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Representation of memories in the cortical-hippocampal system: Results from the application of population similarity analyses

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Abstract

Here we consider the value of neural population analysis as an approach to understanding how information is represented in the hippocampus and cortical areas and how these areas might interact as a brain system to support memory. We argue that models based on sparse coding of different individual features by single neurons in these areas (e.g., place cells, grid cells) are inadequate to capture the complexity of experience represented within this system. By contrast, population analyses of neurons with denser coding and mixed selectivity reveal new and important insights into the organization of memories. Furthermore, comparisons of the organization of information in interconnected areas suggest a model of hippocampal-cortical interactions that mediates the fundamental features of memory.

Large brains benefit from localization of function in which distinct regions extract and process different information to create a representation of experience. Systems neuroscience seeks to explain which neural patterns constitute a memory representation and, further, to understand how neural representations in different brain regions interact to support cognition. Here, we will explore how neural population analysis can support these goals.

Until recently, the field of neurophysiology has tackled the problem of how brain areas represent information by characterizing tuning curves that define the receptive fields for neurons in each region of a system and then model how successive regions employ the information coded in earlier stages. Within the study of the hippocampal system, this strategy has led the discovery of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971), grid cells in the medial entorhinal cortex (Hafting et al., 2005), and other simple receptive field properties of neurons in neighboring regions (Kropff et al., 2015; Lever et al., 2009; Solstad et al., 2008; Taube et al., 1990; Zhang et al., 2013). Together, the identification

of these putative cell types have been interpreted as evidence of a spatial navigation system (Hartley et al., 2014; McNaughton et al., 2006; Moser et al., 2015). However, we will argue that this approach has, at times, failed to capture the full range of information represented within the hippocampal system and, instead, we suggest that the analysis of neural populations in the hippocampus and associated cortical areas can provide much richer understanding of how this brain system supports memory.

First, we consider some basic theoretical issues central to population coding and the analytical techniques used to address these issues. We then turn to a series of experiments conducted in our lab in which population analysis has revealed new insights into the nature of associative memory representation in connected regions of the hippocampal system. Finally, we will consider how results from these experiments challenge current theoretical views and instead support a new model for how the hippocampus, rhinal cortices, and prefrontal cortex might coordinate to define complex and flexible representational spaces that are useful for both memory and action.

What the ensemble code reveals about the nature of neural representation

It is widely believed that the rate in which a neuron fires is the key determinant in representing information (Ferster and Spruston, 1995; Histed and Maunsell, 2014; Shadlen and Newsome, 1994). The application of this principle to identify the information coded by neurons historically involves a characterization of the receptive field of a neuron, defined as a change in the rate of action potentials associated with parametric manipulations of a stimulus, action, or cognitive variable (Adrian and Zotterman, 1926; Georgopoulos et al., 1986; Hubel and Wiesel, 1962; Kennerley et al., 2011). The neuron is said to "encode" or "represent" those variables that define the receptive field. Identifying tuning curves within a region works well when the dimensionality of the representational space is small and best when its unidimensional. For example, V1 has simple cells tuned to oriented edges (Hubel and Wiesel, 1959), A1 has a tonotopy with frequency-tuned cells (Merzenich et al., 1975), and thalamic nucleus AD has cells tuned to head direction (Peyrache et al., 2015; Taube, 1995). Narrow receptive fields with Gaussian tuning to a single dimension are often considered the hallmark of 'efficient coding' (Barlow, 1961, 1972; Martin, 1994; Olshausen and Field, 1996). This approach was extended from sensory areas to the hippocampus in the pioneering work of John O'Keefe, Robert Muller, David Olton (Muller et al., 1987; O'Keefe and Dostrovsky, 1971; Olton et al., 1978), and others (McNaughton et al., 1983), in their success in identifying receptive fields of hippocampal principal cells. These neurons were called "place cells" because, under circumstances where the representational space was limited to the single dimension of location, they showed narrow, approximately Gaussian tuning to the location of rats in an environment where behavior was controlled (and therefore not considered) across space (Muller et al., 1987). Since the discovery of place cells, the same approach has identified cells in neighboring regions associated with a systematic array of positions (grid cells), head direction, and environmental borders (Hartley et al., 2014).

Though great progress has been made with analyzing single cell tuning curves, there are limitations to this approach that can misguide our understanding of information coding in the hippocampus and associated cortical areas. The first limitation has to do with how

information is distributed across a population of cells, even in simplified behavioral conditions where unidimensional coding is prominent. The second arises when neural activity reflects conjunctive coding to multiple dimensions of information in more complex behavioral conditions.

Sparse vs dense population coding

To illustrate the first limitation of the single cell approach, we consider the coding of two-dimensional space by cells in the dorsal hippocampus (dHPC), the ventral hippocampus (vHPC), and the medial entorhinal cortex (MEC) in rats foraging in open fields. Dorsal hippocampal cells have smaller place fields than those of cells recorded in the vHPC (Jung et al., 1994; Kjelstrup et al., 2008; Komorowski et al., 2013; Royer et al., 2010). Idealized grid cells in the MEC have place fields that tessellate the environment in hexagonal grids (Hafting et al., 2005). Based on the receptive field properties in these areas, a key question is which area provides the most accurate spatial code?

One approach to addressing this question involves using the observed neural signal to decode what the subject was doing. Many classification algorithms exist for this type of analyses (Brown et al., 2004; Haxby et al., 2014; Li, 2014), however, Bayesian decoding has emerged as a favorite since it theoretically provides the best possible classification given certain assumptions (Zhang et al., 1998). Without knowing how the brain decodes itself, the Bayesian approach is therefore a reasonable starting place to determine what *could be* represented.

As compared to the dHPC, cells in the vHPC and grid cells fire in a larger portion of the environment, which might suggest that these regions provide an ambiguous localization signal. However, analyses from ensembles of cells in the dHPC and vHPC show that these regions in fact store the same information but with different coding strategies. In a recent experiment, cells in the dHPC carried information about a limited region of space, due to the smaller spatial extent of the firing field (Keinath et al., 2014). In the vHPC, cells carried less information per unit of space, but were informative over a larger extent of the environment; representation of a single place was therefore distributed across a larger ensemble of cells. Considering ensembles of cells in each area, the dorsal and ventral hippocampus provided equally accurate Bayesian position estimates (Keinath et al., 2014) and therefore theoretically could convey equal spatial information. The dHPC code is known to be sparse (McNaughton and Nadel, 1990) while the distributed code in the vHPC is said to be more dense, both in the sense that single cells are active more of the time and that more cells are simultaneously active at any given time. Dense codes allow for more unique states to be represented across a population of cells (Barak et al., 2013). Since the goal of decoding is to match a unique neural state to a stimulus (position in this example), the preservation of decoding accuracy across the hippocampus is less surprising. A mathematical analysis of the coding space of MEC ensembles reached a similar conclusion: fewer grid cells are needed to uniquely code for a set of positions than in dHPC due to the density of the MEC code achieved by the repetitive firing fields (Fiete et al., 2008).

There are many known benefits of maintaining a sparse network, such as metabolic efficiency, ease of decoding, and less learning related interference in artificial neural

networks (Amari, 1989; Buhmann et al., 1989; Graham and Willshaw, 2009; Mitchison and Durbin, 1989; Rolls and Treves, 2015). The relative value of dense versus sparse coding has had a profound influence on theoretical accounts of the hippocampus (McClelland et al., 1995; McNaughton and Morris, 1987; Rolls, 1990, 2013) that will be discussed below.

