral task emphasizes the event-based memory system. Later, during continued or longer-term learning, the event-based memory system will only become critically engaged in situations where trial-unique (or novel) information needs to be rapidly and flexibly utilized.

The event-based memory system is involved in episodic memory processing because it is capable of rapidly binding short series of events into coherent behavioral episodes. This memory system also mediates short term retrospective memory processes. The organization of individual attributes within the event-based memory system is as short-term, plastic, transient, and cognitive representations that interact with each other. This memory system can be described as a short-term working memory system (Olton and Papas, 1979; Olton, 1979). Importantly, the event based memory system is the memory system that includes pattern separation processes that are critical for the rapid, orthogonal encoding of information.

6.2. Knowledge-based memory system

The knowledge-based memory system provides lasting, relatively inflexible, intermediate and long-term representations of information previously encoded by the event-based memory system as well as direct sensory/perceptual input. The result of this processing can be thought of as general knowledge of a given task or world at large, similar to semantic memory processing in human research. The knowledge-based memory system is capable of processing information in an egocentric frame of reference and can derive allocentric frames of reference from the egocentric representations (Redish, 1999; Rolls and Kesner, 2006). The knowledge-based memory system is important after a task has been initially encoded, given that the situation is invariant and/or sufficiently familiar. The knowledge-based memory system mediates intermediate and long-term retrospective memory. The individual attributes within the knowledge-based memory system take many forms, usually as sets of attribute-dependent, long-term, cognitive representations and their interactions. The knowledge-based memory system can be thought of as an intermediate-term and/or long-term reference memory system (Olton and Papas, 1979). The knowledge based system is the memory system wherein pattern completion processes occur due to the recall of information previously encoded within the event-based memory system to guide behavior.

6.3. Rule-based memory system

The rule-based memory system receives information from the event-based memory system, knowledge-based memory system, as well as direct sensory information and integrates these information along with applying rules and strategies to guide subsequent actions. The rule based memory system not only computes and provides goal-related information to guide future behavioral decisions, but also allows for behavioral flexibility and generalization among contexts, rules, and strategies, depending upon task requirements and the individual or animal's previous behavioral experience. The rule-based memory system mediates both retrospective and prospective memory processes, but is particularly import for processes associated with prospective memory. The organization of individual attributes within the rule-based memory system is based on a high order set of rules and schema to guide behavioral decisions across contexts and during novel behavioral experiences. The rule-based memory system contributes to both working and reference memory processing by providing a representation of internal contexts to guide behavioral decisions and responses (Olton and Papas, 1979). Important to the biasing of the hippocampus toward pattern separation or pattern completion, the rule based memory system involves the representation of the internal state of the animal, as well as the requirements of the given behavioral task and representations of long term goals. This information can be used to emphasize the importance of dentate gyrus mediated pattern separation processes to guide encoding or the perforant path and recurrent collateral mediated pattern completion processes to optimally retrieve the data necessary to perform the given task.

6.4. The attributes that make up each memory system

6.4.1. Sensory/perceptual

The sensory/perceptual attribute within the current framework involves memory representations of sensory/perceptual stimuli that are part of a specific experience. Each sensory/perceptual modality (*e.g.*, olfactory, visual, auditory, vestibular, somatosensory, gustatory) is represented by the sensory/perceptual attribute. Although these sensory/perceptual stimuli are often used to compute and generate maps of space to be used by the spatial attribute (O'Reilly and Rudy, 2000, 2001; Rolls and Treves, 1994; Rolls, 1996), or used to generate sensory–response and action–outcome contingencies that are represented by the response attribute (Yin and Knowlton, 2006), the sensory/perceptual stimuli also are represented as independent entities that can be used or acted upon to guide behavioral performance (Cohen et al., 1997; Hunsaker et al., 2007c; Rolls and Kesner, 2006; Rolls, 2007, 2010; Rolls et al., 2008).

6.4.2. Temporal

The temporal attribute within the attribute model of memory processing involves memory representations of the duration of a sensory/perceptual stimulus and the temporal sequence or order of noncontiguous stimuli. From a "time" perspective, the temporal attribute defines a memory representation as past, present, or future relative to any and all other representations available for comparison, providing a sort of nonspatial temporal context (*cf.*, Howard et al., 2005). The temporal attribute is involved not only for temporal ordering and sequencing, but also for providing directionality and continuity to stimuli that are either spatially or temporally discontinuous (*e.g.*, separated by distance or a trace interval; Kesner and Hunsaker, 2010; Kesner, 2005; Kesner et al., 2005, 2010; Rogers et al., 2006). It is also involved in the formation of associations between noncontiguous sensory/perceptual stimuli. It has also been demonstrated that the temporal attribute may contain information about time *per se* (*e.g.*, interval duration), as demonstrated during delay-dependent differential conditioning as well as temporal reproduction tasks (*e.g.*, the "time left" paradigm; Cordes et al., 2007).

6.4.3. Space

The spatial attribute within the framework of multiple memory systems under the attribute model of memory processing involves memory representations of egocentric and allocentric spatial locations and relationships between spatial locations and sensory/perceptual stimuli. These processes are exemplified by the ability to rapidly encode and retrieve spatial maps (*e.g.*, cognitive maps; O'Keefe and Nadel, 1978; *cf.*, Tolman, 1948) and to localize sensory/perceptual stimuli in both egocentric and allocentric reference frames (Gallistel, 1990; Redish, 1999). The spatial attribute specifically refers to processed information that is the result of a combination of all the available sensory/perceptual cues into

an egocentric and allocentric representation of the environment (O'Keefe and Nadel, 1978; Vann and Aggleton, 2004). These processes underlying the computation and generation of "space" have been modeled extensively as configural or conjunctive processes (O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000, 2001), as competitive pattern separation and pattern completion processes (O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000, 2001; Rolls and Kesner, 2006; Rolls and Treves, 1994; Rolls and Webb, 2012; Rolls et al., 2002, 2006; Rolls, 1996, 2000, 2007, 2010; Treves et al., 2008; Treves, 2004), or as relational processes subserved by the hippocampus (Cohen et al., 1997; Eichenbaum et al., 1989, 1992). Memory representations of the spatial attribute are further subdivided into more specific features including allocentric spatial distance, egocentric spatial distance, allocentric direction, egocentric direction, allocentric location in space, and egocentric location in space, as well as categorical and coordinate (metric and topological; Gallistel, 1990) relationships among contextual elements.

