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Hippocampal representations as a function of time, subregion, and brain state

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ABSTRACT

How does the hippocampus represent interrelated experiences in memory? We review prominent yet seemingly contradictory theoretical perspectives, which propose that the hippocampus distorts experiential representations to either emphasize their distinctiveness or highlight common elements. These fundamentally different kinds of memory representations may be instantiated in the brain via conjunctive separated codes and adaptively differentiated codes on the one hand, or integrated relational codes on the other. After reviewing empirical support for these different coding schemes within the hippocampus, we outline two organizing principles which may explain the conflicting findings in the literature. First focusing on *where* the memories are formed and stored, we argue that distinct hippocampal regions represent experiences at multiple levels of abstraction and may transmit them to distinct cortical networks. Then focusing on *when* memories are formed, we identify several factors that can open and maintain specialized time windows, during which the very same hippocampal network is biased toward one coding scheme over the others. Specifically, we discuss evidence for (1) excitability-mediated integration windows, maintained by persistently elevated CREB levels following encoding of a specific memory, (2) fleeting cholinergically-mediated windows favoring memory separation, and (3) sustained dopaminergically-mediated windows favoring memory integration. By presenting a broad overview of different hippocampal coding schemes across species, we hope to inspire future empirical and modeling research to consider how factors surrounding memory formation shape the representations in which they are stored.

1. Introduction

It has been over half a century since patient HM's surgery first demonstrated the critical role of the hippocampus in memory formation (Scoville & Milner, 1957), and seemingly countless researchers are still enthralled by this complex, mysterious structure. Indeed, we learn about new and important hippocampal functions every day; in addition to memory formation and retrieval, new findings suggest its role in flexible cognition more broadly, including navigation (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012), reasoning (Sheldon, McAndrews, & Moscovitch, 2011; Zeithamova, Schlichting, & Preston, 2012), decision making (Barron, Dolan, & Behrens, 2013; Palombo, Keane, & Verfaellie, 2015; Shohamy & Daw, 2015), and imagination (Addis & Schacter, 2011; Mullally & Maguire, 2014)—to name just a few. How does the hippocampus support such diverse behaviours? One possible answer is in its apparent ability to represent our experiences at multiple levels of abstraction, allowing our memories to be simultaneously high fidelity and flexible.

Theoretical and computational modeling of these hippocampal representational schemes have guided memory research since the 1970's (Marr, 1971). These ideas, however, have only recently become the subject of empirical investigation, in part due to prior barriers in 'reading out' the structure of hippocampal representations. The recent wellspring of machine learning and pattern analysis approaches in both human (Kriegeskorte, Mur, & Bandettini, 2008) and rodent (McKenzie et al., 2016) neuroscience combined with advances in data acquisition methods finally enable the characterization of memory-specific neural patterns required to test these entrenched theories (Box 1). In this review, we provide a high-level overview of different theoretical representational schemes along with recent evidence from rodent and human literatures. Throughout, we focus on how hippocampal contributions to memory are shaped by the nature of its *representations* and *memory traces,* terms we use to refer to any pattern of neural activity that encodes a specific memory and enables subsequent retrieval.

As we review below, however, the answers emerging from representational investigations are not always straightforward. Rather than supporting the simple dominance of one scheme over the others, data suggest that the hippocampus may employ multiple schemes.

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Box 1
Measuring hippocampal representation in humans.

Recent developments in fMRI acquisition and analysis methods have made it possible to characterize the representation of specific memories within the hippocampus. First, what do we mean by 'representation,' and why would we want to measure it? We use the term 'representation' to refer to the kind of information stored in the brain about a given experience or element thereof. For instance, the neural representation of an everyday object might include perceptual (e.g., size, colour, shape), conceptual (purpose, possible actions), and/or associative (co-occurs with, is related to) features. One particularly powerful aspect of measuring representation is that it allows for an empirical test of formal models of cognition, which may make predictions about the type of information stored (representation, usually experience-specific) in addition to that information is acted upon (process, usually common across a class of experiences) (Davis & Poldrack, 2013). Neural response associated with specific events are (typically) compared with other event responses from the same individual, as the particular spatial layout of representations is expected to be conserved in this case. By abstracting the data away from its specific neuronal implementation, researchers can also directly compare the representational structures across individuals, species, and imaging modalities (Cichy, Pantazis, & Oliva, 2016; Kriegeskorte, Mur, Ruff, et al., 2008; Kriegeskorte et al., 2008; Salmela, Salo, Salmi, & Alho, 2016).

A now-popular family of 'multivariate' analytic approaches gains their power by leveraging information coded across multiple voxels, or a 'pattern' of fMRI data. For a more in-depth review of these approaches, we refer the reader to (Davis & Poldrack, 2013; Walther et al., 2016). Briefly, the term 'multivariate' is used to contrast with more standard 'univariate' approaches, which average activation across voxels to yield just a single value per region and condition or trial. One example of a multivariate method is decoding or classification analysis, which uses a series of 'training' example fMRI patterns to predict an outcome—for instance, a cognitive state—from a new 'test' activation pattern (for a recent review, see Haynes, 2015). Outcomes are most often categorical (e.g., is this a chair or a shoe? Haxby et al., 2001), but may also be continuous (e.g., how similar is this stimulus to stored category knowledge? Mack, Preston, & Love, 2013) in nature. This technique leverages the representational structure of the training data—i.e., commonalities across example activation patterns with similar outcome values—to generate predictions about new experiences. A second multivariate analysis method is representational similarity analysis (RSA), which measures the pairwise similarity in a continuous fashion among a set of events (Kriegeskorte et al., 2008). Using this approach, the researcher can either search for regions of the brain that reflect a particular hypothesized representational structure (based on e.g., a formal model or behaviour) or create a multidimensional map of representational space (Edelman, 1998) in a more exploratory manner.

Additional challenges arise for memory researchers looking to quantify representation within tiny hippocampal subfields. First, as multivariate methods leverage distributed patterns of activation, a sufficiently large number of voxels[2] are required for any sort of pattern analysis. In the realm of hippocampal subfields, high-resolution functional MRI (roughly ≤ 1.7 mm voxels) is required to achieve a sufficiently large number of voxels within each structure of interest. Moreover, while high-resolution structural scans afford reasonable confidence in hippocampal subfields anatomically (despite differences in these tracing protocols across labs; Yushkevich et al., 2015), the spatial resolution of functional data is significantly coarser. The fact that multivariate methods are only sensitive to representations distributed across multiple voxels (Davis & Poldrack, 2013)—each of which average across hundreds of thousands of neurons even in high-resolution fMRI—restricts the application of such techniques to representations with relatively coarsely distributed topography.

One method that could achieve sub-voxel resolution is repetition suppression, which leverages the fact that particular neurons show a diminished response when a given stimulus is repeated (Barron, Garvert, & Behrens, 2016). This approach has been used to demonstrate that certain hippocampal subfields respond similarly to the initial presentation of a novel object and a second, highly similar object, taken as evidence that the objects are treated as distinct (i.e., pattern separated) within the hippocampus (Bakker et al., 2008). Other data suggest that repetition suppression paradigms can be used to measure map-like representations of both spatial (Morgan, MacEvoy, Aguirre, & Epstein, 2011) and non-spatial (Garvert, Dolan, & Behrens, 2017) relationships, with hippocampal adaptation tracking with real world distance between two familiar landmarks and position within a structured item sequence, respectively. While promising, the use of repetition suppression depends on the assumption that repetition reduces neural firing. This assumption requires further testing in the hippocampus and medial temporal lobe, as single cell recordings show that neurons can respond to repetitions with either decreases or increases in firing rates (Rutishauser, Mamelak, & Schuman, 2006). Also, while it is tempting to equate pattern analysis and repetition suppression approaches, a direct comparison (Ward, Chun, & Kuhl, 2013) reveals that across a widespread set of neocortical regions, pattern similarity and repetition suppression measures show differential relationships with to behaviour—tracking with explicit and implicit memory, respectively. Repetition suppression effects in neocortex are also argued to potentially be contaminated by 'carryover' activation from connected regions (Mur, Ruff, Bodurka, Bandettini, & Kriegeskorte, 2010) and/or top-down cognitive influences (Larsson & Smith, 2012). Whether the same is true for hippocampal representations is an important avenue for future inquiry.

Without organizing principles or the identification of key regulatory factors, this could be a theoretical calamity for memory research. Here, we focus on two factors that determine the representational code employed within a hippocampal network: (1) location within the hippocampus, as different subregions are biased toward different kinds of representations and may have separate outputs; (2) the state of neurons leading up to a given experience, including their excitability levels and the surrounding concentrations of specific neuromodulators.

2. Making memories for related events

In the lab, we often engineer to-be-remembered events to be as distinct as possible. However, such distinctiveness is supremely artificial. In the real world, so many of our experiences are interconnected via familiar people, places, and things. How do we store memories for such interrelated events? This review will focus on three prominent types of codes—pattern separation, integration, and

[2] A general rule of thumb regarding the number of voxels required for multivariate analyses does not yet (to our knowledge) exist. Many factors of both the data acquisition and analysis approach would be expected to influence what is the ideal number of voxels that make up a pattern in a given experiment. However, empirical studies (Cox & Savoy, 2003) and simulations (Etzel, Zacks, & Braver, 2013) investigating classifier performance as a function of the number of voxels in the fMRI patterns suggest that decoding accuracy plateaus at around 100–200 voxels. Given the lower signal to noise ratio of high-resolution fMRI data, the ideal number of voxels for researchers investigating representation as a function of subfield is likely even higher.

