Place cells, spatial maps and the population code for memory
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The study of population dynamics in hippocampal place cells has emerged as one of the most powerful tools for understanding the encoding, storage and retrieval of declarative memory. Recent work has laid out the contours of an attractor-based hippocampal population code for memory in recurrent circuits of the hippocampus. The code is based on inputs from a topographically organized, path-integration-dependent spatial map that lies upstream in the medial entorhinal cortex. The recurrent networks of the hippocampal formation enable these spatial inputs to be synthesized with nonspatial event-related information.

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Introduction
It is generally accepted that the hippocampus has a fundamental role in the fast encoding of some types of associative long-term memory [1]. Attempts to understand the algorithms by which information is processed in hippocampal neurons began in the late 1950s and early 1960s [2,3], only a few years after the mnemonic functions of the hippocampus had been uncovered [4]. For a long time, these physiological studies were motivated more by the structural simplicity of this area of cortex than by its potential role in the formation of memory; however, an important milestone was reached when it was reported in the early 1970s that neurons in the hippocampus have strong and reliable behavioural correlates of firing [5,6]. By far, their most striking correlate was found to be the tendency to fire if, and only if, the subject is in a particular place in its environment [5,7,8].

Since their discovery, these 'place cells' have provided an important window into the representation of the physical world as discharge patterns of single hippocampal neurons. With the more recent invention of techniques for large-scale recordings in neuronal ensembles [9,10], place cells have emerged as one of the most powerful tools for studying hippocampal population dynamics during distinct mnemonic operations.

In this review, we show how hippocampal place cells have been recently used as a model system to advance our understanding of how location and memory are represented and computed by the collective activity of cell populations in well-defined neural architectures of the hippocampal formation.

A spatial map outside the hippocampus
For more than three decades, place cells have been considered to be the key elements of a neural map of the spatial environment [5,7,11,12]. The confined spatial nature of the place cell discharge renders it one of the most striking behavioural correlates among cortical neurons, but accumulating evidence has suggested that the functions of place cells extend well beyond a specific role in mapping the physical space [13,14]. Place cells have been shown to respond to various nonspatial sensory inputs [13], and to alternate between multiple representations in the same location [15–22], reflecting both salient physical properties of the place [15,16] and events associated with the place, either at present [17,18] or in the past [19–22,23••,24••]. These and several other observations have implied that the hippocampus has a broad role in the encoding of context-specific or episodic memories in which spatial location is a crucial but non-exclusive part of what is stored in the hippocampus.

The multiplicity of hippocampal representations has introduced the possibility that the metric calculation of current position occurs outside the hippocampus [25]. One of the strongest pieces of evidence suggesting that this calculation has a hippocampal location was the apparent contrast between the low spatial information of neural activity in some areas of the entorhinal cortex and the high spatial information in downstream hippocampal place cells [20,26,27]. This contrast suggested, at the time it was discovered, that the location-specific signal is computed internally in the hippocampal circuitry. Recently, it has become clear that the spatial information carried by neural activity in the entorhinal cortex has been underestimated, largely because the entorhinal cell population was undersampled.

Spatial representations in the entorhinal cortex are now known to follow a strict, two-dimensional anatomical topography. First, the extent of spatial modulation varies between the two main subdivisions of the structure: the

lateral and the medial entorhinal cortex [28••]. Neurons have stable and sharply delineated firing fields in the medial subdivision, but seem to completely lack spatial modulation in the lateral subdivision. Second, in the medial entorhinal cortex, firing fields become gradually sharper and more concentrated along a ventromedial-to-dorsolateral axis [29••]. In the ventromedial-to-intermediate bands, where the early recordings were made [20,26,27], firing fields are broad and dispersed. Towards the dorsolateral end, however, firing fields get smaller and more confined. The dorsolateral band contains most of the projection neurons from the medial entorhinal cortex to the well-defined place cells of the dorsal hippocampus. The collective activity of a dozen of neurons in the dorsolateral medial entorhinal cortex is sufficient to reconstruct the current position of a rat with an error of only a few centimetres [29••], suggesting that neurons in this area map precisely the spatial environment of the rat. The localized firing of these neurons can be maintained without a functional hippocampus. Thus, the key features of the map are probably not mere reflections of hippocampal output. The fact that the dorsolateral band serves as a convergence site for head-direction output from the dorsal presubiculum [30], and visuospatial and move-ment-related output from the postrhinal cortex [31] also supports the notion that the position vector is computed, at least partly, in the medial entorhinal cortex itself.