6.4.4. Affect

The affect attribute involves memory representations of reward value (both of positive and negative valence), positive or negative emotional experiences, and associations between sensory/perceptual stimuli with associated rewards or punishments. The affect attribute increases or reduces the saliency of each element of information present during a given experience by aggregating a reward valence to each of the individual stimuli (O'Reilly and Frank, 2006). This is accomplished online during a behavioral episode or offline after the behavioral episode has concluded and is being consolidated to provide behavioral and internal contextual saliency to memory representations based on previous and subsequent experience.

6.4.5. Response

The response attribute refers to the cumulative habit, stimulus–response associations, and action–outcome contingencies available during an experience. A response attribute within this framework encapsulates memory representations of motor responses (often based on vestibular and proprioceptive sensory/perceptual stimuli), actions upon egocentric direction (*i.e.*, right and left), and memory representations for learned stimulus–response associations. Also, the response attribute subserves action–outcome learning (Gallistel, 1990; Redish, 1999; Yin and Knowlton, 2006).

6.4.6. Language

The language attribute is, presumably, unique to humans, and contains the semantic and phonological processes underlying language production, comprehension, and information coding *via* semantic or phonological mechanisms. Within this framework, a language attribute involves memory representations of phonological, lexical, syntactical, and semantic (or verbal) information.

7. Quantifying pattern separation across attributes

There are two important features that must be fulfilled by research into pattern separation processes: the first is parametric alteration of the interference among stimuli, and the second is the need for a function of behavioral responses that scales with interference. Although not one of the above critical features, it is also important that tasks evaluating pattern separation be encoding tasks – since pattern separation, by definition, is the process by which information is encoded in such a manner to minimize interference among memory representations/stimuli and facilitate later recall. This point is not trivial as a recent trend has emerged suggesting a wide range of impairments in memory are attributable to impairments in pattern separation processes (*cf.*, Hanson and Madison, 2010), which is a claim that cannot be substantiated unless all the above features of pattern separation experiments are fulfilled.

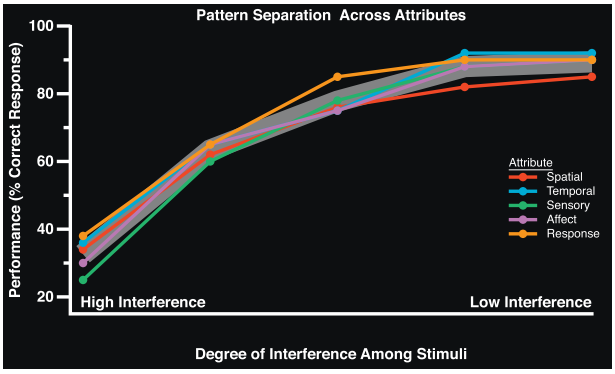

Fig. 2. Pattern separation functions across attributes. Scaled pattern separation functions demonstrate similarities among pattern separation across attributes. In all cases these functions are from the lesion groups. In these experiments the control animals performed at approximately 80–95% correct across interference levels. The grey line in the back represents the mean pattern separation function independent of attribute. Data replotted from the authors' studies as mentioned in the text.

Fig. 2 shows representative pattern separation functions across spatial, temporal, sensory/perceptual, affect, and response attributes (*cf.*, Barnes et al., 2008; Chen et al., 2012; Gilbert and Kesner, 2002b, 2003b; Gilbert et al., 2001; Kesner and Gilbert, 2006; Kesner et al., 2010, 2011). For these tasks, the data plotted are from the experimental subjects (rats or mice) that showed impairments for pattern separation, as the control animals were able to overcome the interference to properly perform at or near ceiling on the tasks(>85% in most cases). The critical aspect of these data is the similarity in the shape of the pattern separation functions across attributes being evaluated. Parametrically manipulating the amount of interference that must be overcome to properly encode the information necessary for task performance is directly (albeit not linearly) reflected in the behavioral output in affected animals.

7.1. Sensory/perceptual pattern separation

7.1.1. Odor pattern separation

As a prototypical example of pattern separation processes being performed directly upon incoming sensory stimuli is the recent work in the olfactory system. Wilson and co-workers (Barnes et al., 2008; Sahay et al., 2011a; Wilson, 2009; Wilson and Sullivan, 2011) have demonstrated that in mixtures of odorants, there is a clear pattern separation effect when a single odorant is replaced with another. This effect takes place at the level of the olfactory bulb, suggesting that at this earliest stage of processing stimuli are already processed in an orthogonal manner so far as possible.

7.1.2. Object pattern separation

Rats with perirhinal cortex, hippocampal, or sham lesions were trained on a successive discrimination go/no-go task to examine recognition memory based on pattern separation for an array of visual objects with varying interference among the objects in the array (Gilbert and Kesner, 2003b). Rats were trained to recognize a target array consisting of four particular objects that could be presented in any one of four possible configurations to cover baited food-wells. If the four target objects were presented, the rat should displace each object to receive food. However, if a novel object replaced any one or more of the target objects, then the rat should withhold its response. The number of novel objects presented on nonrewarded trials varied from one to four. The fewer the number of novel objects in the array, the more interference the array shared

with the target array, therefore increasing task difficulty requiring an object pattern separation mechanism to solve the task. The results indicated that an increased number of novel objects resulted in a pattern separation effect with less interference for the target array as indicated by decreased task difficulty. Although accuracy was slightly lower in rats with hippocampal lesions compared to controls, the learning of the groups was not statistically different. In contrast, rats with perirhinal cortex lesions were significantly impaired in utilizing a pattern separation function compared to both control and hippocampal lesioned rats. The results suggest that pattern separation for objects is affected by stimulus interference in rodents with perirhinal cortex damage.