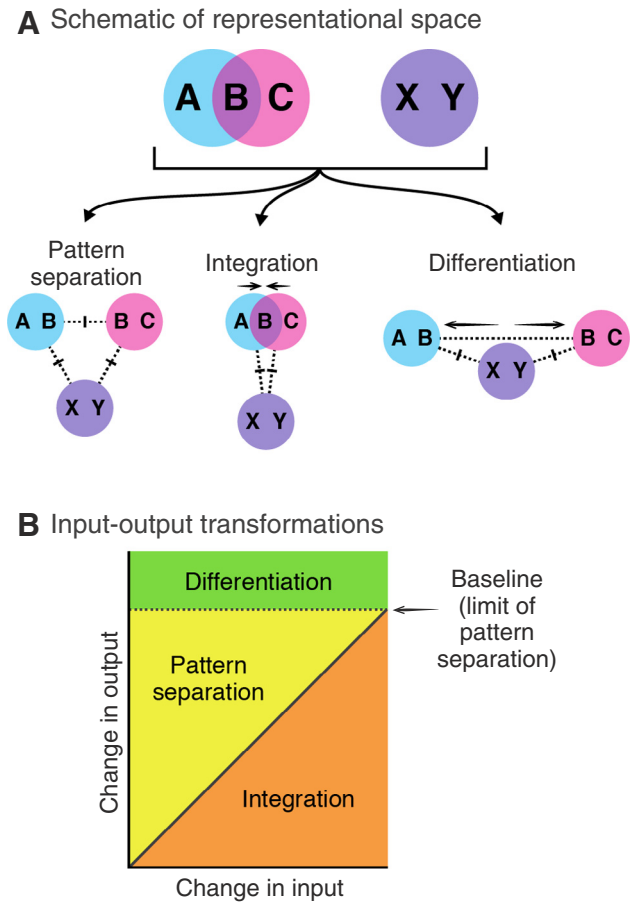

Fig. 1. Hippocampal representational codes. (A) Top, AB and BC denote experiences that overlap via a common element (B). XY is an unrelated experience that shares no features. Bottom, possible neural representations of AB, BC, and XY experiences. Under complete pattern separation, the three experiences are stored as equally similar to one another (equal distances denoted by hash marks), despite AB and BC having higher levels of objective overlap. Under integration, AB and BC representations are brought closer together due to the common element B, whereas XY is stored separately. Under differentiation, the B overlap is resolved by AB and BC representations being pushed apart. (B) Output change as a function of input change. The y = x line (solid) represents no transformation. An exaggerated change in output for a given change in input (i.e., reducing neural similarity) is defined as pattern separation (yellow area). The further above the diagonal a point lies, the more extreme the pattern separation. Conversely, an attenuated change in output for a given change in input (i.e., increasing similarity) is defined as integration (orange). We propose that the change in output for two unrelated events serves as an appropriate baseline (dashed line) to distinguish pattern separation from differentiation (green). Importantly, the input-output mapping for differentiation should be even more exaggerated than pattern separation, yielding less similar neural representations for related events that have been differentiated versus two unrelated events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

differentiation—which are defined by the representational transformations they perform, alternatively accentuating or minimizing minor differences between related events in memory (Fig. 1). To illustrate the complexities of real world memory, we need a real-world story that follows a character through a series of interrelated experiences. Our protagonist will be Priya, a senior graduate student in search of a postdoc. Through the trials and tribulations of her postdoc search, we will come to understand the costs (e.g., over- or under-generalization) and benefits (e.g., guiding flexible behaviour) of different hippocampal coding schemes.

Take, for example, Priya's back-to-back dinner interviews scheduled during the Society for Neuroscience meeting (SfN). The best part of the first interview was the restaurant; the risotto was incredible and the servers were much more engaging than her prospective advisor. Priya was excited when her second interview was scheduled for the same restaurant—at least she knew the food would be tasty! However, the shared restaurant will also create two experiences that could be connected in memory space via the similar food, staff, and context. How will all of this overlap influence her memory for these two different interviews and prospective advisors?

First, let's consider the most researched of the hippocampal coding schemes—pattern separation. This coding scheme reduces the overlap among memory representations, such that (at its extreme) all experiences are represented as equally distinct—regardless of how similar the experiences were (Yassa & Stark, 2011). If Priya's hippocampus successfully engaged in pattern separation, her memory representations of the two interviews would be just as distinct as her memory for completely unrelated events. In fact, the capacity of hippocampus for pattern separation is thought to prevent 'catastrophic interference' among related memories (McClelland, McNaughton, & O'Reilly, 1995; Yassa & Stark, 2011). But how is this separation achieved? The answer lies in conjunctive coding. Rather than representing the individual features or elements of an experience, each hippocampal neuron would only represent (i.e., have a receptive field for) the full conjunction of elements that comprise an experience. Thus, two experiences that differ in as little as one feature (e.g., the advisor) could activate distinct sets of hippocampal neurons.

The conjunctive codes generated by pattern separation come at a cost—they lose track of which features are shared across experiences. However, coding such shared features is critical for flexible behaviour (cf. Kumaran & McClelland, 2012; a model of how inferences could be drawn with conjunctive codes); it is often adaptive to either capture common threads across memories or, conversely, to highlight their unique features. These functions could be supported by two alternative hippocampal coding schemes: one that *integrates* across related experiences to emphasize the common elements and 'downweight' the idiosyncrasies; and one that *differentiates* to selectively reduce neural and psychological overlap between interrelated experiences, driving them further apart than unrelated experiences. While early models have generally ascribed both integration and differentiation primarily to neocortex (McClelland et al., 1995; Norman, Newman, Detre, & Polyn, 2006; O'Reilly & Rudy, 2001), recent empirical evidence (Chanales, Oza, Favila, & Kuhl, 2017; Collin, Milivojevic, & Doeller, 2015; Favila, Chanales, & Kuhl, 2016; Hulbert & Norman, 2014; Schlichting, Mumford, & Preston, 2015) and modeling work (Schapiro et al., 2016) suggest that both representational schemes may in fact exist within the hippocampus proper.

An integrated hippocampal coding scheme distorts representational space so that common elements pull interrelated experiences closer together in memory. According to integrative encoding frameworks (Shohamy & Wagner, 2008; Wimmer, Braun, Daw, & Shohamy, 2014; Zeithamova, Dominick, & Preston, 2012), memory integration is driven by reactivating past experiences while encoding new, related ones. As described below, the hippocampus is also well equipped to perform this reactivation via a process called pattern completion (Treves & Rolls, 1992). In the example of Priya's second interview, she may recall the tiramisu that she tried in her first interview even though she ordered the crème brûlée on her second. Though not physically present, the reactivated memory of tiramisu could then be integrated with her new dessert memory on the second dinner, effectively linking the two desserts through their shared relationship with the restaurant. Neurally, integration might take place by strengthening each co-activated memory representation as well as the connections between them. It should be noted that this coding scheme is fundamentally non-conjunctive, but rather has a relational structure (Cohen & Eichenbaum, 1993) in which the explicit representations of shared features serve as common 'nodes' to link memories. These integrated memories are thought to be crucially important for guiding a number of flexible behaviours that tap multiple experiences (Eichenbaum, 2004;

Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Schlichting & Preston, 2015); however, they may also be maladaptive, giving rise to memory interference, misattribution, or overgeneralization (Kumaran & McClelland, 2012). In Priya's case, it may be adaptive for her to generalize across the restaurant's desserts when giving restaurant recommendations to a friend, but generalizing across interviews could also leave her with a poorer impression of the second prospective advisor than she deserved.

This risk of over-generalizing across interrelated experiences is reduced in the third coding scheme: differentiation.[3] While pattern separation would be sufficient to tease apart related experiences in most cases, in reality, it may only partially transform representational space; while interrelated experiences may become decorrelated, they could still be closer together in memory space than unrelated experiences. By contrast, differentiation selectively drives apart those events that are most similar, such that their resulting memory representations are actually further from one another than they are to unrelated events (Fig. 1B). Over the last few years, differentiated representations have been reported in the human hippocampus (Chanales et al., 2017; Collin et al., 2015; Favila et al., 2016; Hulbert & Norman, 2014; Kim, Norman, & Turk-Browne, 2017; Schapiro, Kustner, & Turk-Browne, 2012; Schlichting et al., 2015), with some evidence in the rodent hippocampus as well (McKenzie et al., 2014). Similar to the integrative encoding mechanism described above, existing models (Hulbert & Norman, 2014) of this phenomenon rely on the capacity of the hippocampus to reactivate related memory representations during a new experience. When there is a moderate level of reactivation (Detre, Natarajan, Gershman, & Norman, 2013; Newman & Norman, 2010; Poppenk & Norman, 2014) as well as conflict detected with information in the environment—i.e., memory 'mispredicts' current experience—memory traces for the retrieved information are weakened (Kim, Lewis-Peacock, Norman, & Turk-Browne, 2014). Neurally, this is proposed to happen through a specific combination of synaptic strengthening and weakening. First, neurons coding the features shared across two memories are allocated to the new trace, and their connections with the old memory are eroded (Norman et al., 2006; Norman, Newman, & Detre, 2007). Differentiation occurs when there are subsequent opportunities to strengthen the initial (i.e., now weakened) memory. In particular, if the initial information is re-encountered, its representation is strengthened and expands away from the new memory to include more non-overlapping neurons (Hulbert & Norman, 2014). Thus, differentiation appears to require moderate levels of reactivation, misprediction, as well as re-study (Kim et al., 2017). This process severs the relationships between memory traces, beyond the limits of separated conjunctive coding. Within this framework, Priya reactivating her first interview during her second might weaken her memory for the first experience. Further, if she were to run into the first prospective advisor again later, the memory representations for the two prospective advisors would become even more distinct.

Of note, one key feature of both integration and differentiation is that these schemes may emerge over time, as stored memories are reactivated—either during a task (Hulbert & Norman, 2014; Zeithamova, Dominick, et al., 2012) or during passive periods like rest or sleep (Lewis & Durrant, 2011; Stickgold & Walker, 2013). Such iterative reactivation would allow for memories either to be pulled together or pushed apart. The degree to which memories are reactivated appears to be critical in determining whether it results in integration or differentiation (Detre et al., 2013; Newman & Norman, 2010; Poppenk & Norman, 2014). In particular, high levels of reactivation may lead to strengthening and integration, whereas moderate reactivation leads to initial weakening and, provided the information is subsequently re-encountered, differentiation.