The main difference between place-responsive cells in the hippocampus and those in the entorhinal cortex is perhaps that neurons in the latter area do not signal individual places. Instead, each place-modulated cell in the entorhinal cortex has several regularly spaced firing fields. Together, the multiple fields of a neuron form a tessellating triangular grid that spans the whole extent of the environment [32••] (Figure 1). Neighbouring cells have grids with similar spacing and orientation, but the grids scale up gradually from the dorsolateral towards the ventromedial end of the medial entorhinal cortex [29••,32••]. Grids of neighbouring cells are displaced relative to one another: in other words, their phases are distributed. An implication of this structural organization is that the representation of the environment is repeated over and over across the surface of the topographical map, but at a range of scales and orientations. This repetitive modular arrangement is reminiscent of the columnar organization of many sensory areas of the neocortex [33,34].

Figure 1
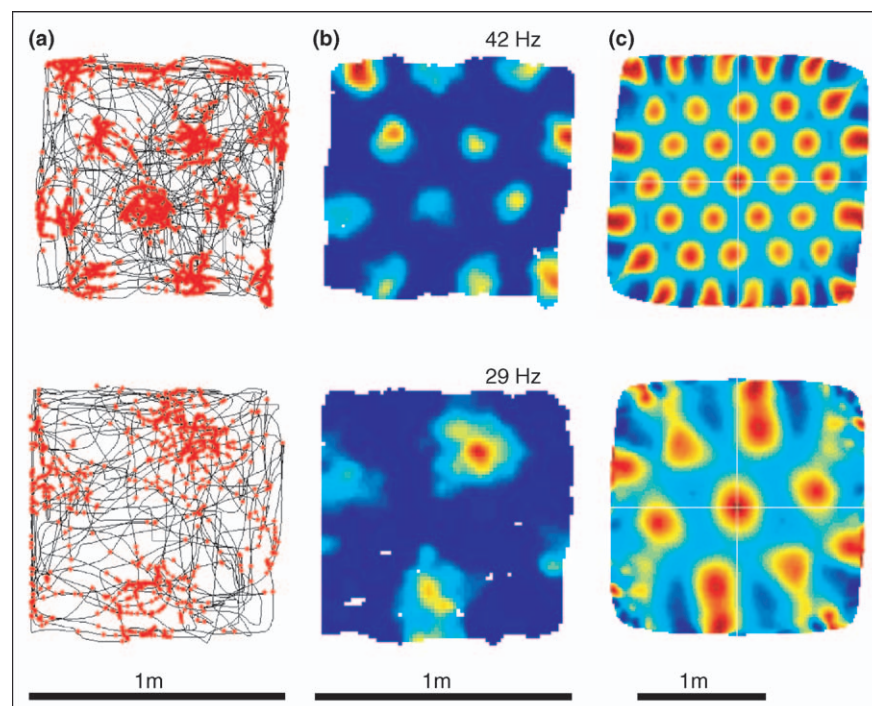
Tessellating firing fields of grid cells in the medial entorhinal cortex. Firing rate distributions are shown for two cells (top and bottom rows, respectively) that were recorded during running in a square enclosure. **(a)** Trajectory of the rat (black line) with superimposed spike locations (red dots); **(b)** rate map; **(c)** spatial autocorrelation for the rate map in (b). Maps in (b) and (c) are colour-coded. In (b), blue is 0 Hz, red is peak rate. In (c), the scale is from blue (r=−1) through green (r=0) to red (r=1.0). Scale bar indicates size of recording enclosure. Note that the distance scale in the autocorrelation diagrams is half of that of the original maps, with points along the perimeter showing correlations between positions spaced by a distance similar to the width of the enclosure. The distributions were recorded from cells located at different distances from the dorsal border of the medial entorhinal cortex; the top cell was most dorsal. Modified, with permission, from [32••].