In a distributed code, the joint pattern of neuronal activity can theoretically convey information beyond that available from the independent information provided by each cell of an ensemble (Johnson, 1980; Panzeri et al., 1999). Trial-to-trial variability in how neurons fire to the same stimulus tends to be correlated (Averbeck and Lee, 2003; Deweese and Zador, 2004; Lin et al., 2015; Shadlen and Newsome, 1998) and these noise correlations may increase or decrease the ability to decode information from ensemble activity (Averbeck and Lee, 2006; Averbeck et al., 2006), and may or may not affect overall coding capacity of the network (Abbott and Dayan, 1999; Narayanan et al., 2005; Shamir and Sompolinsky, 2006; Zohary et al., 1994). Typically, the importance of these noise correlations is assessed by shuffling each cell's trial-by-trial activity and testing whether there are any differences in the ability to discriminate stimuli based off of the observed versus shuffled ensemble activity patterns (Averbeck and Lee, 2006; Latham and Nirenberg, 2005). The empirical contributions of noise correlations to coding appears modest (Averbeck and Lee, 2004, 2006; Nirenberg et al., 2001; Oram et al., 2001), though theoretical work has shown that such contributions scale with network size (Zohary et al., 1994) and therefore conclusions based off of small ensembles may underestimate the role of these correlations to computation. From a theoretical perspective, there may be an interesting relationship between the sparsity and density of a code and the relative importance of noise correlations, since dense codes would offer more pairwise (and higher order) interactions. The existence of noise correlations in the hippocampal system is well documented (place cells: Harris et al., 2003; grid cells: Tocker et al., 2015; head direction cells: Peyrache et al., 2015), but the relationship of these correlations to information coding awaits further study.

Unidimensional receptive fields versus mixed selectivity

A second challenge to the single cell receptive field approach occurs when cells are sensitive to multiple streams of information that do not map neatly onto an observable continuous variable. This mixed selectivity is the more typical situation in everyday behavior and is also known to be particularly dependent upon computations within the hippocampal system (Eichenbaum et al., 2007; Ergorul and Eichenbaum, 2004; Gaffan, 1994; Parkinson et al., 1988). Furthermore, brain regions dedicated to coding of a single dimension may be exception rather than the rule (Pouget et al., 2002), especially in higher order brain areas, as demonstrated below.

In the case where cells show such mixed selectivity for conjunctions of task features, Rigotti et al (2013) have argued that analysis of neural population activity patterns can reveal the nature and organization of dimensions represented. In their study, firing properties of cells in the prefrontal cortex were analyzed as monkeys learned the order in which objects were presented (Rigotti et al., 2013). In general, the receptive fields were jointly conditional, in a non-linear fashion, on the interaction of object identity, the order of object presentation, and the nature of the memory demands. By artificially removing the main effect differences from

how each cell differentiated task conditions, while leaving intact the non-linear interaction terms, the authors were able to test whether these non-linearities contained important task information. Indeed, the conjunctive code was highly informative on the ensemble level as decoding based on the ensemble of non-linear, interaction terms was accurate despite the inability to extract information from the modified single cell responses. Furthermore, on the ensemble level, use of conjunctive coding greatly expanded the dimensionality of the representational space thus allowing for a greater computational complexity that correlated with task performance.

Estimating the dimensionality of a coding space is a difficult challenge. Rigotti et al.'s estimate was based on an analysis of the number of binary, linear classifications that can be made between pairs stimuli based on ensemble firing patterns. However, the existence of curved planar (low dimensional) spaces have been suggested in other systems (Khan et al., 2007; Koulakov et al., 2011) which would have incorrectly been assessed as high dimensional in Rigotti and colleagues' experiments due to their assumption of linear classification.

Given the success in identifying unidimensional spatial receptive fields in principle cells of the hippocampus, how is the problem of mixed selectivity, and the application of population analyses, relevant to our current interest in this brain area? In fact, hippocampal neuronal activity is correctly characterized as unidimensional spatial coding only in situations where only space is the relevant dimension. In any situation where behavior becomes salient and systematic, place cells are strongly influenced by the velocity and the direction of movement (Markus et al., 1995; McNaughton et al., 1983). Furthermore, when the animal must learn about important non-spatial stimuli or differential significance of different paths through the same space, the neurons also encode all of the relevant stimuli, contingencies, and accompanying behaviors (e.g., Wood et al., 1999, 2000). These observations challenge the simplistic approach in which single spatial receptive fields, along with other unidimensional spatial firing patterns, are combined to localize the animal in space or to perform navigational calculations of the "inner GPS" (e.g., Barry and Burgess, 2014). Instead, as we will show below, most hippocampal neurons have high-dimensional mixed selectivity in behavioral situations that emphasize multiple dimensions of experience (Eichenbaum and Cohen, 2014).

The coding of non-metric stimuli by hippocampal cells complicates any straightforward analysis of a receptive field, as there is no obvious continuous axis with which to plot firing rate. A similar challenge exists in the olfactory domain as continuous changes to an odorant do not map on to continuous changes in perception or neural activity (Koulakov et al., 2011; see also Stettler and Axel, 2009). The lack of a continuous coding variable for objects and odors is in contrast to the relationship between sound frequency and pitch, light wavelength and color, and space and time. It is notable that topographies often arise in systems in which cells encode a low dimensional stimulus space such that neurons with similar coding properties tend to be physically nearby (Knudsen et al., 1987). The benefits of such computational maps would be severely diminished for cells coding more dimensions than there are physical axes in the brain (n = 3). Whether high dimensional coding of non- metric information drives the lack of topography in both olfactory system and hippocampal system

is an open question, though other possibilities for the lack of topography have been offered (Haberly, 2001; Samsonovich and McNaughton, 1997; Schultz and Rolls, 1999).

Can population analyses resolve that nature of neuronal representations in situations where behavior depends upon associating metric and non-metric information? We will show that, as rats perform such a task, hippocampal neurons show varying levels of mixed selectivity and sparsity: from extremely conjunctive, 'grandmother cells', that fire uniquely as animals sample a particular object in a specific place, to broadly tuned cells that fire in response to multiple objects in a single location or to a single object in multiple locations. The multimodal, and varied nature of the tuning profiles of individual cells suggests a high dimensional representational space on the population level, similar to that observed in the aforementioned study of prefrontal neurons (Rigotti et al., 2013), and different in kind from networks that generate simple receptive fields.

To probe how multiple dimensions of experience are represented by ensemble firing patterns, we employed a Representational Similarity Analysis (RSA; Kriegeskorte et al., 2008) to identify features of events that generate similar ensemble firing patterns and interpreted ensemble similarity as a metric by which different events are related in a brain area. Such an analysis requires an operationalization of what is meant by a memory representation and for the sake of our analyses we define such representations as the instantaneous pattern of firing rates observed across neurons. It is also necessary to consider how one defines a similar pattern of activity among a population of neurons. There are several metrics available to probe the similarity of population firing rate vectors. The choice of the similarity metric depends upon the conceptualization of what information is important in a neural read out. For example, when using correlation coefficients, the magnitude of the distance metric is normalized and only the relative differences in firing rates are important. This normalization implies that the brain has some way to account for the total amount of activity arriving from the pre-synaptic inputs, an assumption that has some experimental support (Carandini and Heeger, 2012; Louie et al., 2011; Pouille et al., 2009). On the other hand, Euclidean and cosine distance metrics preserve aspects of the absolute rate values. It is important to recognize the strengths and limitations of these and other assumptions in development of population analyses.