Each of these coding schemes—pattern separation, integration, and differentiation—is defined by the unique and mutually incompatible representational transformations they perform. As we discuss in more detail below, there are growing bodies of evidence supporting the existence of each type of representation within the hippocampus and connecting them to different memory behaviours. With support for these fundamentally different coding schemes, the field is left wondering: Is the hippocampus a pattern separation module that rapidly forms inflexible memories with minimal interference? Is it a relational processing module, which capitalizes on shared features to integrate memories in service of flexible decisions? Or, might it be strategically differentiating the most competing memory traces? In the following sections, we first discuss evidence for these coding schemes across different subfields of the hippocampus. We then describe physiological factors that may influence hippocampal coding schemes, focusing mainly on pattern separation and integration, as they are the most widely described.[4] For a discussion of cognitive factors that may influence representation, see Box 2.

3. The emergence of complementary codes across hippocampal subregions

How might the hippocampus simultaneously maintain these different kinds of representations? One answer may lie in the heterogeneity of hippocampal structure and function across the transverse, longitudinal and radial planes. Here, we focus on heterogeneity in the transverse plane, reviewing both classic models and recent evidence for representational differences across subfields, beginning in the dentate gyrus (DG) then moving through the *cornu ammonis* fields (CA) 3 and 1. See Box 3 for discussion of representational differences across the longitudinal axis and Geiller, Royer, & Choi (2017) for a recent review of representational differences along the radial axis of area CA1.

3.1. Dentate gyrus is poised for pattern separation

Several physiological properties of DG are ideally suited to pattern separate input from the entorhinal cortex (ERC) (O'Reilly & McClelland, 1994; Rolls, 2007). First, DG granule cells (the most abundant class of excitatory neurons in the DG) outnumber those in ERC (the input structure) by roughly a factor of four (West, Slomianka, & Gundersen, 1991); thus each ERC representation is recoded into a relatively small proportion of the larger DG network, resulting in 'sparse' representations. This sparse coding scheme is further enhanced by (1) the many-to-one mapping of ERC input and (2) high levels of inhibition within the DG. Thus, DG granule neurons should only fire when a high proportion of their many ERC converging inputs are simultaneously active; for this to occur, the same combination of elements encoded by ERC neurons (e.g., a dinner and advisor) must be present (Fig. 2A). This is the hallmark of conjunctive coding. Consistent with its hypothesized sparseness, recent DG granule cell recordings demonstrate that only 9% of

[3] We echo the distinction made by Hulbert & Norman (2014) between the terms *pattern separation*—a scheme resulting from the sparse codes in the hippocampus applied equally to all experiences, and *differentiation*—which reduces or eliminates the representational overlap entirely in an effort to resolve mnemonic competition and avoid future misprediction (Kim, Sambeth, & Blokland, 2017).

[4] Differentiation may be empirically difficult to tease apart from pattern separation, as they perform similar transformations (i.e., they decrease the neural similarity of two inputs). We propose that two approaches for distinguishing these phenomena are: (1) explicit comparison with a meaningful baseline and (2) mapping out representational change over time. Specifically, differentiation but not separation should yield representational similarities that dip below baseline, such as a reliability negative correlation (zero as baseline) in rodent electrophysiology (McKenzie, Robinson, Herrera, Churchill, & Eichenbaum, 2014), or a reliability lower correlation between related versus unrelated events (unrelated events as baseline; Chanales et al., 2017; Favila, Cowan, 2016; Markus et al., 1995; Schapiro, et al., 2012; Schlichting, Zeithamova, & Preston, 2015). Moreover, differentiated but not separated representations should emerge—and may continue to diverge—over repeated exposures across time (Bostock, Muller, & Kubie-i-, 1991; Chanales et al., 2017; Kim et al., 2014; Lever, Wills, Cacucci, Burgess, & Keefe, 2002; Schapiro et al., 2012; Schlichting et al., 2015).

Box 2
Modulation by goals and strategies.

Several complex factors that may influence hippocampal representation are perhaps best described at a cognitive level. These include goals, strategies, and active inhibition. For example, pattern separation is often measured in continuous recognition paradigms, in which large hippocampal responses across small changes in perceptual input suggest that even highly similar stimuli are treated as 'new' (Bakker et al., 2008; Yassa & Stark, 2011). However, these neural signatures depend on whether participants make a memory judgment based on the semantic category rather or the particular item (Hashimoto et al., 2012; Lohnas et al., 2017). Furthermore, recent work suggests that attention modulates hippocampal response during memory formation (Aly & Turk-Browne, 2016, 2017), and is even reflected in the active representations that guide choices about specific items (Mack et al., 2013). With respect to strategy, people may spontaneously adopt explicit integration strategies (Richter, Chanales, & Kuhl, 2016) while learning overlapping pairs of stimuli by, for example, imagining scenarios in which all elements interact. Cognitively, this strategy may protect memory from proactive interference and retrieval-induced forgetting (Anderson & McCulloch, 1999) while also supporting later inferences (Richter et al., 2016); note, however, that awareness does not appear to be required for integration to take place (Shohamy & Wagner, 2008). While cognitive factors may be particularly important for human representations, rodent hippocampal codes also appear to be influenced by complex task factors. In a key example, teaching rats that two spatial environments are associated with different behavioural contingencies leads to differentiated (i.e., negatively correlated) hippocampal representations of the environments (McKenzie et al., 2014). Conversely, elements that convey similar behavioural significance are integrated (i.e., have hippocampal representations that are positively correlated).

Presumably, behavioural advantages that result from goals and strategy are mediated through integrated or differentiated hippocampal representations, rather than automatically separated ones. However, much work is needed to explain the mechanisms by which these cognitive factors regulate hippocampal codes. One possibility is that the prefrontal cortex (PFC) directly (Rajasethupathy et al., 2015) (or indirectly via the nucleus reuniens; Cenquizca & Swanson, 2007; Varela, Kumar, Yang, & Wilson, 2014) regulates patterns of hippocampal activity. However, the means through which the sparse topography of these connections might regulate specific memory representations is unclear. Alternatively, the PFC may be better positioned to regulate the contents of hippocampal input via well-established attentional mechanisms. In this way, hippocampal input perhaps should not be thought of as a perceptual map but rather a pre-processed selection of the most behaviourally-relevant features of an experience, combined with maintained representations of goals and strategies. Analogously, prefrontal-guided retrieval or inhibition of related memories reinstated by hippocampus in sensory cortex may strengthen or weaken hippocampal-cortical connections, respectively, in a memory-specific manner.

cells are active in a given environment, as compared to 29% of CA3 neurons (GoodSmith et al., 2017). Further demonstrating sparse DG coding, granule cells were found to be 6x less likely than CA3 cells to have multiple place fields, and also to fire at lower rates within their place fields (Senzai & Buzsáki, 2017). Of note, these findings are in contrast to earlier electrophysiological studies (Jung & McNaughton, 1993; Leutgeb, Leutgeb, Moser, & Moser, 2007) that suggested DG and CA3 neurons are similarly excitable. However, these earlier studies did not rigorously distinguish between granule cells and DG mossy neurons, which have since been shown to be significantly more excitable (GoodSmith et al., 2017; Senzai & Buzsáki, 2017). Thus, the results of recent technical advances suggest that DG granule cells do, in fact, employ the type of sparse coding hypothesized to support pattern separation.

Sparse coding on its own, however, is not sufficient evidence for pattern separation. Rather, direct evidence for pattern separation in DG would require demonstrating that it (DG) represents interrelated events with more distinct codes than ERC (its input structure)—i.e., that DG distorts memories to make them less similar. This is further complicated by the suggestion that medial and lateral subdivisions of ERC might store different kinds of representations (Deshmukh & Knierim, 2011; Hargreaves, Rao, Lee, & Knierim, 2005). In rodents, mapping out representation transformation is often approached by systematically varying the similarity between pairs of spatial environments while animals forage for food. For example, researchers have (a) parametrically morphed the features of local enclosures (Colgin et al., 2010; Leutgeb et al., 2007; Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005) or (b) rotated the local enclosure with respect to global cues to create different degrees of misalignment, termed the double rotation paradigm (Knierim & Neunuebel, 2016). Although DG and ERC recordings have yet to be directly compared within a study, DG recordings have been qualitatively compared to recordings from the lateral and medial ERC across experiments using the double rotation paradigm (Knierim & Neunuebel, 2016). This comparison shows that medial ERC place fields track global cues across rotations, whereas DG and lateral ERC neurons instead tend to remap their place fields, especially for larger misalignments. On one hand, a lower threshold for DG remapping as compared to its medial ERC input provides evidence for DG pattern separation. On the other hand, the pronounced representational differences across the ERC (stronger global cue representations in medial vs. lateral) makes it challenging to interpret input-output transformations, because ERC input does not provide a single representational code. Do medial ERC neurons appear more robust to environment changes because they are primarily driven by global cues, which remain intact in double rotation experiments, whereas DG neurons integrate global and local features? Does DG only show lower remapping thresholds in artificial situations in which medial and lateral ERC representations are driven in different directions? More broadly, how can we compare DG representational space to its input when its input has heterogenous representational spaces? One solution may stem from refining experimental manipulations to elicit similar representational shifts in lateral and medial ERC (e.g., degrading both local and global features in tandem).

Spatial manipulations have also been used in human fMRI studies investigating pattern separation (e.g., shifting the location of a target; Azab, Stark, & Stark, 2014), but more often participants are asked to discriminate between perceptually and conceptually similar objects. These studies often employ repetition suppression to assess sub-voxel representations (see Box 1 for more details). Being unable to disentangle signal arising from DG and CA3, fMRI studies conducted on a research-standard 3T MRI have found that combined DG/CA3 regions are sensitive to (i.e., show repetition suppression for) subtle changes (Bakker, Kirwan, Miller, & Stark, 2008; Yassa & Stark, 2011), moreso than ERC input or downstream hippocampal subfields (CA1 or subiculum; Bakker et al., 2008). More recently, research using high-field 7T MR imaging to tease apart the DG and CA3 subfields has isolated these pattern separation signatures to the DG (Berron et al., 2016). Of note, a recent study employing multivoxel pattern analyses (Box 1) in the combined DG/CA3 region found that related objects elicited more distinctive patterns of activity than unrelated objects – the hallmark of

Box 3
Anterior-posterior differences.