Recent studies have extended visual object pattern separation processes into humans using modified continuous recognition paradigms (Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011; Toner et al., 2009). These experiments have demonstrated using fMRI that the dentate gyrus/CA3 area (as they cannot distinguish the two on MRI at present due to resolution limitations) reflect pattern separation processes, especially during trials wherein the participant correctly identifies a novel stimulus as novel or a highly similar foil as different from the target stimulus. Although these data seem not to match the findings from studies with rodents that suggest the perirhinal cortex, but not hippocampus, contribution to pattern separation for sensory/perceptual attributes, it is likely that human subjects are using linguistic tags to mentally describe the objects – thus involving the language attribute into task performance. As rodents do not have language as defined in humans, we suggest they perform sensory/perceptual pattern separation in a more process pure manner.

7.2. Temporal pattern separation

Although there are data to support the existence of memory for order information, it is not always clearly demonstrated whether memory for a particular sequence has been learned and can be accurately recalled. Estes (1986) summarized data demonstrating that, in human memory, there are fewer errors for distinguishing items (by specifying the order in which they occurred) that are far apart in a sequence than those that are temporally adjacent. Other studies have also shown that order judgments improve as the number of items in a sequence between the test items increases (Fortin et al., 2002; Hampstead et al., 2010; Johnson and Kesner, 1997; Madsen and Kesner, 1995). This phenomenon has been referred to as a temporal distance effect (sometimes referred to as a temporal pattern separation effect; Kesner et al., 2004; or a recency gradient if interpreted as a judgment of recency process *cf.*, Fortin et al., 2002). The temporal distance effect is assumed to occur because there is more interference for temporally proximal events than for temporally distant events (*cf.*, Howard and Natu, 2005).

Gilbert et al. (2001) tested memory for the temporal order of items in a one-trial sequence learning paradigm in rodents based on an experiment designed by Chiba et al. (1994). In the task, each rat was given one daily trial consisting of a sample phase followed by a choice phase. During the sample phase, the animal visited each arm of an 8-arm radial maze once in a randomly predetermined order and was given a reward at the end of each arm. The choice phase began immediately following the presentation of the final arm in the sequence. In the choice phase, two arms were opened simultaneously and the animal was allowed to choose between the arms. To obtain a food reward, the animal had to enter the arm that occurred earlier in the sequence that it had just followed. Temporal separations of 0, 2, 4, and 6 were randomly selected for each choice phase. These values represented the number of arms in the sample phase that intervened between the arms that were to be used in the test phase. After reaching an 80% performance criterion, rats received excitotoxic lesions to CA1.

Following surgery, control rats matched their preoperative performance across all temporal separations. In contrast, however, rats with CA1 lesions performed at chance across 0, 2, or 4 temporal separations and only somewhat better than chance in the case of a separation of 6 items – but there was evidence for a numerical improvement in performance as a function of temporal distance. The results suggest that the CA1 subregion is involved in memory for spatial location as a function of temporal separation of spatial locations; lesions of the CA1 decrease efficiency in temporal pattern separation. CA1 lesioned rats cannot separate events across time, perhaps due to an inability to inhibit the mnemonic interference that may be associated with sequentially occurring events. The increase in temporal interference impairs the rat's ability to remember the order of specific events – resulting in increased levels of temporal imprecision.

Although CA1 lesions have been shown to produce a deficit in temporal pattern separation (Gilbert et al., 2001), some computational models (Levy, 1996; Rolls and Kesner, 2006) have suggested that the CA3a,b region is an appropriate part of the hippocampus to form a sequence memory, for example, by utilizing synaptic associativity in the CA3a,b–CA3a,b recurrent collaterals that entail a temporally asymmetric component. Therefore, it was of interest to investigate the performance of CA3a,b-lesioned rats on the temporal order task previously described in order to determine whether the CA3a,b subregion of the hippocampus is necessary for sequential learning. The results showed that rats with CA3a,b lesions displayed similar impairment in the performance of the temporal order for spatial location information task as described above for rats with CA1 lesions (Gilbert et al., 2001). However, this impairment is likely to be the case only for spatial information.

The hippocampus is known to process spatial and temporal information independently (Hunsaker and Kesner, 2008; Kesner and Hunsaker, 2010). In the previous experiments, sequence learning and temporal pattern separation were assessed using spatial cues. Therefore, one possibility is that the CA1 and CA3a,b deficits were due to the processing of spatial rather than non-spatial temporal information. To determine if the hippocampus is critical for processing all domains of temporal information, it is necessary to use a task which does not depend on spatial information. Because the hippocampus does not mediate short-term memory for odors during delayed nonmatching to sample tasks (Dudchenko et al., 2000; Eichenbaum et al., 1992), it is possible to test whether the hippocampus performs a critical role in memory for the temporal sequence of odors.

Therefore, memory for the temporal order for a sequence of odors was assessed in rats based on a varied sequence of five odors, using a similar paradigm described for sequences of spatial locations. Kesner et al. (2002) found that rats with hippocampal lesions were impaired relative to control animals for memory for all temporal distances between the odors, despite an intact ability to discriminate between the odors (Kesner et al., 2002). Fortin et al. (2002) reported similar results with combined fimbria/fornix lesions (a method of disrupting hippocampal function by eliminating subcortical efferent/afferent pathways without directly ablating the principal cells of the hippocampus). In further subregional analyses using the same behavioral paradigm, rats with dorsal CA1 lesions showed a mild impairment relative to sham operated control rats, but rats with ventral CA1 lesions showed a severe impairment in memory for the temporal distance for odors (Kesner et al., 2010, 2011). Thus, the CA1 appears to be involved in separating events in time for spatial and nonspatial information, so that one event can be remembered distinct from another event; however, the dorsal CA1 might play a more important role than the ventral CA1 for spatial information (Chiba et al., 1994, 1997; Hunsaker et al., 2008c; Jackson-Smith et al., 1993), and conversely

the ventral CA1 might play a more important role than the dorsal CA1 for odor information (*cf.*, Hunsaker et al., 2008c).