In our analyses, we normalize firing rates and calculated pairwise similarities by correlating population firing rate vectors between pairs of distinct behavioral events. The correlation coefficients across many such pairings are amassed in a similarity matrix that we subsequently query to identify the underlying structure of the correlations. Often, there are clearly interpretable meanings of each pairwise comparison, though this may not always be the case.

In our experiments, each ensemble representation (population vector) was recorded in trials that differed by the spatial context in which a trial was performed, the position of an object within a context, the identity of a presented object, and the reward potential of that object. Therefore, we could use these four dimensions of the animals' experience to study the organization of the representational similarity among the memories the animal formed. The goal of the analysis was to determine whether the similarity of the ensemble representation

is higher for memories that share common features as opposed to those that differ by that feature. To use object coding as an example, we can pool pairwise population correlations for events with common objects and compare those to events in which the objects differed. If the difference is larger than expected from a bootstrap distribution in which event labels are shuffled, then we can conclude that object coding was present. We can quantify the degree of object coding as the magnitude of the difference in ensemble similarity recorded after the subject samples the same object twice versus sampling events in which the objects differ. These analyses inform us about the representational distances, and the significance of those distances, between different conditions of each task dimension.

In addition, dendrograms are useful in revealing the organization of representations for the set of memories the animal acquires in this task. The construction of the dendrogram begins with a set of trial-averaged population vectors, one for each type of event that the animal must remember (i.e., a particular object with a specific reward value in a specific location and context). Then, the events are grouped into pairwise clusters according to which pairs of representations are most similar. Next, these pairwise clusters are compared and merged again according to the correlations between pairs of clusters, and so on, until only two clusters remain. The dendrogram provides a read out of what causes pattern separation in the data, as the top branching points explains the largest separation in the representations and, moving downwards, each subsequent branch point reflects smaller degrees of separation in the underlying neuronal representations. This hierarchical clustering algorithm necessarily splits and groups data points and therefore it is necessary to consider the magnitude of separation and the significance of the separation, which can be assessed indirectly through the bootstrap analysis described above or directly from similar Monte Carlo procedures developed for the analysis of dendrograms (Park et al., 2009).

Next, we will show how this RSA reveals the organization of memory representations in several components of the hippocampal system as well as striking differences in the organization of memories across brain regions.

The hippocampus, MEC, LEC, OFC and perirhinal cortex create distinct organizations of the memories

Our use of RSA to interrogate information coding has focused on rats performing a task where they employ the current spatial context to retrieve specific object memories. This task models the everyday way we use spatial and meaningful contexts to retrieve memories that are appropriate for that context. For example, when we arrive at work we remember the projects and meetings that are scheduled for that workday, and when we return home we remember chores and other home activities. In our model of context-guided memory, mice (Rajji et al., 2006) and rats (Komorowski et al., 2009) learn to use the current spatial context to guide memory for object-reward associations. Animals move between two environmental contexts where they are presented with a pair of objects distinguished by olfactory, visual, and tactile cues (Figure 1). In Context 1, one of the objects (A+) contains a buried reward and the other (B−) does not, whereas in Context 2, the contingency is reversed (A−/B+) regardless of the positions of the objects within each context. Normal learning in this task is

hippocampal dependent (Komorowski et al., 2013; Rajji et al., 2006) and we have extended this paradigm to add, on alternative trials, two additional objects (C & D) presented under the same rules and in the same contexts (McKenzie et al., 2014). In our recent study we used multiple tetrodes to identify a large fraction of CA1/3 pyramidal cells that fire associated with multiple dimensions of events in this task (McKenzie et al., 2014).

Across brain regions, single cell responses show receptive fields jointly modulated by the identity of the sampled object, the position and context occupied by the rat, and the anticipated reward potential (Figure 2). Such conjunctive mixed selectivity prevents analyses of receptive fields that rely upon an assumption of unimodal tuning on continuous axes. The heterogeneity of responses within a region and the qualitative similarity of responses across regions add to the challenge of understanding computational function based off of evoked responses. These challenges can be circumvented through the use of representational similarity analysis which compares the similarity of ensemble firing rate vectors from neurons recorded during the period of object sampling prior to the behavioral response. By considering which events evoke similar neural responses, at the population level, a hierarchy can be established amongst task dimensions that elicit similar neural activity versus those that evoke divergent responses. Such analysis reveals different organizational strategies across brain regions.

Dorsal hippocampus

In recordings from dorsal CA1 & CA3 principal cells (Figure 3A), RSA revealed a systematic hierarchical organization of ensemble representations of distinct events - we call it a "neural schema" (McKenzie et al., 2014). Figure 3A illustrates the relationships between representations of each type of event (x-axis) as linked (y-axis) by specific task dimensions (right). At the top of this neural schema, events that occur in different contexts are widely separated in representational space (black lines), indicated by anti-correlation (mean correlation coefficient = −0.21) between events that occur in different contexts, putting context as the highest superordinate dimension. Within each context-based network, events are then separated by positions (dark red lines; mean correlation coefficient ~= 0.0) within a context (i.e., positions are subordinate to contexts. Next, events that occur within the same positions are separated according to the associated reward outcome (green lines, mean correlation coefficient ~ 0.3), i.e., reward association is subordinate to position. Finally, closest together in this neural schema are events that involve different objects that have the same reward association in the same location and context, i.e., object identity (light blue lines, mean correlation coefficient = 0.3 to 0.5) is subordinate to reward values. Two additional aspects of this neural schema are notable. First, the basic organization of the schema (except the lowest level) is fully established when animals initially learn the A vs B objects. When C vs D are learned the next day, the schema rapidly assimilates the new memories by elaborating the lowest level of the schema (McKenzie et al., 2014). Second, events that are closest together (A & C, B & D in each position) are never experienced in the same trial. Yet the proximity of their representations in the schema is likely to support strong indirect associations between these items, potentially mirroring inference and generalization properties of a schema.

Notably, many previous studies have identified spatial and non-spatial coding by single hippocampal neurons (e.g., reviewed in Eichenbaum, 1999a, 2004). But these studies do not identify how these dimensions of representation are integrated to link related memories. By contrast, RSA reveals an emergent network representation of the organization of memories. Furthermore, the observations revealed through this analysis strongly support the notion that the hippocampus develops an organized representation of a network of related memories that reflects key properties of a schema, including a prominent separation of sub-schemas for each context, rapid assimilation of new memories within each sub-schema, and a network structure that would support inference between indirectly related memories.

Ventral hippocampus

In RSA analyses of neuronal firing patterns in the ventral hippocampus (Figure 3B), we observe a similar hierarchical organization as that observed in the dHPC. However, the dendrogram for the vHPC reveals that positions within a context are associated with more correlated representations than those in the dHPC (vHPC r ~ 0.2 vs dHPC r ~ 0.0), suggesting that the ventral hippocampus generalizes across specific memories that occur within the same context and, simultaneously, strongly pattern-separates events that occur between the two contexts (Komorowski et al., 2013).