How does this network of grid cells contribute to navigation? Navigation probably relies on a large parahippocampal network of head-direction cells [35], grid cells, and cells with conjunctive firing properties [36•]. Nonetheless, grid cells are unique in that their firing rate expresses information about position (grid vertices), direction (grid orientation) and distance (number of grid cycles) [32••]. Whether neurons in the entorhinal cortex or elsewhere can read and synthesize this information remains to be determined. Presumably, the computation of exact location would require a mechanism for integration over time (e.g. see [37]), as well as across differently tuned spatial modules (e.g. see [38]). The persistence of grid-like firing after the removal or displacement of extrinsic sensory input [32••] probably indicates that path integration is a primary mechanism for generating a continuously updated metric representation of the spatial environment [11,12]. In addition, the grids might be aligned with landmarks specific to individual environments [32••]. The proposed role of path integration is consistent with recent studies showing that severe impairments in short-distance navigation and homing behaviour occur after lesions in areas including the dorsolateral band of the medial entorhinal cortex [39,40].

## Attractor networks in the hippocampus

Although important elements of the spatial map have moved out of the hippocampus, place cells are receiving increasing attention as a tool for understanding the dynamics of cell populations during memory processes

(e.g. [10]). A key issue is how the brain identifies consistent patterns among never-identical physical inputs at the same time that it successfully prevents interference between patterns with common elements. Recent studies suggest that the solution might be based on attractor dynamics in recurrent networks of the hippocampus.

Attractor networks with modifiable synaptic weights represent powerful models of the storage and retrieval of associative memory [41]. An attractor network has one or several preferred positions or volumes in state space such that when the system is started from any other location, it will evolve until it arrives at one of the attractors and will then stay there in the absence of new inputs[42,43] (Figure 2). In this type of network, stored memories can be recalled from degraded versions of the original input stimuli (pattern completion), while at the same time the retrieved pattern stays separate from other, more dissimilar memories in the same network (pattern separation). The extensive recurrent circuitry of the hippocampus represents an ideal neural architecture for attractor dynamics [41,44–47], but direct experimental evidence for attractor functions in the hippocampus has remained scarce.

Place cells have several properties that suggest that the network performs pattern completion and pattern separation, such as, respectively, the persistent spatial firing of place cells after the removal of significant subsets of the original input [48–50] and the tendency of place

Figure 2
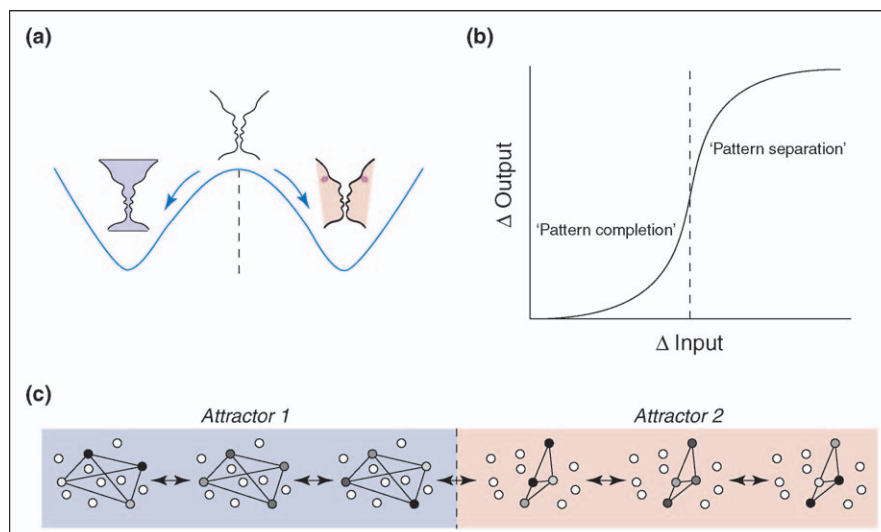
Cell assemblies with attractor dynamics. **(a)** Patterns that are ambiguous converge to a matching familiar pattern (pattern completion) and, at the same time, diverge from similar interfering patterns (pattern separation). The nonlinear nature of this process can be illustrated by a visual illusion of an ambiguous object. The perceived image fluctuates between two familiar images (blue or pink) instead of stabilizing in the middle (white). **(b)** Attractor networks are thought to induce sharp transitions between network states during progressive changes in the input pattern [46]. **(c)** Each multidimensional attractor can span a state space with large differences in relative firing rates within the cell assembly (shown as different shades of gray within each attractor). This property allows different conditions to be integrated into a constant reference frame without switching to an independently activated cell population [24••].