It is not yet known whether for odors the ventral CA3a,b plays an important role. It is noted that, in these order tasks, the animals are not required to recall the sequence (for example by retracing their steps). Instead, the animals are asked which of two items occurred earlier in the list. To implement this type of memory, some temporally decaying memory trace or temporally increasing memory trace *via* a consolidation process might provide a model (Marshuetz, 2005); in such a model, temporally adjacent items would have memory traces of more similar strength and would be harder to discriminate than the strengths of the memory traces of more temporally distant items.

As mentioned above, studies have extended visual object pattern separation processes into humans using modified continuous recognition paradigms (Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011; Toner et al., 2009). These experiments have demonstrated that the dentate gyrus/CA3 area reflect pattern separation processes, especially during trials wherein the participant correctly identifies a novel stimulus as novel or a highly similar foil as different from the target stimulus. Although we include these experiments as sensory/perceptual as well as temporal and linguistic, it is possible that there is a temporal component to the pattern separation and pattern completion functions reported by these groups that has not to date been fleshed out by these authors. In other words, there may be an effect for the temporal lag between a given object and a repetition of that object or the object and a very similar foil that may complicate any description of pattern separation and pattern completion processes using these tasks.

7.3. Spatial pattern separation

To examine the contribution of the dentate gyrus to spatial pattern separation, Gilbert et al. (2001) tested rats with dentate gyrus lesions using a paradigm which measured short-term memory for spatial location information as a function of spatial similarity between spatial locations. Specifically, the study was designed to examine the role of the dentate gyrus subregion in discriminating spatial locations when rats were required to remember a spatial location based on distal environmental cues and to differentiate between the to-be-remembered location and a distractor location with different degrees of similarity or overlap among the distal cues.

Animals were tested using a cheeseboard maze apparatus (the cheese board is similar to a dry land water maze with 177 circular, recessed holes on a 119 cm diameter board) on a delayed-match-to-sample for a spatial location task. Animals were trained to displace an object which was randomly positioned to cover a baited food well in 1 of 15 locations along a row of food wells. Following a short delay, the animals were required to choose between objects which were identical to the sample phase object: one object was in the same location as the sample phase object and the second object was in a different location along the row of food wells. Rats were rewarded for displacing the object in the same spatial location as the sample phase object (correct choice), but they received no reward for displacing the foil object (incorrect choice). Five spatial separations, from 15 to 105 cm, were used to separate the correct object and the foil object during the choice phase.

Rats with dentate gyrus lesions were significantly impaired at short spatial separations; however, during the choice phase performance of dentate gyrus lesioned animals increased as a function of greater spatial separation between the correct and foil objects. The performance of rats with dentate gyrus lesioned matched control rats at the largest spatial separation. The graded nature of the impairment and the significant linear improvement in performance as a function of increased separation illustrate a deficit in pattern separation. Based on these results, it was concluded that lesions of the dentate gyrus decrease the efficiency of spatial pattern separation, which results in impairments on trials with increased spatial proximity and increased spatial similarity among working memory representations.

Thus, the dentate gyrus may function to encode and to separate events in space producing spatial pattern separation. Such spatial pattern separation ensures that new highly processed sensory information is organized within the hippocampus, which in turn enhances the possibility of encoding and temporarily remembering one spatial location as separate from another.

Based on the observation that neurogenesis occurs in the dentate gyrus and that new dentate gyrus granule neurons can be formed across time, it has been proposed that the dentate gyrus mediates a spatial pattern separation mechanism as well as generates patterns of episodic memories within remote memory (Aimone et al., 2011). Thus far, it has been shown in mice that disruption of neurogenesis using low-dose x-irradiation was sufficient to produce a loss of newly born dentate gyrus cells. Further testing indicated impairments in spatial learning in a delayed non-matching-to-place task in the radial arm maze. In the Clelland et al. (2009) study, mice with reduced neurogenesis were run on a delay match to position task using an 8 arm maze. There were two conditions in this experiment: conditions wherein the sample and the foil location were separated by only 1 arm on the 8 arm maze and a condition wherein the locations were separated by 2–3 arms, resulting in reduced spatial interference relative to the condition with the test arms separated by only one. In this experiment, mice with reduced neurogenesis were impaired for performance when the arms were close together, but not when they were separate. Furthermore, in a study using dentate gyrus lesions using rats, a similar effect was observed. These data also suggest the hippocampus, and more specifically the dentate gyrus, are involved for spatial pattern separation by overcoming spatial interference to discriminate between spatial locations that share a large amount of overlap (Morris et al., 2012).

Another study in mice provided evidence that the disruption of neurogenesis using lentivirus expression of a dominant Wnt protein produced a loss of newly born dentate gyrus cells; as well, and were observed in an associative object-in-place task with different spatial separations as a function of the degree of separation, again suggesting a spatial pattern separation deficit (Clelland et al., 2009). These data suggest that neurogenesis in the dentate gyrus may contribute to the operation of spatial pattern separation.

More recently, a study demonstrated in a schizophrenia mouse model that shows increased neurogenesis was associated with increased pattern separation abilities, whereas reduced neurogenesis was associated with impaired pattern separation processes using a modified metric task to evaluate the ability of mice to discriminate distances between two objects that were parametrically adjusted closer or further apart, resulting in graded performance across distance or interference (Chen et al., 2012). Taken together, these data suggest spatial pattern separation may play an important role in the acquisition of new spatial information and there is a good possibility that the dentate gyrus may have been the subregion responsible for the impairments in the various tasks described above.