Rhinal cortex

We have also used the same behavioral task to examine population firing patterns of neurons in cortical areas that interact with the hippocampus, including the lateral entorhinal cortex (LEC), medial entorhinal cortex (MEC), and perirhinal cortex (PRC). These areas are key components that are bidirectionally connected with the hippocampus in service of memory functions (Figure 4). The LEC and MEC are the end points of the classic cortical "what" and "where" streams wherein it is commonly conceived that the LEC selectively processes information about objects and events and the MEC selectively processing spatial information (Davachi, 2006; Eichenbaum et al., 2007; Ranganath, 2010). Contrary to the view that the PRC and LEC are specialized for object processing and MEC is specialized for spatial processing (Van Cauter et al., 2013; Deshmukh et al., 2012; Hargreaves et al., 2005; Henriksen et al., 2010), in animals performing our task that demands association of object with the places they are rewarded, single neurons in the PRC, LEC and MEC, including those in both superficial and deep cortical areas and in grid and border cells of MEC, have a highly similar range of selectivity to object and spatial dimensions of the task. Furthermore, contrary to the common emphasis on unidimensional spatial coding in MEC grid and border cells (Witter and Moser, 2006), we observed that grid cells, border cells, and head direction cells exhibited greater selectivity for all task dimensions, including those involving object selectivity, relative to the remaining MEC population (Keene et al., 2014).

By contrast to similar mixed selectivity in single PRC, LEC and MEC neurons, RSA of population activity revealed a key distinction in the organization of information in these areas, such that LEC and PRC populations prioritized object over location information whereas MEC populations prioritized location over object information (Figure 3C,D,E). Specifically, at the top of the hierarchy for PRC, LEC and MEC, representations were strongly separated by events that occurred in different contexts, similar to the hippocampal

schema. Next, however, in both PRC and LEC (Figure 3D, E), events within each context were separated by the object presented, then positions were separated within each object representation. By contrast, in MEC (Figure 3C), the second level of pattern separation is defined by events within each context that occurred in different positions. Finally, objects were separated within each position representation. In the three areas, representations of identical events are most closely associated (correlation of odd/even trials). Thus, although PRC, LEC and MEC exhibit similarity in mixed selectivity at the single neuron level, RSA reveals that information is organized in distinct but complementary ways (see also Ahn and Lee, 2015; Beer et al., 2013; Deshmukh and Knierim, 2011; Ohyama et al., 2012).

Orbitofrontal cortex

We have also examined population activity in the orbitalfrontal cortex (OFC), a prefrontal area thought to be particularly important for coding reward associations of stimuli, which are prominent in our task (Farovik et al., 2015). Like neurons in each of the medial temporal areas, single neurons in OFC also showed mixed selectivity encompassing each of the task dimensions. OFC neurons encoded the full range of dimensions that characterize each object-sampling event. Substantial proportions of the neurons fired differentially in response to object, position, or context dimensions, although showed firing that could be explained by any single dimension. Most notably, the largest proportion of OFC neurons distinguished combinations of objects and the context in which they were sampled, and the firing pattern of most of these neurons was characterized by activation during sampling of different objects in the opposing contexts, thus reflecting the common reward value of these events. However, reward associations did not fully account for differences in the activity across object-context combinations in many other cells.

RSA showed that OFC neuronal ensembles represented distinct value-based schemas, each composed of a systematic organization of the representations of objects in the contexts and positions where they were associated with reward or non-reward (Figure 3F). Events associated with opposite reward value involved strongly pattern-separated representations. This observation indicates the establishment of distinct OFC neural schemas that encode events that were associated with reward and non-reward. The separation of these schemas for opposing object-reward associations could support reduction of interference between events that share object, position, or context features but lead to opposite outcomes. Within each distinct value-based schema, objects in different contexts that predict the same outcome are differentially represented, whereas distinct objects that were not associated with reward were coded as similar across contexts, suggesting that object-context representation depended on reward status. Within each context representation, events were separated by position within the context, and finally within each position representation, events having the same object identity and value were encoded most similarly. The hierarchical coding revealed by our RSA is consistent with a mapping of contextual cues and specific stimuli to behavioral responses and the values of consequent reinforcement envisioned by Wilson et al., (2014).

This representational organization is strikingly different than the representation developed by the hippocampus in animals performing the same context-guided object association task

(McKenzie et al., 2014). As described above, the hippocampal network strongly pattern separates events by the context in which they occur, thus, establishing distinct representational networks that include both rewarded and non-rewarded events that occur in different contexts. Within each distinct context-defined schema, events are separated by the locations where they occur within a context. Within representations of locations, events were separated by reward value, and within representations of reward values, events were separated by object identity. Thus, whereas the hippocampus develops a context-based schema, the OFC develops a value-based schema. The distinctive organizations of task dimensions in OFC and the hippocampus suggest commonality in the information contained in these brain areas, and complementary organization of information processing relevant to this memory task.

How are schemas composed during learning?

An influential theory of hippocampal function suggests that the hippocampus learns new associations quickly and then, through reactivations of hippocampal patterns, transmits these new associations to the cortex to be gradually woven into the stable attractor space that defines our semantic memory or schema (McClelland et al., 1995). In McClelland and colleagues' seminal analysis, the exact mechanism of learning in the hippocampus was omitted but subsequent computational models have filled in the gaps. The common thread across this work is that the role of the hippocampus is to store representations of dense, correlated cortical inputs in independent sparse networks that can be queried with partial input to reinstate, via pattern completion, the activity that was present during initial learning (Hasselmo et al., 1996; Marr, 1971; McNaughton and Morris, 1987; McNaughton and Nadel, 1990; O'Reilly and McClelland, 1994; Treves and Rolls, 1994). In these models, pattern completion is thought to be limited to recreating a pattern of activity during encoding. Novel conjunctions of familiar elements would not associatively activate prior traces but instead create a new representation that is ideally independent of that for the originally experienced conjunctions (Kumaran and McClelland, 2012; O'Reilly and McClelland, 1994). Accordingly, these theoretical transforms on the signal within the hippocampus "by nature tend to support episodic memory at the expense of capturing the higher order structure of a set of experiences" (Kumaran and McClelland, 2012).

The observation that place cells generate independent spatial mappings in different contexts (Alme et al., 2014; Hayman et al., 2003; Kubie and Ranck, 1983; Leutgeb et al., 2004; Paz-Villagrán et al., 2004; Spiers et al., 2013) and the random nature in which new place fields are laid down within an environment (Rich et al., 2014) have been used as evidence for a random orthogonalization process. In a majority of place cell studies, a foraging task is employed in which reward is evenly distributed across the environment and behavior is randomized over space. This task guarantees that the only organizing principal of the experience is the spatial layout of the environment; the subject is tested in a low dimensional space and the data are analyzed assuming low dimensional coding.

Our findings are also at odds with key predictions of the model described above, as can be seen clearly in the hippocampal dendrogram that shows that the degree of similarity and pattern separation depends on task demands. We found that the higher order structure for a

set of experiences defines the organization of the hippocampal representation, just as it does in the cortex, though different areas emphasize different dimensions of the task structure. There was no greater degree of 'orthogonalization' in the hippocampus as compared to upstream cortical regions, as predicted by the classic model. Instead, all medial temporal areas strongly separate representations of events in different contexts. Different medial temporal areas prioritized position and object dimensions differently, but all manifest a range of separations. Instead, the systematic hierarchical organization of memories is most striking and offers a different way to think about memory representation as organized schemas throughout this system.