cells to show complete 'remapping' after only minor changes in the sensory input [15–22]. These nonlinearities, however, could merely reflect a disproportionally strong influence of the particular stimuli that are common to, or distinguished among, the conditions. In a recent study, Wills et al. [51**] resolved this ambiguity by assessing completion and separation in CA1 during systematic and quantifiable transformation of the very same input stimuli. They showed that morphing the recording environment from one familiar shape to another led to a sharp transition in the hippocampal network state near the middle of their sequence when the intermediate shapes were presented in a scrambled order. Their study provides perhaps the strongest experimental evidence so far for the expression of attractor states in the hippocampus.

Although hippocampal cell ensembles show some of the key features of an attractor network, the anatomical location of the attractors remains to be established. Paradoxically, the experimental evidence in favour of the attractor network has been obtained almost exclusively from CA1, which generally lacks the associative connections needed to form dynamic ensembles [52]. Attractor dynamics in CA1 is usually thought to reflect autoassociative processes in the recurrent CA3 network located one synapse upstream [41,44–47], but this assumption has not been proved. Recent work has provided experimental evidence for both pattern separation and pattern completion in CA3 [53•]. Place cells in this subfield orthogonalize overlapping experiences more completely than do place cells in CA1 [54••,55••], and ensembles in CA3 respond more coherently to changes in the external input than do those in CA1 [55••,56••].

These observations, however, do not necessarily imply that the processes originate in CA3. For example, a marked architectural feature of the dentate gyrus is the divergence of cortical input onto a granule cell population with many more neurons than the input layer. This feature is a potentially effective construction for decorrelating incoming signals from the neocortex [44,57], which, together with the sparse firing of the granule cells [58,59•] and their low number of synapses with CA3 neurons, raises the possibility that pattern separation begins in the dentate gyrus [41,60]. Moreover, attractor dynamics is probably a general property of cortical networks that contributes to several higher cognitive functions including perception and categorization [61–63]. Nonlinear response patterns in the neocortex could influence hippocampal place cells both through the trisynaptic circuit and through direct connections with the hippocampal subfields [64]. The relative contribution of hippocampal and parahippocampal subdivisions [53•,65•] might be resolved by simultaneous recording from connected areas during conditions that favour completion or separation.

Attractor networks and episodic memory

Several studies have indicated that the hippocampus is a key structure involved in the storage of sequentially organized episodic information [1,66,67]. Neuronal network models that allow quantitative estimates of the amount of stored information suggest that the recurrent networks of the hippocampus might have an enormous storage capacity [68], enabling them potentially to represent a very large number of event memories. The extensive number of hippocampal representations makes retrieval vulnerable to interference. Attractor-based networks might solve this problem, as they could allow events to be recalled from moderately distorted input stimuli without being confounded by other representations with similar elements.

If hippocampal networks consisted exclusively of discrete attractors, however, the ensembles would probably fail to encode in full the continuous stream of information that is characteristic of an episode. The network might not be able to maintain a unified representation of the flow of experience if it fluctuated between pre-formed states whenever the input was intermediate in relation to any set of previously stored conditions. Several observations suggest, however, that place cells can assimilate gradual or moderate input changes into pre-existing representations. Dislocation or replacement of a salient part of the environment might alter firing in nearby place fields, whereas the representation of the rest of the environment remains unaltered [69–71,72••]. Moreover, when one familiar environment is morphed gradually into another, stable states can be attained along the whole continuum between two pre-established representations [24••]. This ability to represent continua might enable hippocampal networks to encode and to retrieve consecutive inputs as uninterrupted, distinguishable episodes.