Hippocampal representation also might differ along its longitudinal axis, from anterior to posterior in primates, and from ventral to dorsal in rodents. One important reality to keep in mind that due to difficulty with recording from ventral hippocampus in rodents, most of the rodent findings described in this review actually reflect the coding scheme employed by subfields within the dorsal hippocampus (Strange, Witter, Lein, & Moser, 2014).

Across subfields, empirical work has demonstrated that ventral hippocampal (head) cells have broader place fields than those in the more dorsal body and tail (Kjelstrup et al., 2008); this observation has led to the hypothesis that the granularity of memory representations might correspondingly differ along the longitudinal axis (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Strange et al., 2014). In particular, memory representations might exist along a gradient, being more integrated in anterior and differentiated or separated in posterior hippocampus. Consistent with this idea, rodent work shows that while dorsal hippocampus responds to specific item-context conjunctions, ventral hippocampus generalizes across items within a given spatial context, consistent with a relational coding scheme in this region (Komorowski et al., 2013). Direct empirical support for a representation gradient has been provided in two recent human fMRI studies (Collin et al., 2015; Schlichting et al., 2015). One measured the hippocampal representations of individual items that were studied as elements of overlapping pairs (Schlichting et al., 2015; Fig. 2C). Using a representational similarity approach, the neural patterns evoked by specific memory elements were compared from pre- to post-study to answer the question, do indirectly associated items become more or less similar as a function of experience? Relative to pre-study, items that were indirectly related through a common associate became reliably more distinct in posterior hippocampus, but (for some conditions) became more similar in anterior hippocampus. In particular, anterior hippocampal representations differed as a function of learning condition, showing integration for blocked and differentiation for intermixed training orders. These conditions align with the circumstances we describe in Section 2 under which integration and differentiation, respectively, are more likely to occur: Namely, blocked training promotes strong initial memories that might yield greater reactivation and strengthening. Conversely, initial memories are relatively weak during an interleaved learning task, resulting in lower levels of reactivation, memory weakening, and re-study, which should theoretically drive differentiation. Importantly, in that study indirectly related items became less similar to one another, both (1) than they were prior to learning and (2) than they are to unrelated items (Schlichting et al., 2015). These results, thus, can be interpreted as selective integration and differentiation of memories that share common features in the hippocampus.

Anterior (ventral) and posterior (dorsal) hippocampus also differ in their anatomical connections, both within the hippocampus and with other parts of the brain. On top of the dense connections across the transverse axis, the hippocampus also has pathways allowing for information flow in the anterior-posterior direction (Kondo, Lavenex, & Amaral, 2008, 2009). Patterns of intrinsic structural connectivity along the long axis suggest a relatively abrupt boundary between the hippocampal head and the combined body and tail, with few connections between them (Fanselow & Dong, 2010; Sloviter & Lømo, 2012). Notably, this boundary appears to be more abrupt in rodents (Fricke & Cowan, 1978) than in monkeys (Kondo, Lavenex, & Amaral, 2009), and it is unknown whether it exists in humans. In contrast, extrinsic connectivity with cortex appears to change gradually along the long axis (Strange et al., 2014), with the dorsal-to-ventral axis of hippocampus showing preferential connectivity along a roughly dorsolateral-to-ventromedial gradient of ERC in rodents (Witter, 1993); however, it is worth noting that such claims are based on the (often small) differences in the relative distribution of connections, rather than their strict presence versus absence.

Human fMRI work has shown relatively greater functional coupling with perirhinal cortex for anterior and parahippocampal cortex for posterior hippocampus (Libby, Ekstrom, Ragland, & Ranganath, 2012). Perirhinal and parahippocampal cortices are thought to belong to anatomically and functionally distinct large-scale brain networks (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Lavenex, Suzuki, & Amaral, 2002; Libby et al., 2012), with greater connectivity with anterior temporal lobe and prefrontal regions observed for perirhinal and with posterior medial temporal, parietal, and occipital regions for parahippocampal cortex (Kahn, et al., 2008; Libby, et al., 2012).

What might these differential biases in connectivity mean for behaviour? One still quite speculative possibility is that integrated codes in the anterior hippocampus and separated codes in posterior hippocampus might be communicated to separable neocortical networks via distinct output pathways. The potential for multiple hippocampal outputs has important implications for asking questions of memory representations that support a range of behaviours—from perceptual judgments based on highly specific memory features to judgements tapping a memory's 'gist'—under different conditions. We highlight this question as an important area for future investigation.

differentiation (Dimsdale-Zucker, Ritchey, Ekstrom, Yonelinas, & Ranganath, 2018).

Further support for the causal contributions of DG to pattern separation- (or perhaps differentiation-) dependent memory comes from a recent patient study showing that selective DG damage impaired the patients' ability to distinguish between interrelated or perceptually similar experiences (Baker et al., 2016), mirroring selective lesions in rodents (Gilbert, Kesner, & Lee, 2001). Together, research in humans supports the long-standing theory that DG decorrelates ERC input to reduce interference in hippocampal memory representations; however, the complexities raised by higher-precision rodent neuroscience techniques (e.g., with respect to medial versus lateral ERC representation) need to be addressed.

3.2. Area CA3 can perform pattern separation or completion

CA3 principal neurons have three excitatory sources of input, each of which could promote a different coding scheme. First, DG neurons provide strong (and presumably pattern separated) input because they synapse close to CA3 cell bodies (Brown & Johnston, 1983; Brown, Wong, & Prince, 1979; O'Reilly & McClelland, 1994; Rolls, 2007; Yamamoto, 1982). Moreover, due to the many-to-one mapping between DG and CA3 neurons (Claiborne, Amaral, & Cowan, 1986), CA3 could serve to further separate these representations. However, added complexity arises from the second source of excitatory input: other CA3 neurons. These 'recurrent connections' are thought to support pattern completion—i.e., the reactivation of a previously stored pattern of activity given partially overlapping input (Marr, 1971; McClelland et al., 1995; Treves & Rolls, 1992). Crucially, if pattern completion (high

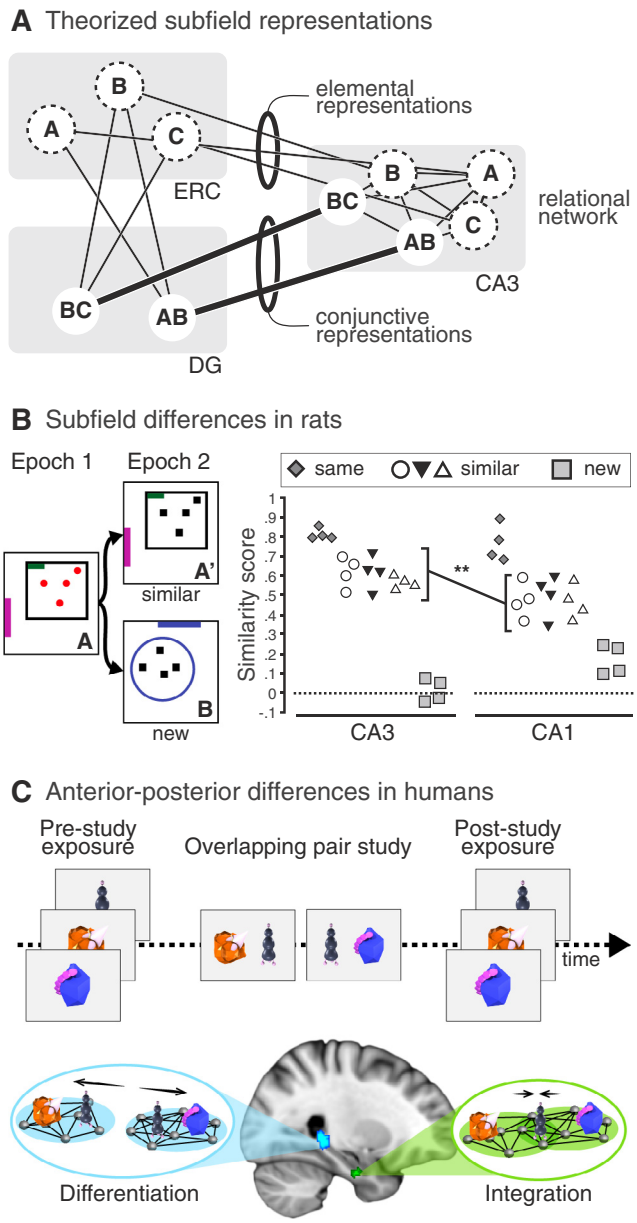

Fig. 2. Multiple codes within the hippocampus. (A) Representation of two overlapping experience (AB and BC) within ERC, DG, and CA3. Entorhinal cortex (ERC) conveys information about elements of the current experience (A, B, and C; dashed circles) to dentate gyrus (DG), which stores conjunctive codes of the two events (AB and BC; open circles). Conjunctive representations are then communicated to CA3 (bold lines). At the same time, ERC also conveys elemental representations to CA3 (thin lines), allowing for a relational network storing both conjunctive and elemental information. Diagram is simplified for ease of interpretation; in reality, many neurons would represent each A, B, C, AB, and BC within each hippocampal subfield. The thick lines connecting DG to CA3 reflect the relative strength of this input as compared to ERC. (B) Left, rats explored one environment (A) in Epoch 1. After a 20-minute delay, they then explored the same (A; not depicted), similar (A′), or new (B) environment. Right, CA3 showed greater Epoch 1-Epoch 2 neuronal overlap ('similarity score') for the similar conditions than did CA1 but less overlap when larger changes were introduced. This suggests that upstream pattern completed (more overlap) and separated (less overlap) transformation are not always reflected in CA1, which tracks change in a more linear manner. Three variables were manipulated to generate A': object identity (white circles on scatterplot), object configuration (black triangles), and global environment (white triangles). Adapted with permission from Vazdarjanova & Guzowski, (2004). (C) Top, human participants learned overlapping AB and BC pairs. Both pre- and post-study, participants were exposed to single objects to enable the estimation of an fMRI pattern associated with each object. Pre- and post-study exposure patterns were compared to assess how object representations changed as a function of study. Bottom, anterior hippocampus showed evidence of integration, whereas posterior hippocampus showed differentiation (see Box 3). Adapted from Schlichting, et al. (2015).

levels of memory reactivation) is combined with synaptic plasticity, memories for ongoing events could be stored using integrated coding schemes within CA3 and downstream structures by linking the reactivated details with new experiences. A similar combination of pattern completion and plasticity could also yield differentiation, particularly when reactivation levels are relatively lower. Consistent with this idea, one recent fMRI study showed differentiation specifically within a combined DG/CA3 region (Kim et al., 2017).