There have been analyses of pattern separation and pattern completion related cellular activity in rats exposed to environments that have been parametrically altered (Leutgeb et al., 2005, 2007). What remains to be evaluated are the actual cellular firing patterns in the hippocampus during behavioral tasks mentioned above. Particularly, the evaluation of metric distance between stimuli has been a focus for pattern separation studies (*cf.*, Gilbert et al., 2001; Goodrich-Hunsaker et al., 2005, 2008; Hunsaker et al., 2008a), but to date no studies have been reported quantifying

cellular correlates of performance for this task using either single unit or immediate early gene analysis techniques. These data are critical to bridge the gap between the cellular and behavioral descriptions of spatial pattern separation processes. Furthermore, such studies in rodents would directly complement the human fMRI research evaluating pattern separation and pattern completion (*cf.*, Yassa and Stark, 2012).

In an extension of these spatial pattern separation paradigms into humans, Holden et al. (2012) presented participants with a simple dot on a screen. After a brief delay and the dot was removed from the screen, the dot and a foil dot in a location either 0, 0.5, 1.0, or 1.5 cm away was presented and the participant was asked to select the dot in the location that was first presented. They found a gradient of behavioral performance with the trials at the largest separation being clearly easier than those with higher spatial interference. The function they found in the behavioral performance was interpreted as an indication of a pattern separation process. Holden et al. (2012) demonstrated that in cognitive aging, there is a breakdown in this spatial pattern separation process such that the older individuals show a reduced performance improvement as a function of decreasing spatial interference (*i.e.*, the pattern separation function flattens out at suboptimal performance levels). They interpret their findings as evidence for a decrease in hippocampal integrity with age (Holden and Gilbert, 2012; Holden et al., 2012). They report that aged participants that do not perform well on standard memory tests are impaired in displaying a pattern separation function. One limitation of the dot task is that it does not assess the ability to separate spatial patterns in the real world. In order to assess real world spatial pattern separation, hypoxic subjects with hippocampal damage and matched normal controls were administered a geographical spatial distance task (cities on a map; Hopkins et al., 1995). The subjects were shown 8 cities on a map of New Brunswick one at a time for 5 sec each. Subjects were instructed to remember the city and its spatial location on the map. In the test phase the subjects were presented with the names of two cities that occurred in the study phase and were asked which of the cities was located further to the east (on separate trials, subjects were asked which city occurred further north, south, or west). There were two trials for each compass direction. Spatial distances of 0, 2, 4, and 6 as measured by the number of cities in the study phase that were geographically situated between the two test cities were measured. There were 8 trials for each distance. The hypoxic subjects were impaired for all spatial distances for spatial geographical information compared to control subjects who displayed a pattern separation function for distance (Hopkins et al., 1995). Thus, the dentate gyrus may function to encode and to separate locations in space to produce spatial pattern separation. Such spatial pattern separation ensures that new highly processed sensory information is organized within the hippocampus, which in turn enhances the possibility of encoding and temporarily remembering one spatial location as separate from another.

7.4. Affect pattern separation

Long-Evans rats were tested on a modified version of the anticipatory contrast paradigm described by Flaherty and co-workers (Flaherty and Rowan, 1986; Flaherty et al., 1989) to assess pattern separation for reward value. Prior to testing, each rat received either a control, hippocampal, or amygdala lesion (Gilbert and Kesner, 2002b). In the home cage, each rat was allowed to drink a water solution containing 2% sucrose for 3 min followed immediately by a water solution containing 32% sucrose for 3 min. Across 10 days of testing, the rats in each lesion group showed significantly increased anticipatory discriminability as a function of days. In order to assess the operation of a pattern separation mechanism, each rat was then tested using the same procedure except, the 2% solution was followed by a 16% solution for ten days and then the 2% solution was followed by an 8% solution for 10 days. Control and hippocampal lesioned rats continued to show high discriminability when the 2% solution was followed by a 16% solution, however, the amygdala lesioned rats showed low anticipatory discriminability. On trials where the 2% sucrose solution was followed by an 8% sucrose solution, all groups showed low discriminability scores suggesting that when two reward values are very similar even control animals are not able to overcome the interference between the two reward valences in memory. However, the results of a simple choice preference task revealed that all groups can perceptually discriminate between a 2% and an 8% sucrose solution when the solutions were provided simultaneously. The data suggest that the amygdala, but not the hippocampus, is involved in pattern separation of affective valence–at least for reward.

7.5. Response pattern separation

A delayed-match-to-sample task was used to assess memory for motor responses in rats with control, hippocampus, or medial caudate nucleus lesions (Kesner and Gilbert, 2006). All testing was conducted on a cheeseboard maze in complete darkness using an infrared camera. A start box was positioned in the center of the maze facing a randomly determined direction on each trial. On the sample phase, a phosphorescent object was randomly positioned to cover a baited food well in 1 of 5 equally spaced positions around the circumference of the maze forming a 180-degree arc 60 cm from the box. On each trial, the door to the start box was opened, the rat exited, displaced the object to receive food, and returned to the box. The box was then rotated to face a different direction. The food well in the same position relative to the box was baited and an identical phosphorescent object was positioned to cover the well. A second identical object was positioned to cover a different unbaited well.

On the choice phase, the rat was allowed to choose between the 2 objects. The object in the same position relative to the start box as the object in the sample phase was the correct choice and the foil object was the incorrect choice. The rat must remember the motor response made on the sample phase and make the same motor response on the choice phase to receive a reward. Four separations of 45, 90, 135, and 180 degrees were randomly used to separate the correct object from the foil on the choice phase. Hippocampus lesioned and control rats improved as a function of increased angle separation and matched the performance of controls. However, rats with medial caudate nucleus lesions were impaired across all separations. Results suggest that the medial caudate nucleus, but not the hippocampus, may support working memory and/or a process aimed at reducing interference for motor response selection based on vector angle information in a manner consistent with pattern separation across other attributes.