If hippocampal networks contain both continuous [24••] and discontinuous [51••] representations, do these representations mediate different types of information? A recent study suggests that the hippocampus contains at least two independent coding schemes: one for locations, and one for the stimuli and events associated with each location [73••] (Figure 3). Pyramidal cells were recorded from the hippocampus while rats were tested either in the same box at two different locations or in two different boxes at the same location. In the former condition, the distributions of firing location and firing rate in CA3 cells were independent. In the latter condition, however, only the rate distribution varied. This dissociation suggests that, at the initial stage of hippocampal processing, the location and rate of firing convey independent types of information (spatial and nonspatial information, respectively). A different, dual coding scheme, based on a dissociation of theta phase and rate, has been proposed for location and movement information in individual CA1 cells [74,75]. It is possible that the rate distribution is

Figure 3
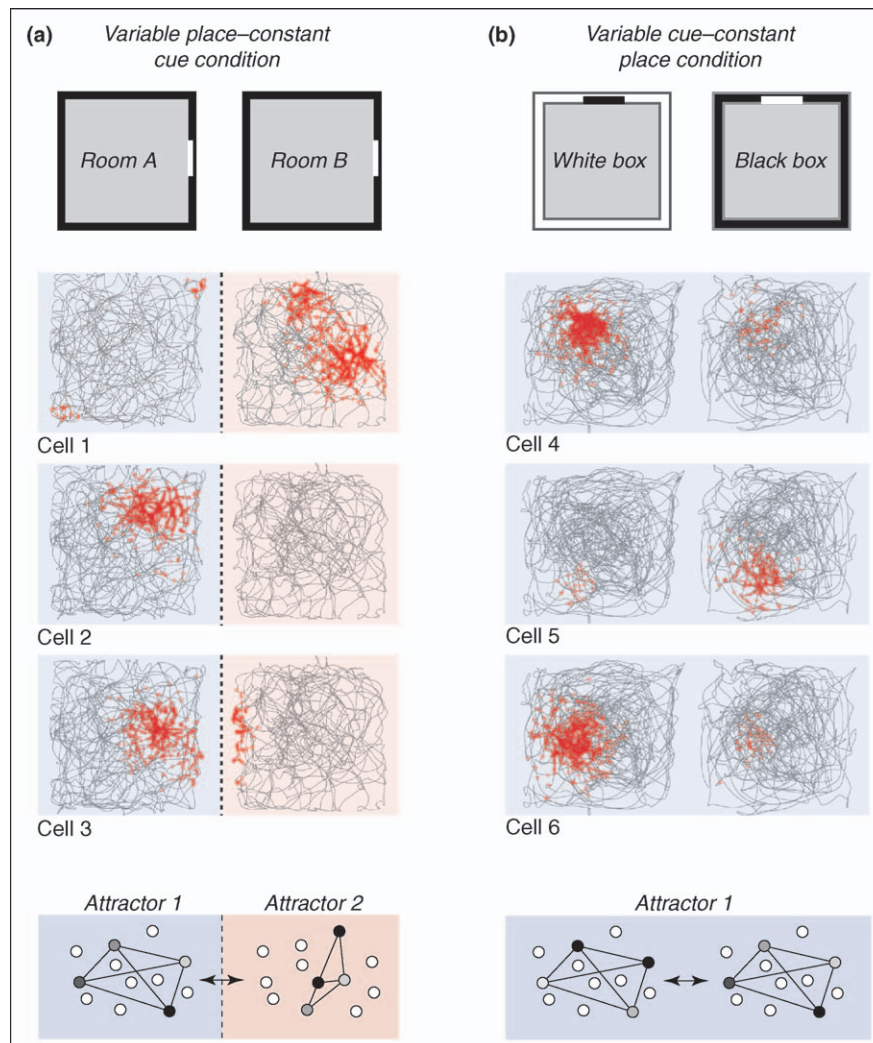
Independent codes for spatial and episodic information in hippocampal place cells. Spikes (red dots) were recorded from pyramidal cells in CA3 of a rat that was running in a square box. Grey lines indicate the path of the rat. **(a)** Place fields were tested after the recording room but not the local cues were changed, **(b)** or after the local cues but not the recording room were changed. Three cells are shown for each condition. When the room changed (a), the distributions of firing rate and firing position were completely orthogonalized, suggesting that the population vector spanned statistically independent vector subspaces (shown at the bottom as a switch between attractors 1 and 2). When only the cue configuration was changed (b), there was a substantial change in firing rates but no change in firing location, suggesting that the population vector spanned the same subspace (shown at the bottom as different states of the same attractor). This marked dissociation suggests that the hippocampus contains one code for locations and another for the stimuli and events that are associated with these locations. The exact conditions for inducing selective rate remapping, as in (b), remain to be determined, but the phenomenon can apparently account for remapping in several previous studies in which cues or tasks were altered without a change in test location [17–22,88]. Modified, with permission, from [73••].