How does CA3 pattern complete to related memories if it mainly receives pattern separated inputs from DG, which by definition ignore such relationships? There are two possible solutions. First, DG may not fully separate inputs. Under this probable scheme, DG would reduce interference between Priya's interviews, but the interviews would still be closer to each other in her memory space than either one is to, say, a camping trip, allowing CA3 to reactivate more related memories. A second potential mechanism is the third source of CA3 excitatory input: ERC. While thought to provide relatively weaker input than DG due to the fact that its synapses are further from CA3 cell bodies (Amaral, Ishizuka, & Claiborne, 1990; Randall C. O'Reilly & Norman, 2002; Rolls, 2007), ERC input is still significant, forming an order of magnitude more synapses than DG (Amaral et al., 1990). This third source of information would reintroduce the shared elements across experiences into the CA3 network, even if DG input is fully separated (Fig. 2A).

Empirical evidence is consistent with CA3 having a more complex and variable representational scheme. Work using double rotation manipulations found that CA3 neurons are less likely than DG neurons to remap in response to misaligned global and local cues (Neunuebel & Knierim, 2014), perhaps reflecting the impact of ERC input or pattern completion. Other manipulations to local and global cues, however, appear to result in similarly pattern separated representations in both the DG and CA3 (GoodSmith et al., 2017; Leutgeb, et al., 2007) or even stronger separation in CA3 as compared to DG granule neurons (Senzai & Buzsáki, 2017). Of note, CA3′s tendencies toward pattern completion vs. separation may also vary along its transverse axis (Lee, Wang, Deshmukh, & Knierim, 2015; see Box 3 for discussion of long axis differences).

The sequence of representational changes from DG to CA3 yield a conundrum: Why invest so much energy in maintaining a highly inhibited DG network to perform pattern separation that is then often undone by ERC inputs to and pattern completion in area CA3? To our knowledge, this question is yet to be solved, but we speculate that it may allow for multiplexed separated and integrated representations. Specifically, DG input may drive strong within-event connections, both through CA3 recurrent connections and DG-CA3 synapses. Cross-event connections may be overlaid on top of these pattern separated traces, linking related experiences via ERC inputs containing shared features. This hybrid coding scheme would result in the recall of distinct conjunctive codes when CA3 pattern completion is inhibited, but the recall of integrated memories under lower levels of inhibition—as pattern completion can spread to more weakly connected elements. Over time, the relative strength of separated and integrated traces may shift: Repeated reactivation of an integrated trace could strengthen the previously weak connections such that contents of the memories become merged and idiosyncratic details lost. This would be consistent with recent evidence that hippocampal representations of related stimuli become integrated over a week (Tompary & Davachi, 2017). Conversely, opportunities to strengthen just the separated components of a memory previously weakened via reactivation could yield differentiation.

3.3. Area CA1 integrates CA3 codes with ERC input

CA1 receives input from both CA3 and ERC, but contains minimal internal excitatory connections (Amaral & Lavenex, 2006). Representation in CA1 thus should heavily depend upon the information conveyed by CA3—potentially including reinstated memories, as

suggested by high-resolution fMRI studies in humans (Mack & Preston, 2016; Tompary, Duncan, & Davachi, 2016), and/or pattern separated codes. Due to CA1 receiving information regarding both reinstated memories (from CA3 pattern completion) and the current experience (from ERC), this region is also well positioned to compare past with present experience and compute a prediction error (Chen, Olsen, Preston, Glover, & Wagner, 2011; Duncan, Ketz, Inati, & Davachi, 2012; Hasselmo, Wyble, & Wallenstein, 1996; Lisman & Grace, 2005). This prediction error signal may then be used to shape memory representations within CA1. For example, engagement of CA1 during memory formation has been related to behavioural success on flexible memory judgments (Schlichting, et al., 2014), suggesting the importance of this region in forming integrated memories. High prediction error has also been linked with memory weakening (Kim et al., 2014) on a trial-by-trial basis, which might later result in differentiation (Kim et al., 2017). CA1 may thus act to resolve any discrepancies between memories by further integrating memories (Schlichting et al., 2014) when prediction errors co-occur with strong reactivation or differentiating memories (Hulbert & Norman, 2014) when prediction errors co-occur with weaker reactivation.

Consistent with its dependence on CA3 input, CA1 representations have been shown to track environmental changes in lock-step with CA3 under some conditions (Colgin et al., 2010). In this and a related study (Wills et al., 2005), CA1 representations showed evidence of attractor dynamics: CA1 places cells abruptly and coherently shifted their representations when animals were exposed to incremental morphs of two learned environments. In both cases, the initial training was structured so as to generate distinct (pattern separated/differentiated) representations of the two environments, which would serve as attractor states. Then, when small changes were made to local enclosures, activity patterns were so drawn to these previously stored states (presumably via CA3 pattern completion) that small changes were not coded. Thus, these results demonstrate how CA1 codes may reflect the representational transformations performed by the DG and area CA3 rather than perceptual features. Though conducted at too coarse a resolution to identify subfields, one recent fMRI study found evidence for similar attractor dynamics in the human hippocampus (Steemers et al., 2016).

Similar environmental manipulations, however, have also identified differences between CA3 and CA1 coding schemes (Guzowski, Knierim, & Moser, 2004; Fig. 2B), suggesting that CA3 is more likely to show attractor dynamics whereas CA1 is more likely to track linearly with perceptual changes. Specifically, small perceptual changes including double rotation procedures and manipulation to single features within an environment yield less place cell remapping within CA3 as compared to CA1 (Lee, Yoganarasimha, Rao, & Knierim, 2004; Vazdarjanova & Guzowski, 2004). Conversely, larger changes to multiple features in an environment result in more pronounced CA3 remapping as compared to CA1 (Leutgeb, et al., 2004; Vazdarjanova & Guzowski, 2004). Human fMRI studies also support a roughly linear treatment of perceptual changes in area CA1 (Duncan, Ketz, et al., 2012; Lacy, Yassa, Stark, Muftuler, & Stark, 2011) as opposed to attractor dynamics. The presumably more perceptually driven CA1 responses may be driven by ERC connections as opposed to pattern separated/completed CA3 input, raising currently unanswered questions about the circumstances under which CA3 vs. ERC input drive CA1 neurons.

The theoretical importance of ERC-CA1 connections has been investigated in a recent computational model, which suggests that they drive memory integration (Schapiro et al., 2016). In this model, CA1 is simulated as having relatively low inhibition and a slow learning rate, akin to cortex. Even in the absence of CA3 input, area CA1 was able to rapidly develop integrated codes to reflect statistical regularities across events, suggesting that the ERC-CA1 functional loop is sufficient for rapid acquisition of integrated representations. This is consistent with empirical findings of schematic, integrated representations in area CA1 across species (Dimsdale-Zucker et al., 2018; McKenzie, et al., 2013). Crucially, rodent goal representations generalized across environments, consistent with relational network theories but not conjunctive pattern separated coding. It should also be noted that similar generalized or integrated representations have been shown across studies which did not isolate specific subfields; see McKenzie et al (2016) for a review.

3.4. To what end—hippocampal output pathways

The hippocampus has two major output pathways: the fornix, which projects primarily to subcortical areas, and ERC, which transmit hippocampal signals to the cortex (Amaral & Lavenex, 2006). ERC connections have received considerable theoretical treatment, as this pathway could allow the hippocampus to reinstate the content of memories throughout representational cortices. Crucially, the DG and CA3 do not directly project to ERC; rather their representations must first be filtered through area CA1, which projects to ERC both directly and indirectly via the subiculum (Amaral & Lavenex, 2006). In this sense, the coding scheme employed by CA1 is the coding scheme which the hippocampus uses to reinstate memories. If, however, CA1 codes reflect perceptual changes communicated by ERC just as often as the processing performed by DG and CA3, the conundrum of why the hippocampus transforms representations within its circuit becomes even more challenging. One solution may lay in a growing body of research uncovering the distinct cell populations along the radial axis of CA1—neurons in deep vs. superficial layers have distinct representations of environments, receive partially non-overlapping input from area CA3 (and CA2) and project to different cortical areas (Geiller et al., 2017). Thus, the radial dimension is emerging as a possible organizational structure which could allow the hippocampus to simultaneously reinstate memories at multiple levels of abstraction. (See Box 3 for discussion of how the longitudinal axis may play a similar role.) The fornix may provide another means through which CA3 representations could bypass CA1 filtration. The hippocampal projections within the fornix originate primarily from CA3 and subicular cells, with a smaller proportion from CA1 cells (Saunders & Aggleton, 2007). The majority of the CA3 fibers are thought to project to the septum (Swanson & Cowan, 1977), which may contribute to cholinergic regulation. Though this pathway is less likely to directly mediate memory reactivation, as discussed below, acetylcholine likely has important mnemonic functions.