8. Quantifying Pattern Completion Across Attributes

There are two important features that must be fulfilled by research into pattern completion processes: the first is parametric alteration of the number or degree of degradation to retrieval cues, and the second is the need for a function of responses that scales with this degradation. Although not one of the above critical features, it is also important that tasks evaluating pattern completion be retrieval tasks–since pattern completion, by definition, is the process by which a degraded retrieval cue results in recall for a previously stored memory trace. This point is not trivial as a recent trend has emerged suggesting impairments in generalization can be attributed to impairments in pattern completion processes, which is a claim that cannot be substantiated unless all the above features of pattern completion experiments are fulfilled.

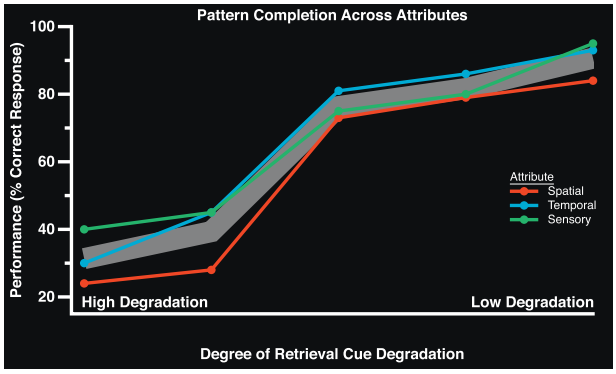

Fig. 3. Pattern completion functions across attributes. Scaled pattern completion functions demonstrate similarities among pattern completion across attributes. In all cases these functions are from the lesion groups. In these experiments the control animals performed at approximately 80–95% correct across degrees of retrieval cue interference. The grey line in the back represents the mean pattern completion function independent of attribute. Data replotted from the authors' studies as mentioned in the text.

Figure 3 shows representative pattern completion functions across spatial, temporal, and sensory/perceptual attributes (*cf.*, Bartko et al., 2007a,b; Eacott et al., 2003; Barnes et al., 2008; Hoang and Kesner, 2008; Gold and Kesner, 2005; Kesner and Warthen, 2010). For these tasks, the data plotted are from the experimental subjects (rats or mice) that showed impairments for pattern completion, as the control animals were able to efficiently recall the stored memory using the degraded cues to properly perform the tasks. The critical aspect of these data is the similarity in the shape of the pattern completion functions across attributes being evaluated. Parametrically manipulating the amount the retrieval cues were degraded is directly reflected in the behavioral output in affected animals. To the best of our knowledge, response and affect attributes have not been evaluated for pattern completion.

An important note on observation of this figure is the similarity between this figure and the figure commonly used to describe pattern separation and pattern completion as two ends of the same process best described by a sigmoid function (*cf.*, Guzowski et al., 2004) as well as the pattern separation and pattern completion plots from Leutgeb et al. (2005, 2007). As the behavioral data plotted in Figure 3 are behavioral results collected during retrieval tests that span attributes, it is possible that these previous descriptions of pattern separation and pattern completion functions were biased toward the influence of pattern completion over pattern separation during their experiments due to e nature of this tasks emphasizing recall or remembering of information over new learning or encoding.

8.1. Sensory/Perceptual pattern completion

8.1.1. Object pattern completion

In rat studies, it has been demonstrated that the perirhinal cortex plays a role in pattern completion for object information using both mnemonic and perceptual tasks evaluating pattern separation. In one set of experiments Bartko et al. (2007a,b) evaluated the ability of rats with perirhinal cortex lesions to perform object recognition and oddity discrimination tasks with no delay to eliminate memory confounds that would otherwise complicate and interfere with any interpretation of task performance. In these tasks, there was a clear function for task performance in sham lesioned animals along the domain of perceptual similarity, meaning that the rats were biased to retrieve the similar features among the stimuli. Perirhinal cortex lesioned animals were unable to perform these tasks. Similarly, Eacott and co-workers (2003) demonstrated that rats demonstrated a pattern separation gradient along the domain of feature ambiguity. These tasks lacked the range of ambiguity/similarities needed to form clear pattern completion gradients, but they provide preliminary support for object-related pattern completion in the perirhinal cortex of rats.

Recent studies have extended visual object pattern completion processes into humans using modified continuous recognition paradigms (Bakker et al., 2008; Kirwan and Stark, 2007; Lacy et al., 2011; Toner et al., 2009). These experiments have demonstrated that the CA1/Subiculum areas reflect pattern completion processes, especially during trials wherein the participant incorrectly identifies a novel stimulus as familiar or a highly similar foil as the same as the target stimulus.

8.1.2. Odor pattern completion Piriform cortex

As a prototypical example of pattern completion processes being performed directly upon incoming sensory stimuli is the recent work in the olfactory system. Wilson and co-workers (Barnes et al., 2008; Sahay et al., 2011a; Wilson and Sullivan, 2011; Wilson, 2009) have demonstrated that in mixtures of odorants, rats react when when the odorant mixture is missing an odor from the mixture–resulting in a partial cue condition. In the piriform cortex of rodents, a clear pattern completion effect is observed, in that the cellular firing as well as behavioral outputs associated with the original mixture is recalled from the degraded cue. Importantly for pattern completion, the piriform cortex has been shown to have a recurrent collateral system sufficient to perform an autoassociative function (Barkai and Hasselmo, 1997).

8.2. Temporal pattern completion

Since the hippocampus is assumed to process temporal information, an experiment was designed to examine the effects of dorsal hippocampus, dorsal CA3, dorsal CA1, and control lesions on performance of a temporal sequence task (Hoang and Kesner, 2008). The rats were trained on a sequential task for six spatial locations on a radial 8-arm maze. After initial training followed by surgery, it was found that all lesioned animals (dorsal hippocampus, dorsal CA3, dorsal CA1 or sham control) performed at very high levels for the original learned sequence when started from the beginning of the sequence. To test for temporal sequence completion, the animals were started at different positions in the previously learned sequence and expected to complete the remainder of the sequence. The results indicate that control rats had no difficulty completing the sequence, regardless of starting point. In contrast, the rats with dorsal hippocampus, CA3a,b, or CA1 lesions were impaired and made many errors. These results suggest that the dorsal hippocampus and specifically the dorsal CA3a,b in conjunction with CA1 may mediate retrieval of temporal sequences *via* a temporal sequence completion process. Similar results have been found in episodic recall tasks requiring the pattern completion of a sequence of trajectories along a linear track (Hunsaker et al., 2008d).