These findings parallel previous observations of hippocampal neurons that link memories in humans and animals. As pointed out before (Cohen and Eichenbaum, 1993; Eichenbaum, 1999b) place cells represent the set of experiences within a particular location, which may be a particularly important feature in linking episodic memories that have shared common locations. A similar phenomenon has been observed in rats where cells fire at behaviorally equivalent positions on different arms of a maze or different mazes (Singer et al., 2010). Other striking examples of semantic representations that link specific experiences in the hippocampus comes from studies in human epileptic patients in which cells increase firing rate in response to pictures all from the same category of stimuli such as houses or faces (Kreiman et al., 2000) or, most remarkably, from cells that respond only to symbols that represent an individual, such as a cell that responded to colored photographs, line drawing, and the written name of the actor Halle Barry (Quiroga et al., 2005). Similar category cells have been reported in the monkey during a delayed matching task (Hampson et al., 2004). Our studies have shown that hippocampal system areas link memories in highly systematic organizations that are specific to each area.

The data presented here show that the hippocampal representation can reflect a highly organized hierarchical structure that matches the relationship between learned associations and the structure of representation in some cortical areas. However, the theoretical pattern separation function of the dentate and CA3 was critical in computational models of episodic memory to prevent 'catastrophic interference'. How can the hippocampus rapidly encode episodic memories in a representational space that preserves the long-term structure that defines memory schemas?

The considerations of sparsity and density that have shaped many memory models assumed that the hippocampus would adopt the same coding principal to all stimuli. This may not the case. When rats learn to associate reward with a location, the goal locations begin to accumulate place fields (Dupret et al., 2010). Similarly, when rats stop on a track to gaze at the surroundings, a new place field is laid down (Monaco et al., 2014). This experience-dependent overrepresentation increases the density of the neural code for the associated events. A cognitive model of learning nicely illustrates the dual value of this overrepresentation. First, these overrepresentations are easier to pattern match with a subsequent repetition. Second, it is more difficult to retrieve false positives with other patterns being incorrectly mistaken for the target representation (Criss et al., 2011). Indeed, when rats learn that a location possesses a hidden reward, the representation of that location becomes decorrelated with those of the surrounding areas (McKenzie et al., 2013). The

overrepresentation and conjunctive firing fields may act together to increase the dimensionality of the representational space, which allows more unique patterns to be observed, though the precise relationship between sparsity and memory capacity depends upon how the network learns and how the neural code is read out (Barak et al., 2013; Rigotti et al., 2013; Treves and Rolls, 1991; Willshaw and Dayan, 1990; Zhang and Sejnowski, 1999).

Below we present a model of how the hippocampus, rhinal cortices and prefrontal cortex might interact to bias which aspects of an experience define the representation space embodied by the interactions of these regions.

Cortical-hippocampal dialog is essential for maintaining high dimensional, multi-modal coding spaces

Our experiments have revealed a network of connected brain regions that code for overlapping events in the animal's experience. Recent intervention studies suggest that the mixed selectivity observed in each region is supported by an anatomical loop between the prefrontal cortex, the rhinal cortices and the hippocampus. Here we review evidence for a systems-level model for context guided memory (Preston and Eichenbaum, 2013) and put forward the hypothesis that the bidirectional connections between the hippocampus and the cortex generate a high dimensional coding space tuned to the behaviorally relevant stimuli.

The model focuses on the interaction between the prefrontal cortex, the rhinal cortices and the hippocampus (Figure 4). Most anatomical studies have shown that the prefrontal cortex does not project directly to the hippocampus, but instead projects indirectly either through the rhinal cortices or the nucleus reuniens (Cenquizca and Swanson, 2007; Herkenham, 1978; Swanson and Cowan, 1977; Varela et al., 2014; Witter and Amaral, 2004), however, a recent report shows that such a connection may exist (Rajasethupathy et al., 2015). Our model focuses on the well-established indirection prefrontal cortex to hippocampus connection. The dorsal hippocampus also lacks direct connections to the prefrontal cortex, but can influence prefrontal activity through the ventral hippocampus which does show strong monosynaptic efferents (Burwell and Witter, 2002; Verwer et al., 1997).

The multimodal, conjunctive properties of the dorsal hippocampus depend upon integrity of the prefrontal and rhinal cortices. When rats were trained on the context guided memory task described above, muscimol inactivation of the medial prefrontal cortex (mPFC) caused a decrease in the degree to which objects could influence firing rates, though place fields remained intact (Navawongse and Eichenbaum, 2013). The loss of the object coding dimension of the representational space should cause deficits in segregating memories that depend on object recognition. Indeed, this is exactly what we found, as task performance was significantly impaired after mPFC inactivation. Over generalization was also observed in a contextual fear paradigm after mPFC projections were silenced at the level of the nucleus reuniens (Xu and Südhof, 2013). In another study, silencing of the nucleus reuniens reduced a place-by-trajectory conjunctive code in CA1 (Ito et al., 2015), further showing a necessary role for prefrontal-hippocampal interactions in maintaining a high dimensional code that depends on these conjunctive firing properties.

Although these recent reports show a clear role for the nucleus reuniens in coordinating a hippocampal-prefrontal network, we emphasize the role of the rhinal cortices in mediating this interaction due to the size of the reuniens. The small number of neurons in this nucleus puts a limit on the number of possible discernable states and therefore places a bottleneck on how the mPFC could drive pattern separation in the hippocampus. Therefore, our model instead focuses on the role of the rhinal cortices.

There is accumulating evidence that the rhinal cortices play this intermediary role. For example, the conjunctive code between room color and geometry found in area CA3 has been shown to depend upon LEC, as lesions to this region diminish ensemble discrimination of testing chambers that differ solely by color (Lu et al., 2013). In another study, cells in dorsal CA1 developed a conjunctive odor and place code alongside those recorded LEC which coordinated with one another on a fast (beta rhythm) time scale (Igarashi et al., 2014) that is a hallmark of inter-region communication (Rangel and Eichenbaum, 2014). In our studies, muscimol inactivation of MEC did not disrupt item coding (Navawongse and Eichenbaum, 2013), consistent with the stronger item coding seen in the LEC (Deshmukh and Knierim, 2011; Tsao et al., 2013; Figure 3C,D). Perirhinal inactivation, on the other hand, has been shown to disrupt CA1 object coding in an object-place association task (Lee and Park, 2013), suggesting a prefrontal-perirhinal-LEC-dHPC network in creating a conjunctive code for item and place in the hippocampus.