4. Time windows for memory integration and separation

So far, we have treated hippocampal neurons and networks as though they always operate in the same state—i.e., the same two related experiences will always be integrated or separated, with the coding scheme automatically determined by the fixed wiring properties of the hippocampus. Here, we will introduce an essential layer of complexity by considering dynamic molecular mechanisms. Specifically, we propose that shifting concentrations of key molecules open what we call integration or separation 'time windows'—extended periods of time during which the hippocampus is biased toward one coding scheme or another. We consider two types of windows: content-specific and content-general. Content-specific windows are opened by molecular cascades that operate within neurons encoding a specific memory, thus influencing how related events are encoded alongside the memory in question. By contrast, content-general windows influence hippocampal dynamics via diffuse neuromodulator released, biasing how memories formed following a salient event are encoded with respect to all interrelated experiences.

4.1. Encoding and the content-specific window

Pattern separation, integration, and differentiation are defined by which neurons represent (i.e., are allocated to) a memory trace. Traditionally, it was thought that the hippocampal neurons which

receive relevant input about a particular experience will ultimately represent that experience in memory; these neurons should fire together and then wire together to form an attractor state for future retrieval (Hebb, 2005). However, mounting evidence from rodents has identified a crucial factor that complicates this simple rule: neuronal excitability. For starters, excitability determines which neurons represent an ongoing sensory experience in the hippocampus. For example, intracellular recordings reveal that, despite receiving spatially tuned input, many CA1 neurons remain 'silent' due to low excitability levels; however, they can be transformed into well-tuned place cells when researchers artificially depolarize (i.e., excite) them, demonstrating a causal link between excitability and representation of the current experience (Lee, Lin, & Lee, 2012). Naturally occurring fluctuations in excitability may also explain why CA1 representations of a single environment gradually shift across hours (Mankin et al., 2012) and days (Ziv et al., 2013), with only the most excitable cells in a given session expressing their place fields.

Excitability impacts online representations, but does it also determine which neurons are incorporated into a memory trace? Contrary to the traditional view laid out above, only a proportion of the neurons activated during a given experience actually go on to represent that memory (Han et al., 2007; Vazdarjanova & Guzowski, 2004). Across a number of experiments, neural excitability has also emerged as a critical factor determining this allocation, with neurons expressing higher levels of CREB (cAMP/Ca2+ responsive element binding protein) having greater excitability (Lopez de Armentia et al., 2007) and being more likely to join a memory trace (Barco, Alarcon, & Kandel, 2002). Further, artificially manipulating excitability (via CREB or K^+ channel manipulations or using optogenetics) modulates a neuron's chances of being allocated to a particular memory trace—with increased excitability leading to increased odds of allocation, and decreased excitability leading to decreased odds (Han et al., 2007; Park et al., 2016; Rashid et al., 2016; Sekeres, Neve, Frankland, & Josselyn, 2010; Yiu et al., 2014). This demonstrates a causal link between excitability and the stored memory representation. Together, this work suggests that neural excitability impacts how a given experience is represented both online and in memory.

Excitability might also determine which type of representational scheme is used to encode a memory by influencing the integration of specific content. Neurons active during memory formation retain heightened excitability for several hours following the induction of long-term potentiation (LTP), which should make them more likely to join new memory traces formed in the ensuing hours (Fig. 3A). Thus, encoding a memory opens a content-specific time window (for that memory and that memory only) for integration; persistent excitability within the recently formed memory trace increases the likelihood that the specific memory stored within it is linked to other events experienced close in time. This prediction was borne out in the mouse CA1 (Cai et al., 2016) as well as in the amygdala (Rashid et al., 2016): the overlap in neuronal representations for related fear conditioning experiences was greater for events that occurred within a few hours than those that occurred across days or weeks (Fig. 3B). This overlap also resulted in behavioural linkage of the memories, as extinguishing one memory led to extinction of the other—but only when the two memories were initially formed close in time (Rashid et al., 2016). Consistent with these mechanisms and timescales, humans have recently been shown to have more neural and behavioural integration when related experiences occur within a few hours relative to across days (Zeithamova & Preston, 2017; Fig. 3C). Returning to Priya's interviews, excitability-mediated windows would support integration of events that occurred within a single interview separated by minutes to hours, but not across multiple interviews separated by days. Thus, excitability-mediated memory trace allocation is one mechanism by which events experienced close in time become adaptively integrated in memory.

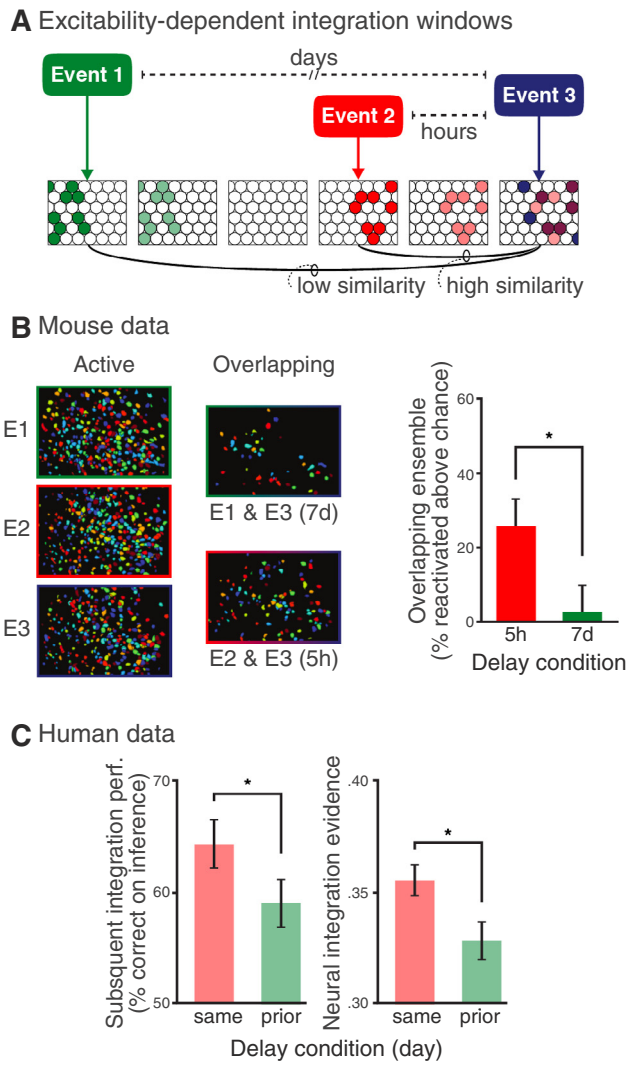

Fig. 3. Neuronal excitability impacts hippocampal representations. (A) Overview of excitability-mediated windows for integration. A set of neurons activated by Event 1 (E1; green) maintain excitation for a few hours (fading neurons), having no impact on the neurons allocated to an Event 3 (E3) memory encoded days later (navy). In contrast, Event 2 (E2; red) happens just hours before E3, and thus neurons encoding it are still highly excitable when the new E3 is encoded. This leads to a high degree of neural overlap (i.e., high representational similarity). (B) Left, calcium imaging in mice visualizes neuronal populations active during E1, E2, and E3 (left images). There is higher overlap in the neuronal populations engaged during events separated by hours (right images; bottom) as opposed to days (top). Right chart, transgenic tagging shows that neuronal overlap between two events is significantly above chance only when the delay between them is short. Adapted with permission from Cai et al. (2016). (C) Human participants learned overlapping AB and BC pairs, where half of the AB pairs were learned on the same day and half were learned on the day prior to BC learning. Left, participants show better integration performance when related pairs were learned on the same day vs. the prior day. Right, there was also more neural evidence for integration during BC learning for the same day pairs, suggesting that temporal proximity promotes behaviour by promoting integrative encoding. Adapted from Zeithamova & Preston (2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.2. Salience and the content-general window

Hippocampal coding schemes may also be influenced by the more widespread neurochemical shifts elicited by salient events, including novelty, reward, punishment, or emotion. A wide array of neuromodulators and hormones, such as norepinephrine (NE; Mather, Clewett, Sakaki, & Harley, 2016; Sara & Bouret, 2012), serotonin (Dale et al., 2016), estrogen (Prange-Kiel & Rune, 2006; Woolley, 1998), and endocannabinoids (Carlson, Wang, & Alger, 2002) may induce

complementary and interacting coding scheme biases within the hippocampus. Here, we focus on just two—acetylcholine (ACh) and dopamine (DA)—that provide a mechanistic framework for connecting physiological effects to coding schemes and, ultimately, human behaviour. As detailed below, ACh and DA evoke persistent brain states that could impact coding schemes by influencing a number of factors, such as the signal-to-noise ratio in hippocampal input, the likelihood of reactivating related prior experience, synaptic plasticity in specific hippocampal subfields, and the sparseness of hippocampal memory traces. Crucially, neuromodulators are often released via volume transmission rather than into specific synapses, thereby impacting hundreds to thousands of nearby neurons (Descarries, Gisiger, & Steriade, 1997; Descarries & Mechawar, 2000; Shohamy & Adcock, 2010)—even those not involved in processing the salient event itself. For example, only 5–56% of DA terminals and under 10% of ACh terminal occur at synapses in the temporal lobe (Descarries & Mechawar, 2000). Moreover, models of DA diffusion estimate that the quantal release of DA from a vesicle can impact up to thousands of synapses, even in regions with higher occurrence of synaptic release (Rice & Cragg, 2008). Thus, unlike the content-specific window described above, the biases evoked by these neuromodulators are unlikely to target specific neurons or specific memories. Rather, they impact how events that occur within a given time window are stored alongside any related memory.

4.2.1. Acetylcholine opens fleeting time windows for separation

High levels of ACh released during periods of active and exploratory wakefulness are proposed to promote feed-forward communication between neurons while inhibiting communication via recurrent or feedback connections (Hasselmo & McGaughy, 2004). In the neocortex, these network dynamics are thought to increase the signal of relevant information compared to background noise, in line with ACh's role in enhancing attention and perceptual acuity (Gratton et al., 2017; Kang, Huppé-Gourgues, & Vaucher, 2014; Klinkenberg, et al., 2011). ACh also produces similar biases throughout the medial temporal lobe, the mnemonic consequences of which have been studied, in particular its promotion of separated memories via proactive interference paradigms (Atri et al., 2004; De Rosa & Hasselmo, 2000; De Rosa, Hasselmo, & Baxter, 2001; Douchamps, Jeewajee, Blundell, Burgess, & Lever, 2013). We will review select pieces of the relevant empirical literature again progressing our way through the hippocampal circuit.