8.3. Spatial pattern completion

Marr (1971) suggested that hippocampal recurrent collaterals should play a significant role during the retrieval of previously stored information patterns in the face of partial inputs to the hippocampus ("collateral effect" or pattern completion). According to McNaughton and Morris (1987) and Rolls and Treves (Rolls and Treves, 1994; Treves and Rolls, 1992, 1994; Treves, 2004), an autoassociative network within CA3a,b should be sufficient to support pattern completion.

Experimental efforts to find evidence of pattern completion within the CA3a,b region have been successful in recent years. For example, a study conducted by Nakazawa et al. (2002) with CA3 NMDA receptor-knockout mice found that animals were impaired

in performing a standard water maze task when 3/4 of the familiar cues were removed from the environment. The result suggests that the NMDA receptor-dependent synaptic plasticity mechanisms in CA3 are critical to perform the pattern completion process in the hippocampus. However,there was never a gradient in performance due to reduction in cues as only the full cue and removal of 3/4 cue conditions were performed. Additionally, it was never clear in that study that the mice were using the specific cues that were removed as the cues were all 90 degrees away from each other at compass directions.

In a similar study (Gold and Kesner, 2005) rats were trained on a on a delayed matching-to-sample task for a spatial location task to study spatial pattern completion. Animals were tested on a cheese board maze surrounded by a black curtain with four extramaze cues surrounding the apparatus. In the sample phase of the task, rats were trained to move a small black block covering a food well which could appear in one of five possible spatial locations that were in front of four extramaze cues (*i.e.*, the rat could see all four cues when approaching the spatial location as they were within the 180 degrees visible immediately upon leaving the start box). During the choice phase of the task, rats were required to find the same food well, with the block removed in order to receive a food reward. After reaching stable performance, rats were randomly assigned to receive bilateral intracranial neurotoxic infusions or vehicle control infusions into the CA3a,b subregion of the hippocampus. Following recovery from surgery, each animal was re-tested on delayed matching-to-sample task. During the sample phase, the animal was presented with all four extramaze cues; however, the number of available cues (zero, one, two, three, or four cues) varied during the choice phase. Control rats performed well on the task regardless of the availability of one, two, three, or four cues, suggesting intact spatial pattern completion. Following the CA3a,b lesion, however, there were impairments in accuracy compared to the controls especially when only one or two cues were available, suggesting impairment in spatial pattern completion in CA3-lesioned rats or rats with disruption of opioidergic plasticity in the CA3a,b subregion (Gold and Kesner, 2005; Kesner and Warthen, 2010)

In a different study, Vazdarjanova and Guzowski (Vazdarjanova and Guzowski, 2004; Vazdarjanova et al., 2006) placed rats into two environments separated by approximately 30 min. The two environments differed greatly in that different objects were located in each room. The authors were able to monitor the time course of activations of ensembles of neurons in both CA3 and CA1, using a new immediate-early gene-based brain-imaging method (Arc/H1a catFISH). When rats were exposed to the same environment, both CA3 and CA1 neuron ensembles displayed a high degree of overlap. However, when cue configurations within the two environments were modified, CA3 neurons exhibited higher overlap in their activity between the two environments compared to CA1 neurons, suggesting that the CA3 region supports a pattern completion process–at least to a higher degree than CA1. Unfortunately, there were never any parametric alterations to the cues in this task, resulting in a binary same-different rather than graded response.

More support for the role of CA3a,b in pattern completion comes from a study conducted by Lee et al. (2004a,b). Lee and co-workers recorded from ensembles of neurons in both CA1 and CA3a,b in freely-behaving animals. Rats were placed on a circular ring track surrounded by a number of cues (local and distal). Across training sessions, cue configurations were held constant; however, during testing phases, cue configurations were altered to varying degrees. The results indicated that population spatial codes in CA3a,b were less disrupted by alterations in cue configurations than were CA1 neuron ensembles, which were disrupted at moderate alterations in cue configurations. Taken together, the results provide evidence for a pattern completion process in CA3a,b due to the maintenance of similar spatial representations of environments, despite alterations of the familiar environments. In other words, in the face of partial information (the cues in the room being all present, but slightly altered), the CA3a,b subregion of the hippocampus reflected the activity pattern previously demonstrated before the cue conflict.

In summary, evidence from lesion studies, electrophysiological analysis of CA3a,b neuronal activity, and early gene analysis of Arc within CA3 provide strong support for the role of CA3a,b in the process of pattern completion or in the completion of a pattern of information based on partial or altered cues.

8.4. Affect pattern completion

To the best of the authors' knowledge, there are no reported studies evaluating pattern completion for information within the affect attribute.

8.5. Response pattern completion

To the best of the authors' knowledge, there are no reported studies evaluating pattern completion for information within the response attribute.

9. Conclusions

Often times in studies into pattern separation and pattern completion, it becomes clear that the operational definitions may influence the direction of the experimental results almost as much as the performance of the research participants or research subjects. At present, it appears behavioral neuroscience is hyperfocused on determining the precise role for the dentate gyrus, and more specifically, neurogenesis, in performance on behavioral tasks requiring pattern separation. However, the focus on the outcome of these experiments appears to cloud the analysis of the behavioral paradigms themselves and often results in the over-interpretation of poor performance on tasks evaluating basic memory processes as indicative of pattern separation deficits (such as water maze impairments being an indication of impaired or intact pattern separation or pattern completion; Garthe et al., 2009; also *cf.*, discussions in Aimone et al., 2011; Sahay et al., 2011a; Yassa and Stark, 2011). Such erroneous interpretations result in conflicting data across laboratories that may be easily reconciled if task parameters and confounds are explicitly taken into account. We propose that by applying the attribute model to the design of all studies into pattern separation and pattern completion that disparate findings in the field may be easily reconciled.