always continuous, allowing various nonspatial stimuli and events to be encoded as integrated sequences, but that the network sometimes recruits independent attractors when the background contexts (e.g. the rooms) are clearly different and separated.

On a shorter timescale, the encoding of sequences might be also reflected in the temporal order of spike activity in the hippocampal cell assembly. Recent data suggest that place cell ensembles fire in reliable sequences across repeated instances of the same running event, and that the order of firing within simultaneously recorded place cells might differentiate between episodes independently of changes in average firing rate (M Shapiro, J Ferbinteanu, personal communication; G Dragoi, G Buzsaki, personal communication; [10]). Spike sequences are also preserved from behavioural trials to subsequent sleep trials [76,77]. Thus, hippocampal cell assemblies can apparently retain sequential information. The underlying mechanism, however, remains to be worked out; most

probably, sequences are segmented spatially by cell assemblies (G Dragoi, G Buzsaki, personal communication) and temporally by network oscillations [78,79]. As a consequence of the tendency of place cells to discharge at progressively earlier points in the hippocampal theta cycle as the rat traverses the field of a cell place [80], the sequence of firing in a set of place cells is reflected on a compressed timescale within each individual theta cycle [81]. This mechanism orders the spiking of sequentially active neurons within the time range of spike-dependent plasticity [82] and thus might link past, present and future events serially even when sequences are longer than a single cycle of the theta oscillation.

Network oscillations also permit different types of information to be processed concurrently by the same neurons without interference, either by applying different frequency ranges for different types of information [78] or by interleaving different information sources across domains of the oscillatory cycle [83,84**]. Lastly, they provide an efficient mechanism for synchronizing hippocampal discharge with neural activity in the output areas of the hippocampal formation [85,86*].

Conclusions
The past two years have witnessed radical advances in our understanding of place cells and their function in spatial representation, navigation and memory. We are seeing the outline of a modularly organized network in the parahippocampal cortices, which might contain many of the algorithms for place computation that were previously thought to be located in the hippocampus. At the same time, the neural underpinnings of recent memory are being disclosed in the hippocampus, much as a result of closer interactions between computational modelling and experimental approaches.

But key questions remain unanswered. For example, what is the function of the dentate gyrus? Why has the hippocampus differentiated into CA3 and CA1? When is CA1 influenced by CA3 and when is it not? How do network oscillations contribute to information coding and plasticity in these subfields? What are the computational modules of the entorhinal cortex? How do the various parahippocampal and hippocampal modules interact? Are these modules and their algorithms pre-wired or dynamic? How are entorhinal grids generated? And how are entorhinal grids converted to place fields in the hippocampus?

As these questions are being addressed in the next few years, it will be useful to remember that the small neuronal circuits of the honey bee are sufficient to generate map-like neural representations [87], which suggests that, although spatial computations are essential algorithms of the network, the mammalian hippocampal and parahippocampal cortices might do a lot more.

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