4.2.1.1. Promotes separation in DG. Artificially triggering ACh release using optogenetics inhibits DG granule cells (Pabst et al., 2016), potentially increasing the sparseness of coding within this already sparse network and promoting pattern separation. Of note, this inhibition begins slowly—over the course of several hundreds of milliseconds—and persists for over 2 s because it is mediated through interactions between astrocytes and inhibitory interneurons (Pabst et al., 2016). In addition to promoting sparse coding in DG, ACh also promotes LTP in the DG (Burgard & Sarvey, 1990), producing an ideal state for forming separated memories within the DG network. The behavioural consequences of these physiological biases remain speculative, however, as they are yet to be tested.

4.2.1.2. Inhibits pattern completion in area CA3. ACh selectively inhibits the recurrent connections among CA3 neurons (thought to mediate pattern completion), but does not inhibit putatively pattern separated input from DG (Hasselmo, Schnell, & Barkai, 1995). This pattern of inhibition has been theorized to serve as a 'switch' on hippocampal processing: It should be biased toward pattern separation in the context of high ACh, and pattern completion (and perhaps integration or differentiation) under low ACh levels. The persistence of this effect is also thought to last on the order of a few seconds (Hasselmo & Fehlau, 2001; Meeter, Murre, & Talamini, 2004). Further, optogenetic stimulation of ACh neurons has recently uncovered another mechanism that could inhibit the reactivation of related memories: hippocampal ACh strongly suppresses the production of sharp-wave ripples (SWR) in area CA3 (Vandecasteele et al., 2014), which have been shown to support the reactivation of engrams (Jadhav, et al., 2012), memory consolidation (Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Marshall & Born, 2007), and have been argued to underlie retrieval itself (Carr, Jadhav, & Frank, 2011). Thus, high levels of ACh could suppress the reactivation of prior experiences within the CA3 network, allowing separated DG representations to dominate hippocampal output as the coding scheme used to store memories.

4.2.1.3. Promotes encoding of current experience in area CA1. ACh also biases the relative strength of CA1 input. Specifically, ACh selectively suppresses excitatory transmission to CA1 dendrites receiving input from CA3 (versus ERC) (Hasselmo & Schnell, 1994). Therefore, high levels of ACh bias CA1 toward ERC input containing information from the environment over recalled memories from area CA3. Although CA3 is not a strong driving force under high ACh conditions, LTP between CA3 and CA1 neurons is nevertheless facilitated by ACh (Blitzer, Gil, & Landau, 1990; Huerta & Lisman, 1995), thereby promoting new memory encoding. Conversely, in low ACh states, disinhibited CA3 recurrent connections are free to recall memories and transmit them through area CA1 to cortex without triggering new encoding.

An elegant aspect of ACh windows is that they allow the hippocampus to self-regulate its coding scheme based on its own expectations (generated through pattern completion in area CA3) and their violation. Specifically, as mentioned previously, area CA1 can compare expectations to reality (ERC input). Because the violation of expectations signals an important opportunity for learning, this hippocampal comparator function has been the cornerstone for multiple theories of adaptive hippocampal neuromodulation, each arguing that expectancy violations trigger the release of neuromodulators to support memory formation (ACh: Easton, Douchamps, Eacott, & Lever, 2012; Hasselmo, et al., 1996; Meeter et al., 2004; DA: Lisman, Grace, & Duzel, 2011; Lisman & Grace, 2005; NE: Vinogradova, 2001). Cholinergic models are unique, however, in their prediction that lower neuromodulator states also serve an important mnemonic role – when expectations are met, then cholinergic input remains low and the hippocampus is primed to continue retrieving expectations but not encode unsurprising outcomes (Easton et al., 2012; Hasselmo et al., 1996; Meeter et al., 2004).

Extrapolating from these cholinergic models, in the seconds following novelty or expectancy violations, performance on tasks that require pattern separation should be improved. Conversely, in the seconds following familiarity or expectancy confirmations, performance on tasks requiring pattern completion or memory integration should be improved. These predictions have been confirmed empirically in a series of behavioural experiments in humans (Duncan & Shohamy, 2016; Duncan, Sadanand, and Davachi, 2012; Patil & Duncan, 2018; Fig. 4A). Across studies, recent exposure to unrelated novel or familiar images was shown to enhance and impair performance, respectively, depending on whether the memory task required pattern separation (i.e., detailed mnemonic discrimination; Duncan, Sadanand, et al., 2012) or completion (i.e., associative recall; Patil & Duncan, 2018). Most pertinently, presenting an unrelated familiar versus novel image seconds before an opportunity for integrative encoding improved the later ability to link related memories (Duncan, Sandand, et al., 2012). While these results are consistent with novelty opening a cholinergically-mediated time window for separation at the expense of integration, future work directly manipulating or measuring cholinergic function in humans is required to more directly support this model.

Although these cholinergic time windows are of considerable theoretical interest, one may question the practical implications of such short-lived effects. It is important to keep in mind, however, that in real life settings these windows will remain open for as long as ACh levels are maintained. In the lab, we often employ short-lasting

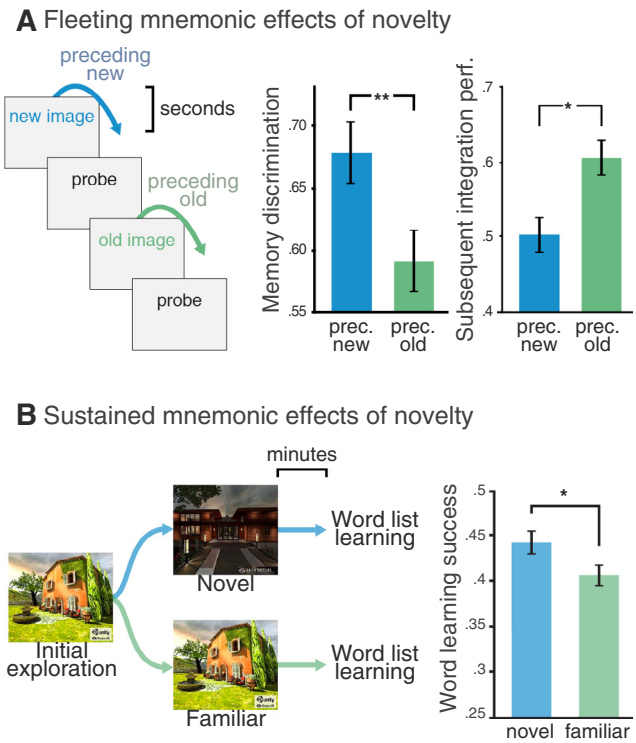

Fig. 4. Novelty opens fleeting and sustained time windows that shape memory representations. (A) Human participants were shown a series of probe images, which differed only in whether they were immediately (i.e., just seconds prior) preceded by an old (familiar) or new (novel) stimulus. Probes were designed to tap either pattern separation (requiring a memory discrimination judgment) or integrative encoding. Recent novelty had opposing consequences for each probe type; it enhanced fine-grained memory discriminations but impaired integrative encoding. The time scale (seconds) and pattern across separation and discrimination tasks are consistent with cholinergic mechanisms. Adapted with permission from Duncan, Sandanand, et al. (2012). (B) After exploring one virtual environment, human participants were exposed to either the previously learned environment (familiar; bottom) or a new environment (novel; top) to manipulate novelty. Minutes later, participants encoded an unrelated list of words. Participants showed better memory when the word list was preceded by novel versus familiar environment exploration, consistent with the DA-dependent enhancement of memory encoding shown in rodents following novelty exposure. Adapted with permission from Schomaker, et al. (2014).

manipulations, either directly using optogenetics or indirectly through behavioural tasks. In the real world, however, one rarely alternates between novel and familiar contexts every few seconds. For example, the second prospective advisor's choice of restaurant for Priya's interview could persistently impact how she links the two advisors in memory: from a cholinergic window perspective, the familiar restaurant will increase the likelihood of her recalling and integrating memories of past interviews with the current. By contrast, a new restaurant might have increased ACh levels throughout the interview, allowing her to form a distinct memory of this particular prospective advisor. Moreover, steep shifts in cholinergic modulation also occur across very long timescales and have been linked to circadian rhythms (Hut & Van der Zee, 2011). This has led to the proposal that the hippocampus is primed to encode separated memories during active periods, when ACh levels are high. Conversely, during slow-wave sleep, low ACh levels allow for the reactivation and consolidation of recently-learned memories (Gais & Born, 2004; Hasselmo, 1999). However, many of our waking hours are spent in restful states associated with intermediate cholinergic levels. These periods may be crucial for encoding integrated memories, as synaptic plasticity is still high but memory reactivation is less inhibited.