The use of the attribute model during the developmental phase of task design emphasizes that the experimenter explicitly account for any confounds and carefully design tasks to emphasize the attribute being tested and control or account for the contribution of all other attributes. The same goes for memory systems. Applying the attribute model in task design and data interpretation would reduce the tendency for experiments focused on retrieval or probe tests to be interpreted as tests relying on pattern separation – as retrieval tests require the knowledge-based memory system and pattern separation resides within the event-based memory system. There is an interaction among these two memory systems, but the event-based memory system is only involved in providing the cue to the knowledge based memory system to guide retrieval or pattern completion of already established memory traces.

Additionally, there is a great need in the field of behavioral neuroscience to account for the rule-based memory system in rodent research. Often times, the fact that it takes rodents a relatively long time to learn a rule to guide behavior can be overlooked in the interpretation of any potential behavioral deficits. For example, lesions to the infralimbic/prelimbic subregions of the rodent rostral

cortex (analog to the human medial prefrontal cortex) resulted in deficits for object-place paired associate learning, whereas lesions to the anterior cingulate and precentral rostral cortex did not. These data could be easily interpreted as a spatial memory deficit in the rostral cortex of rats, but it is more likely that there is an executive component to the biconditional paired associate task (such as overcoming interference between go and no-go responses) that was disrupted by IL/PL lesions in these rats (Kesner and Ragozzino, 2003; Ragozzino et al., 2002). This is an important point because it has been demonstrated that the hippocampus, and more specifically the CA3a,b subregion mediates the spatial associations required in this paired associate task (Gilbert and Kesner, 2002a, 2003a; Kesner et al., 2008).

Specifically as pertaining to pattern separation and pattern completion research, it is critical that a careful eye be placed by the experimenter on the nature of information to be processed, as well as the nature of the task demands. It is quite easy to fall into the trap of over-interpreting data into a simplified model such as pattern completion or pattern separation without due regard to the specificity of the exact definition of those processes as classically accepted and formally modeled (*cf.*, definitions in Aimone et al., 2011; Gilbert et al., 1998, 2001; Kesner et al., 2000, 2004; Kesner, 2007a,b; Leutgeb and Leutgeb, 2007; Myers and Scharfman, 2009, 2011; O'Reilly and McClelland, 1994; Rolls and Kesner, 2006; Rolls, 2007, 2010; Sahay et al., 2011a,b; Yassa and Stark, 2011).

Applying the multiple memory systems approach provides some critical rules of thumb that can guide behavioral design: (1) Pattern separation occurs during encoding. Any analysis or data supporting a pattern separation-focused interpretation must be collected during encoding. Failure to retrieve does not infer failure to encode (and *vice versa*), as has been explicitly shown using a modified Hebb-Williams maze in rats (Hunsaker et al., 2008c). (2) Pattern separation can occur across any attribute, not solely sensory/perceptual and spatial information, but also temporal, affect, and response information. Furthermore, there is no reason to limit the evaluation of pattern separation to neurogenesis, as there is no neurogenesis in CA1 pyramidal neurons, but pyramidal neurons have been implicated in temporal pattern separation on multiple occasions (Gilbert et al., 2001; Kesner and Hunsaker, 2010; Kesner et al., 2000, 2004, 2010; Rolls and Kesner, 2006), and the amygdala does not show neurogenesis but pattern separates affect information (Gilbert and Kesner, 2002b).

Thirdly, pattern completion occurs during retrieval. This means that impaired learning or general memory deficits that result in an animal never being able to perform a task are not indicative of impaired pattern completion. They are general memory deficits. This does not mean there is no pattern completion during encoding, as there clearly is, but there is no way to directly test the influence of this pattern completion as separate from pattern completion using behavioral measures. (4) Pattern completion is defined as a partial (or degraded) cue input exciting the system to retrieve a previously learned memory trace. If a research subject commits an error during a task, but that error is not the retrieval of a previously learned memory trace, then the error is not a pattern completion deficit or a reflection of accessing pattern completion, but rather an error. If the nature of the error is to fall back on a previously learned memory trace, then the error may be evidence for excessive pattern completion–but this is difficult to determine empirically without direct cellular recording/labeling.

In this review we proposed pattern completion can occur across any attribute, not just space, time, and sensory/perceptual domains. It has, to this point, been difficult to design tasks evaluating the affect and response attributes that can provide a partial cue to allow the animal to provide evidence for pattern completion to the already remembered memory state. For the response attribute it may be possible to evaluate pattern completion if the subject learns a series of responses (*i.e.*, 5 or X choice serial reaction time task or a series of movements on a maze similar to DeCoteau and Kesner, 2000; Hoang and Kesner, 2008), and then be started somewhere in the middle of the sequence and see if the subject can pick up the sequence from that point to obtain reward. To the authors' knowledge, no such task has yet been designed. The difficulty with both affect and response attributes for evaluating pattern completion is that both affect and response are tightly linked to the rule based memory system, which may interfere with task performance when starting mid-sequence or mid-affective experience is required.

As research into the consequences of neurogenesis and the foundations of cognitive impairments in models of genetic disease have matured, a strong impetus has been placed on the potential role of imbalanced pattern separation and pattern completion processes as underlying the psychopathology of disease (*cf.*, Hanson and Madison, 2010; Tamminga et al., 2010, 2012). To date, however, the research into these processes has remained limited to behavioral paradigms that already exist and creative interpretations of these data (*i.e.*, water maze or contextual fear conditioning; *cf.*, Hunsaker, 2012a,b), and have also been, for the most part, limited to the spatial attribute or domain. This review has proposed the attribute model as a framework upon which future studies into pattern separation and pattern completion processes may be designed, especially as pertaining to cognitive domains outside space. Such studies will facilitate the design of behavioral paradigms that may be more widely applicable than those currently being employed, as well as provide a more clear understanding of the fundamental processes that are evaluated by each task.

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