It is notable that position coding in the hippocampus is relatively intact after disrupted processing in MEC, LEC, PRC, the prefrontal cortex, and many other regions (Brun et al., 2008; Calton et al., 2003; Van Cauter et al., 2008; Hales et al., 2014; Hok et al., 2013; Kyd and Bilkey, 2005; Lu et al., 2013; Miller and Best, 1980; Navawongse and Eichenbaum, 2013; Suh et al., 2011). The redundant information about space observed across several regions (Figure 3) appears sufficient to drive location specific firing in the dorsal hippocampus. The necessary MEC contribution to the nature of the hippocampal representation remains somewhat of a mystery, though recent evidence suggests a role in establishing temporal relationships amongst hippocampal cells (Schlesiger et al., 2015). The two regions show an impressively similar coding hierarchy for which information drives ensemble similarity, yet MEC lesions do not disrupt the ability of the hippocampus to encode places (Brandon et al., 2014; Van Cauter et al., 2008; Hales et al., 2014; Miller and Best, 1980; Navawongse and Eichenbaum, 2013) or objects that occur in those places (Navawongse and Eichenbaum, 2013). Changes in MEC activity, either endogenous (Fyhn et al., 2007) or experimental (Hales et al., 2014; Navawongse and Eichenbaum, 2013; Rueckemann et al., 2015), reliably cause reconfigurations of the hippocampal firing properties (remapping) with preserved information coded by a different set of cells. This reconfiguration suggests that the MEC provides a broader contextual signal (Eichenbaum and Lipton, 2008) that defines the space of representations with which to encode the specifics of a new memory. This contextual signal may be detected by the similarity analyses outlined here.

As described above, a fundamental difference in coding between the dorsal and ventral hippocampus is the density of the code, which manifests as larger place fields in the ventral hippocampus. It remains to be seen whether coding of non-spatial information shows the

same shift in coding level. A computational benefit of a denser code is better generalization between related cases for a downstream reader (Barak et al., 2013; Keinath et al., 2014). This implies that, when moving down the longitudinal axis of the hippocampus, there is a systematic shift in the generalization gradient (not the spatial resolution), from narrow to broad. This shift in generalization constitutes the contextual code where, in the spatial domain, places represented by correlated inputs can easily be mapped onto common downstream patterns. This same argument could be applied to the grid cell code providing the hippocampus with an evenly sampled generalization signal across a given context. Note that the generalization gradient does not mean that the correlated vHPC patterns *must* be mapped to a common output pattern, as shown by the Bayesian decoding results (Keinath et al., 2014).

The context signal that is available to the mPFC can be used as cue for recalling appropriate rules. It is commonly believed that the 'executive' functions of the PFC derive from its role as a top down hub (Cole et al., 2012; van den Heuvel and Sporns, 2013). In this capacity, the mPFC is thought to sustain the coordinated activity of multiple separate brain areas that are not strongly interconnected (Miller and Cohen, 2001). Here, we propose that the contextual signal from the vHPC activates mPFC ensembles that are associated with a specific cortico-cortico network – this association is the context dependent rule. This prefrontal signal can also act to bias specific hippocampal representations through the rhinal cortices as described above (Figure 4).

In support of this idea, recent experiments have shown the coordination of prefrontal ensembles to the hippocampal theta rhythm as rats learn a set shifting task (Benchenane et al., 2010). Other studies have also shown coordination of rhythms between the regions that tracks learning in rats (Fujisawa et al., 2008; Hyman et al., 2005; Spellman et al., 2015) and monkeys (Brincat and Miller, 2015) that depend upon the integrity of the ventral hippocampus (O'Neill et al., 2013). Furthermore, silencing vHPC terminals to mPFC disrupts spatial working memory and the ability to decode the location of a goal from mPFC ensemble activity, though other, non-spatial, aspects of the mPFC conjunctive code remain intact (Spellman et al., 2015). Therefore, aspects of the mixed selectivity of prefrontal cells are dependent upon hippocampal function.

The hippocampus is often seen as a passive recorder of all attended life events (Morris, 2006). However, salient events define memory more than the inconsequential ones (Dunsmoor et al., 2015; Lisman and Grace, 2005; Morris, 2006; Westmacott and Moscovitch, 2003). Just as the vHPC may select the appropriate rules in the mPFC, there may be a similar operation occurring in prefrontal areas that track valence, such as the OFC. A series of elegant studies in vitro provide an interesting system's level hypothesis for how the OFC could interact with the perirhinal cortex to gate information flow into the hippocampus. These studies show that stimulating the perirhinal cortex is insufficient to cause propagation of activity into the entorhinal cortex and the hippocampus due to the high degree of inhibition at the rhinal sulcus (de Curtis and Paré, 2004; Kajiwara et al., 2003). These results suggest a large degree of information filtering takes places in the rhinal cortices. However, when perirhinal stimulation was paired with coincident activity of the amygdala, activity spread to the entorhinal cortex and the dentate (Iijima et al., 1996;

Kajiwara et al., 2003; Koganezawa et al., 2008). Similarly, spike transmission efficacy in vivo increases between perirhinal and entorhinal cortex when spikes are also observed in the mPFC or amygdala (Paz et al., 2006, 2007, 2009). These results suggest that salience is signaled by the amygdala, and potentially by the OFC, to gate the passage of sensory information in the entorhinal cortex and hippocampus. We propose that the strong value coding seen in our OFC study gates information flow into the hippocampus via its connectivity with the rhinal cortices and the perirhinal cortex in particular.

It is noteworthy that communication between brain regions is often associated with synchrony of brain rhythms at various frequencies (Benchenane et al., 2010; Dickson and de Curtis, 2002; Engel et al., 2001; Fries, 2005; Igarashi et al., 2014; Scheffzük et al., 2011). A separate body of work has showed that such slower timescale synchrony, when observed, is associated with a fast-timescale decorrelation of local activity (Mizuseki and Buzsaki, 2014; Renart et al., 2010; Tan et al., 2014). Theoretically, such network decorrelation has been related to expansions in representational capacity (Hennequin et al., 2014; Kumar et al., 2008; Sompolinsky et al., 2001; Wang et al., 2004), and may be a signature of transient increases in the dimensionality of the coding space. In several studies the synchrony of brain rhythms across regions has been directly related to the formation of mixed selectivities (Igarashi et al., 2014; Ito et al., 2015; Tort et al., 2009) suggesting a close relationship between inter-regional communication and an increase in coding capacity.

Gating of information allows the dimensionality of the hippocampal space to depend upon the behaviorally relevant stimuli. According to this view, ensembles pattern-separate similar stimuli during learning when rewards depend upon discriminating previously neutral stimuli (e.g. Tort et al., 2011). The increased pattern separation may reflect the emergence of a new organization of information. It is important to keep in mind that no two learning trials are identical, so a subject must learn the necessary and sufficient features of a trial that constitute a linked set of memories that predict a reliable outcome. Separations may be supported by cells that discriminate the dimensions of an experience that differentially predict reward, or other differences and commonalities of individual events that have significance. Indeed, cortical representation of objects have been shown to change according to the dimensions in which they are categorized (De Baene et al., 2008; Engel et al., 2001; Goldstone et al., 2001; Sigala and Logothetis, 2002), consistent with modification of a neural schema to reflect new perceptual demands (Meeter et al., 2009).

According to our model, the prefrontal cortex biases retrieval of the context-appropriate memory representations in the dorsal hippocampus (Navawongse and Eichenbaum, 2013) through its action on the upstream cortical areas. Appropriate retrieval in the hippocampus is accomplished by selective disinhibition of representations that are appropriate for the current context, consistent with the finding that the PRC influences LEC via inhibitory regulation that is modulated by the prefrontal cortex (de Curtis and Paré, 2004). Thus the OFC and PRC together may support cognitive control over memory retrieval by biasing the selection of context-based schemas and through inhibition of competing schemas in other medial temporal structures (Bunce et al., 2013; Fernández and Tendolkar, 2006).