4.2.2. Dopamine opens sustained time windows for integration

In rodents, synaptic plasticity between CA3 and CA1 neurons depends on DA, particularly at weakly activated synapses. Applying DA agonists during LTP induction enhances the protein synthesis-dependent late phase of LTP (l-LTP) (Lemon & Manahan-Vaughan, 2006; Li, Cullen, Anwyl, & Rowan, 2003), whereas antagonists block l-LTP (Bethus, Tse, & Morris, 2010; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006). Complementary results have been found in awake behaving rodents: applying DA agonists to CA1 during encoding is associated with better memory, but only when tested at a long (> 1 h) delay (Bethus et al., 2010; O'Carroll et al., 2006), corresponding to l-LTP timing. But which events receive the mnemonic benefits of DA? Phasic DA bursts are reliably evoked by novelty, expectancy violation, and reward (Lisman & Grace, 2005; Montague, Hyman, & Cohen, 2004), suggesting that memories formed in these salient contexts will be more long-lasting. Akin to ACh comparator models, the indirect loop between the hippocampus and dopaminergic midbrain centers has inspired theories about adaptive hippocampal-mediated regulation of DA release, and by extension long-term memory formation (Lisman et al., 2011; Lisman & Grace, 2005): subicular responses to novelty disinhibit DA neurons via a polysynaptic pathway, which then increases DA release in the hippocampus. Others theoretical work has focussed on the how reward and motivation can adaptively enhance memory formation for behaviourally relevant events (Shohamy & Adcock, 2010). Recent optogenetic evidence that hippocampal DA may in fact be released by NE neurons arising from the locus coeruleus (Kempadoo, Mosharov, Choi, Sulzer, & Kandel, 2016; Takeuchi et al., 2016), however, provides a challenge for these prominent perspectives. NE neurons also increase their firing rate in response to novelty and reward; thus, the general environmental causes of DA modulation would be similar regardless of the source. However, the circuits proposed to mediate dopaminergic memory modulation may require revision, at least for posterior (dorsal) regions of the hippocampus. An intriguing consequence of this revision would be new predictions about the relationship between reward, novelty, and memory. Specifically, NE is synthesized from DA, which is why DA reserves are stored in NE terminals (Weiner, 1970). DA is more likely to be released, however, when NE reserves are exhausted (Devoto, Flore, Saba, Fà, & Gessa, 2005), suggesting that DA modulation of hippocampal memory is most likely to occur in response to prolonged exposure to novelty and reward.

Regardless of its source, a remarkable property of DA-dependent hippocampal plasticity is the bi-directionally broad (~20–30 min) time window over which it impacts LTP and memory (Li et al., 2003; Moncada & Viola, 2007; Wang, Redondo, & Morris, 2010). These temporal dynamics have been exploited in both animals and humans to identify the far-reaching impact of novelty on memory encoding. Across species, exposure to novel environments or images for several minutes enhances the encoding of memories formed in the surrounding minutes (Fenker et al., 2008; Li et al., 2003; Schomaker, van Bronkhorst, & Meeter, 2014; Vishnoi, Raisuddin, & Parvez, 2016; Fig. 4B). Furthermore, this novelty boost has been shown to depend specifically on DA in rodents (Li et al., 2003). Converging evidence using fMRI in humans has shown that encoding long-lasting memories of novel associations is related to functional connectivity between CA1 and ventral tegmental area (VTA)—a dopaminergic nucleus and potential site for the release of hippocampal DA (Gasbarri, Packard, Campana, & Pacitti, 1994; cf. Takeuchi et al., 2016)—in the surrounding minutes (Duncan, Tompary, & Davachi, 2014; Tompary, Duncan, & Davachi, 2015). Presumably, other salient cues causing DA release (e.g., reward) should have similar consequences for memory (Shohamy & Adcock, 2010). While there is some evidence for such consequences in humans (Gruber, Ritchey, Wang, Doss, & Ranganath, 2016; Patil, Murty, Dunsmoor, Phelps, & Davachi, 2017), the time window of this retroactive reward modulation on memory is often shorter (tens of seconds; (Murayama & Kitagami, 2014) than the novelty windows identified in across species (tens of minutes), with the proactive effects in motivated memory studies being

even shorter (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Gruber, Watrous, Ekstrom, Ranganath, & Otten, 2013; Murty, Tompary, Adcock, & Davachi, 2017; Wittmann et al., 2005).

Dopamine's capacity to enhance memory for weaker stimuli, and thus broaden memory traces, can be explained by the Synaptic Tag and Capture model (Navakkode, 2015; Wang et al., 2010). According to this model, DA increases the production of plasticity-related proteins (PRPs), which are required for l-LTP. PRPs travel through the post-synaptic CA1 dendrites and can be captured by recently active synapses, which are tagged for LTP. DA could also proactively facilitate the LTP of subsequently activated synapses, because the resulting PRPs are already available when the synapse is activated. This also explains why DA is particularly important for enhancing l-LTP of weakly activated synapses—strong co-activation of pre- and post-synaptic neurons is sufficient to produce PRPs and, thus, l-LTP does not require a third modulatory input for structural synaptic modification.

Although this prior research has focused on how DA opens a time window for memory encoding in general, we speculate that its effects may be particularly important for memory integration. First, DA modulates plasticity specifically in CA3-CA1 synapses (Bethus et al., 2010; Li et al., 2003; O'Carroll et al., 2006; Takeuchi et al., 2016; Wang et al., 2010). As CA3 can convey information about related, reactivated memories to CA1, this pathway may be a key site for memory integration. ACh also modulates plasticity in these synapses (Blitzer et al., 1990; Huerta & Lisman, 1995); importantly, however, ACh could also reduce the reactivation of memories in area CA3, thereby reducing opportunities for integration. Because there is no evidence for DA inhibiting memory reactivation in behaviour or the brain, increased LTP in this pathway could foster the formation of memories which integrate reactivated content with current experience, communicated from ERC. Second, by specifically enhancing l-LTP for weak or moderately activated CA1 synapses (Navakkode, 2015), DA would encourage broader, less sparse memory traces in CA1. Thus, memory traces formed under these conditions would be more likely to share common neurons—the neural instantiation of integration. Lastly, in addition to lowering the threshold for l-LTP, DA also reduces the need for precisely coincident presynaptic input and postsynaptic spiking (Pawlak, Wickens, Kirkwood, & Kerr, 2010). This suggests that memories can reflect greater temporal integration of CA3 input when in a higher DA state. Though highly speculative at this stage, this pattern of DA influence on CA1 plasticity suggests that DA bursts, triggered by novelty or reward, may open bi-directional windows for memory integration.

4.3. Resolving overlapping memory time windows

In isolation, each time window with its corresponding excitability or neuromodulatory mechanisms provides an interesting framework for conceptualizing the dynamic and potentially adaptive flexibility of hippocampal coding. However, these mechanisms do not operate in isolation, but rather overlap in time and potentially interact. There is minimal empirical data characterizing the interactions of these mechanisms because they have primarily been studied and theorized about in isolation; a necessary first step but an unfortunate state of affairs given that the very same salient events are thought to trigger the release of both ACh and DA. In such a circumstance, most theories would argue for the enhancement of memory encoding within the hippocampus, but would the resulting memory trace(s) be encoded within separated or integrated codes? Based on the research surveyed above, we speculate that ACh separation would dominate for memories encoded shortly after a salient event, as ACh could inhibit the reactivation of related memories during this window while ACh and DA could enhance LTP. However, events experienced leading up to the salient event and in the minutes following the event could be more integrated with each other and other prior experience by the broader DA integration window.

Here, we will attempt to explicate these ideas using our real-world example, which will also provide a happy ending to Priya's search for a postdoc. After a series of unsuccessful interviews at SfN, Priya attended an unexpectedly inspiring colloquium at her home institution. She introduced herself to the speaker, who coincidentally had an opening in her lab; one thing led to another and Priya found herself entering the next phase of her scientific career. But how will Priya store the memory of her unexpected discovery of a new advisor? The novelty of the speaker, along with the rewards Priya experienced from the unexpectedly engaging talk should increase the release of neuromodulators (including ACh and DA) to mark their significance. ACh should bias Priya's hippocampus toward forming separated memory traces. Importantly, the influence of this separation window is global in content; the novelty of the speaker could bias Priya to encode the content of the talk as distinct from any related research. The ACh window is short in time, however, and so should only promote separation for the crucial seconds surrounding the novel, rewarding event. By contrast, the integration window opened by DA would extend more broadly in time. It could act in a unique retroactive fashion to enhance encoding of the otherwise routine events that led up to the talk, potentially integrating them together with other memories from her graduate studies. The excitability-dependent window would be broadest temporally but the most specific in terms of content: Neurons recruited into Priya's first memory of her new advisor would remain at a heightened state of excitability throughout the talk and the reception that followed, linking the talk's content with their first conversation. But how would this excitability-driven tendency toward integration interact with the cholinergically-mediated separation bias? Though an empirical question, one speculative possibility is that the cholinergic window would promote separation in the DG and CA3, such that the events of that afternoon are separated from Priya's prior interviews and each other. Conversely, persistently excitable CA1 neurons would ensure that these distinct memories are connected to each other. This would allow Priya to excitedly recall the unique details of the research covered in the talk, but also link them to the plans she later discussed with her new supervisor.

5. Conclusions

A major theoretical challenge is facing memory researchers today—we do not have a clear model of how the hippocampus represents information in memory. At first blush, this statement may seem shocking. How could such a fundamental property of one of the most investigated brain regions remain unknown? Moreover, longstanding models are so entrenched in our work that they can give the false sense of consensus. Some researchers may believe that the hippocampus performs pattern separation and contains only conjunctive representations. Others may think it contains relational structures, which link interrelated experiences. Still others may collapse across these distinctions, as both would bind experiences in memory. Here, we argue that these representational distinctions lay at the heart of hippocampal function, but that existing empirical data does not strongly favour one model over the other. Rather, we propose a middle ground: that the hippocampus can store separated (or perhaps differentiated) conjunctive representations alongside integrated relational structures.

Crucially, we also provide a framework for understanding where, when, and why the hippocampus might form memories using pattern separation, integration, and differentiation. We first focussed on the 'where' factor, reviewing the functionally-segregated networks comprising the hippocampus. In line with Marr's tradition, we recognize that the DG is particularly well suited for pattern separation, removing the common threads that link experiences. However, direct ERC input to the CA fields may sew these threads back into our memories, producing increasingly integrated codes at each stage of hippocampal processing. We also propose a reason 'why' these sequential transformations, which may appear to cancel each other out, are in fact necessary: If the conjunctive DG codes are more strongly stamped into the hippocampus, they could be directly accessed during periods of high

inhibition—for instance, in the context of high levels of ACh—whereas the weaker integrated links could be accessed during periods of low inhibition.

Lastly, we address the 'when' component by discussing the dynamics afforded by molecular factors that could open and close time windows during which these hippocampal networks are optimized for a particular coding scheme. Though motivated by empirical discoveries that range from cellular physiology to human behaviour, our framework requires direct tests. Fortunately, recent methodological advances now allow the decoding of hippocampal representations across species with unprecedented precision, which will accelerate our understanding of the representational structure of hippocampal memories.

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