These considerations do not resolve how prefrontal mechanisms influence processing in the entorhinal cortex and hippocampus, but put the focus on interactions between very different organizations of information in the OFC and perirhinal and lateral entorhinal cortex as a strong candidate for where the critical interactions occur. Future studies that examine the simultaneous activity patterns, along with potentially mediating oscillatory synchronization, during the course of schema formation may offer new insights about how these areas and their representations interact.

Future Directions

We have emphasized the importance of probing neural representations using complex tasks and analyses suited to multidimensional coding spaces. This line of work is in its infancy and many basic questions remain.

The analyses described throughout this paper have been focused on the rate code, however, it is known that the relative timing between cells conveys information in several brain systems (Malhotra et al., 2012; Montemurro et al., 2008; O'Keefe and Recce, 1993; Panzeri et al., 2001; Saitoh and Suga, 1995). In our representational similarity analyses, we ignored this temporal code and it is possible that patterns that are considered similar by a rate analysis can be highly decorrelated if cells are sensitive to the permutations of cell activity in addition to the combinations that we have considered (Branco et al., 2010). The only way to address this issue is to test the sensitivity of postsynaptic areas to temporal permutations in cell activity, as has been done in the olfactory system (Haddad et al., 2013).

Another limitation to the RSA presented here is that there is no account of trial-to-trial variability. This variability may be particularly important in the hippocampus which is known to support episodic memory – memory for events that happen once. Our previous similarity analyses revealed substantial trial-to-trial differences in coding strength by using the instantaneous firing rates observed on each trail rather than the trial-averaged mean firing rate vectors (McKenzie et al., 2014). Dendrogram analysis requires large simultaneous ensembles to ensure adequate coverage of the representational space by the sampled ensemble, though with sufficient sampling, this too can be done on a trial-to-trial basis and statistical methods exist for assessing the reliability of the clustering structure (Park et al., 2009). The more important issue missed in RSA, however, relates to the underlying assumption that neurons encode stimuli by firing at a particular rate and variations from that set-point reflect noise. The possibility that pair-wise (or higher order) 'noise' correlations may provide information, as discussed earlier, is one violation of this implicit assumption. Additionally, there is a growing body of work showing the firing variability may reflect uncertainty. Under this interpretation, the instantaneous firing rate is a consequence of what is present *and* the probability of that presence (Fiser et al., 2010; Ma et al., 2006). This is an important departure from the classic coding perspective embodied by the RSA analysis which assumes that rate is an estimate of some world variable and not the likelihood of that estimate (Ma et al., 2008). The extension of this probabilistic view point to RSA requires storage of the representational organizations, as operationalized as the correlation structure of a set of population rate vectors, *and* the probability of observing such correlation structures. A recent theoretical paper has proposed just such an approach (Johnson et al.,

2012), though empirical validation, and a mechanistic description for how such probability structures become stored is lacking.

Electrophysiology places limitations on the ability to track the same network over many days. New calcium imaging technology (Ghosh et al., 2011) now enables the observation of the full construction of a memory schema from the naïve state to the highly organized memory spaces that we observed. These studies will tell us whether the same cells remain involved in the memory representation over long periods of time. Recent studies have emphasized the transient nature of the hippocampal representation (Attardo et al., 2015; Ziv et al., 2013). However, we (Komorowski et al., 2009; McKenzie et al., 2014), and others (Hattori et al., 2015), have observed long term stability in the rules that dictate network organization. How do these rules get passed from one group of cells to another? One exciting possibility is that multiple high dimensional ensemble representations can be mapped onto a common lower dimensional space that embodies the rules carried from one ensemble to the next.

Our observation of coding of both objects and places in both PRC-LEC and MEC challenges the conventional model where separate object and place pathways converge only within the hippocampus to support conjunctive coding (Eichenbaum et al., 2007). Furthermore, the consistent failure to observe long term place field deficits following MEC lesions or inactivations (Brandon et al., 2014; Van Cauter et al., 2008; Hales et al., 2014; Miller and Best, 1980; Navawongse and Eichenbaum, 2013; Rueckemann et al., 2015; Schmidt et al., 2013) is also contrary to predictions that grid cells are required to form place cells (Moser et al., 2008). It is possible that the multidimensional approach laid out here may reveal the essential contribution of MEC input to hippocampal function, perhaps in the coding of context.

Our studies have shown that, over the course of seconds, there can be shifts in the dominance of place, object, and reward coding (McKenzie et al., 2014). Our context guided memory model (Figure 4) predicts that the shifts in coding dominance observed in the hippocampus is due to OFC or mPFC gating different afferents to the hippocampus at different times. Simultaneous, large-scale recordings between these brain areas may reveal evidence for this gating process (Paz et al., 2009) which may be evidenced by searching for moments of inter-regional oscillatory synchrony (Bieri et al., 2014; Fernández-Ruiz et al., 2012). More generally, it remains an open question as to what determines the hierarchy in the coding regimes that we have observed in each of the brain areas studied.

Conclusion

A major concern in research on the hippocampus and related cortical areas is how to reconcile the role of these areas in spatial mapping versus memory. Here we show that, in situations where memories involve both spatial and non-spatial information, the hippocampus, as well as a set of interconnected cortical areas, systematically organizes all of the information incorporated into the relevant memories. Within the closely interconnected hippocampal and entorhinal areas, ensemble representations reflect a separation of schemas based on spatially and meaningfully distinct contexts, wherein spatial and non-spatial

information are integrated. This observation suggests that the prominent role of space in hippocampal neural activity should be viewed as one of several organizing dimension of events. Furthermore, our findings on the orbitofrontal cortex suggest that other cortical areas may strongly influence the memory schemas within the hippocampus, likely controlling both the establishment of the organization of memories and the retrieval of appropriate memories that are relevant in different contexts. While much remains to be revealed about the mechanisms of cortical-hippocampal interactions, the findings discussed here lead us towards a new understanding of how this brain system supports our capacity for memory.

Acknowledgments

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Highlights

- Here we consider the value of neural population analysis as an approach to understanding how information is represented in the hippocampus and cortical areas.

- We argue that population analyses of neurons with denser coding and mixed selectivity reveal new and important insights into the organization of memories.

- Furthermore, comparisons of the organization of information in interconnected areas suggest a model of hippocampal-cortical interactions that mediates the fundamental features of memory
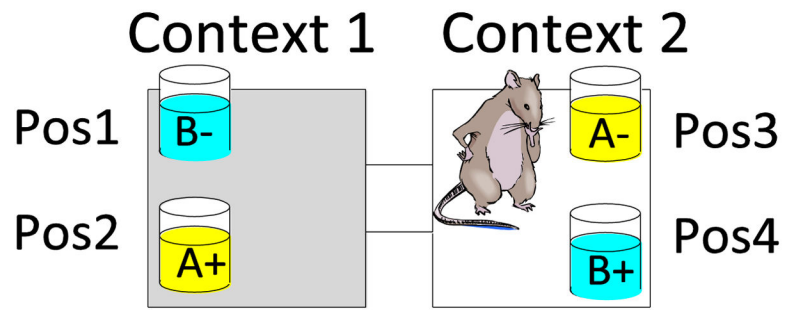
Figure 1.
Context-guided object-association task. On each trial, rewarded (+) and nonrewarded (−) stimuli are presented in the positions shown (Pos1–4) or in the reverse positions within each context. Animals were either trained with two objects A vs B or with four (A vs B, C vs D), and then tested on both problems concurrently.
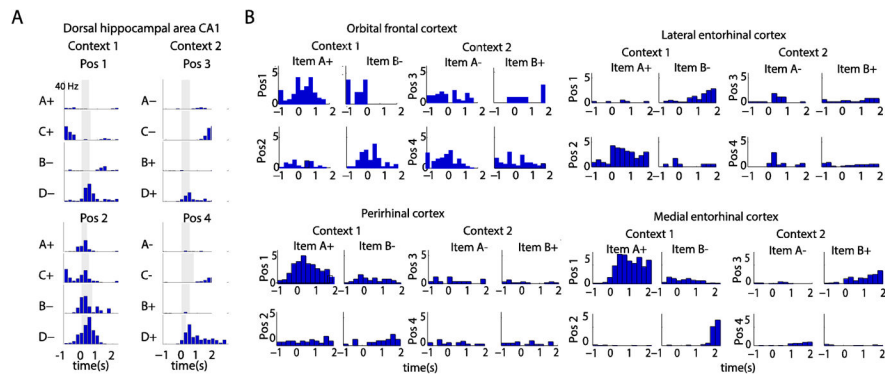
Figure 2.
Firing rate histograms illustrating example neurons with mixed selectivity in different brain regions. Each panel shows the response pattern of a neuron during the sampling of a specific object stimulus at a particular location in one of the two contexts. In each panel neural activity is time-locked to the onset of stimulus sampling (time = 0). (A) An example CA1 cell on the four object (A,B,C,D) version of the task. Gray bars indicate minimum object sampling period used in RSAs. (B) Example cortical cells recorded on the two object (A,B) version of the task.
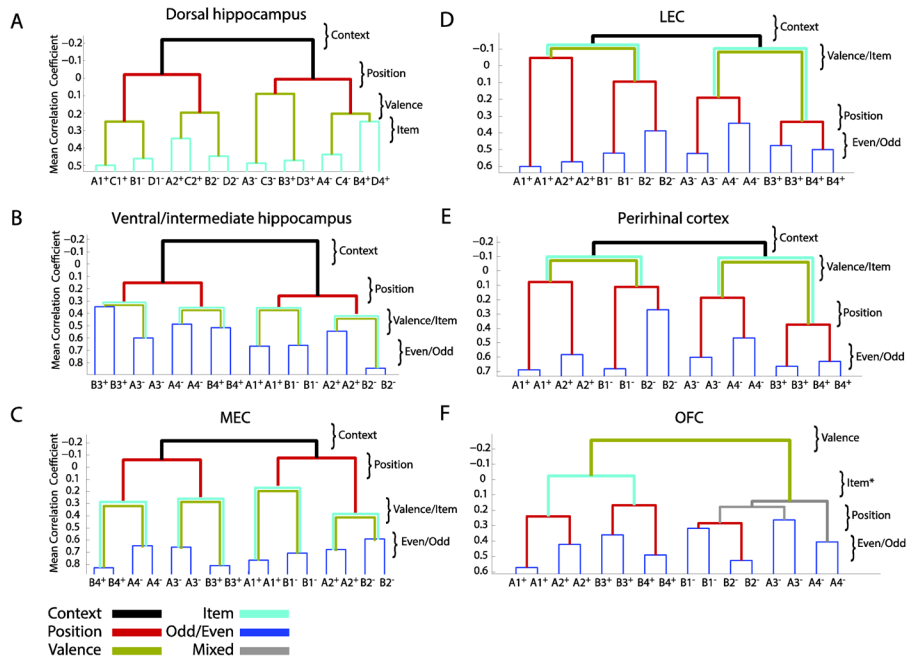
Figure 3.
Dendrograms illustrating the hierarchical organization of memories across different neural schemas. X-axis indicates either 16 distinct events (A) or the even/odd trials of 8 distinct events (B–F). Lines indicate mean correlation coefficients (r) between events and clusters of events. Labels at right indicate task dimensions that correspond to levels of the schema that demarcate superordinate and subordinate dimensions that link and relate distinct memories. In the four item version of the task (Panel A), item and valence coding could be differentiated as there were pairs of items that shared the same context/reward association, unlike the two-item version of the task (Panels B–F) in which the observed coding hierarchy left some ambiguity as to which dimension drove pattern separation (except in the case of OFC). *Note that the Item coding in the OFC is not perfectly maintained across events of different valence, likely due to the more stereotyped behavior for rewarded vs unrewarded sampling events.
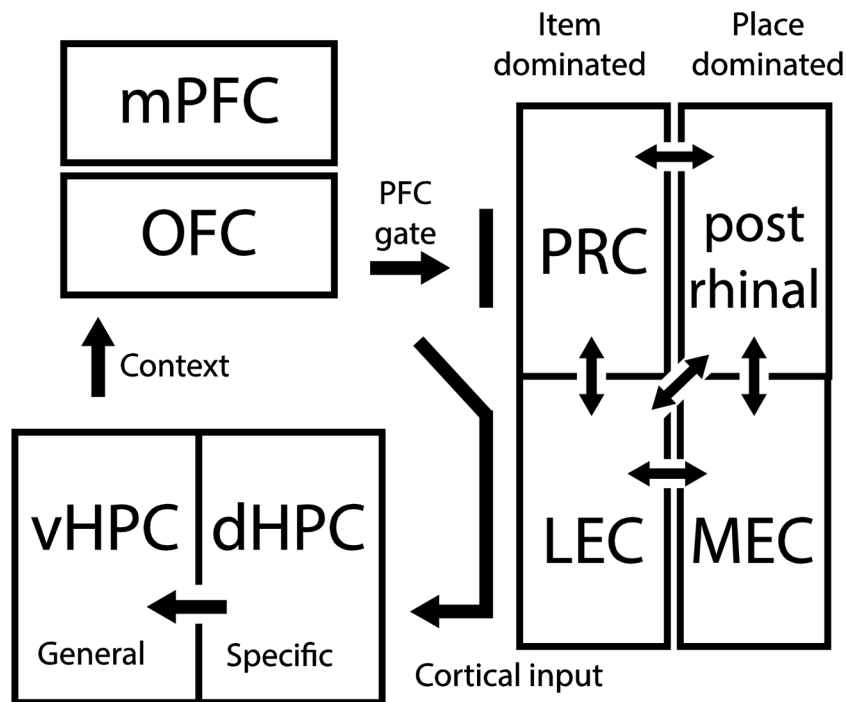
Figure 4.
Circuit model for context-guided memory retrieval and schema formation. Cortical inputs arrive to the hippocampus via the rhinal cortices in which there are partially segregated "what" and "where" processing streams, labeled 'item dominated' and 'place dominated', respectively. In general, there is a large degree of inhibition preventing the flow of information into the hippocampus. However, when the rhinal activity is coincident with inputs from the prefrontal cortex, the 'prefrontal gate', information can arrive into the hippocampus and therefore shape the hippocampal memory space. In the dorsal hippocampus, the sparse representations favor representations for more specific episodes, while the denser representations observed more ventrally are more suitable for generalization – this is the context code. The strong monosynaptic connections from the ventral hippocampus to the prefrontal cortex provide a contextual signal which can then trigger activation of the context-appropriate rules for memory retrieval stored in the prefrontal cortices.