Selection of preconfigured cell assemblies for representation of novel spatial experiences

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Opinion piece

Selection of preconfigured cell assemblies for representation of novel spatial experiences

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Internal representations about the external world can be driven by the external stimuli or can be internally generated in their absence. It has been a matter of debate whether novel stimuli from the external world are instructive over the brain network to create *de novo* representations or, alternatively, are selecting from existing pre-representations hosted in preconfigured brain networks. The hippocampus is a brain area necessary for normal internally generated spatial–temporal representations and its dysfunctions have resulted in anterograde amnesia, impaired imagining of new experiences, and hallucinations. The compressed temporal sequence of place cell activity in the rodent hippocampus serves as an animal model of internal representation of the external space. Based on our recent results on the phenomenon of novel place cell sequence preplay, we submit that the place cell sequence of a novel spatial experience is determined, in part, by a selection of a set of cellular firing sequences from a repertoire of existing temporal firing sequences in the hippocampal network. Conceptually, this indicates that novel stimuli from the external world select from their pre-representations rather than create *de novo* our internal representations of the world.

1. Role of prior experience in the expression of internally generated representations

One of the most fascinating functions of the brain is to form and express internal representations about the external world. Some of these representations are driven online by the current features of objects and events from the external environment and take the form of perceptions. Other representations are internally generated; they are mental representations of objects and events that are not currently present. The internally generated representations are sophisticated forms that include mental travel [1] through virtual space and time. The most common form of internally generated representation occurs when our mind travels back in time into our past as is the case with episodic memory retrieval [2]. Other types of internally generated representations are projections into the future and take the form of imagining [1,3,4]. Probably the most genuine form of internally generated representation occurs during sleep, particularly during dreaming, when the brain is virtually disconnected from the external world. Under abnormal conditions, the internally generated representations can take the form of hallucinations in certain pathological states, like schizophrenia, when the subjects internally generate representations of objects and events that they firmly believe are currently present but that cannot be perceived by the other observers. It is not entirely clear what role prior knowledge plays in the formation of internally generated representations.

The role of prior knowledge and previous experience in generating internal representations about the external world has been a highly debated topic in philosophy. On the one hand, Aristotle and later the British empiricist Locke have argued that at birth our mind has no innate ideas, it is blank, *tabula rasa* and that we cannot represent beyond our experience [5]. Learning is then a
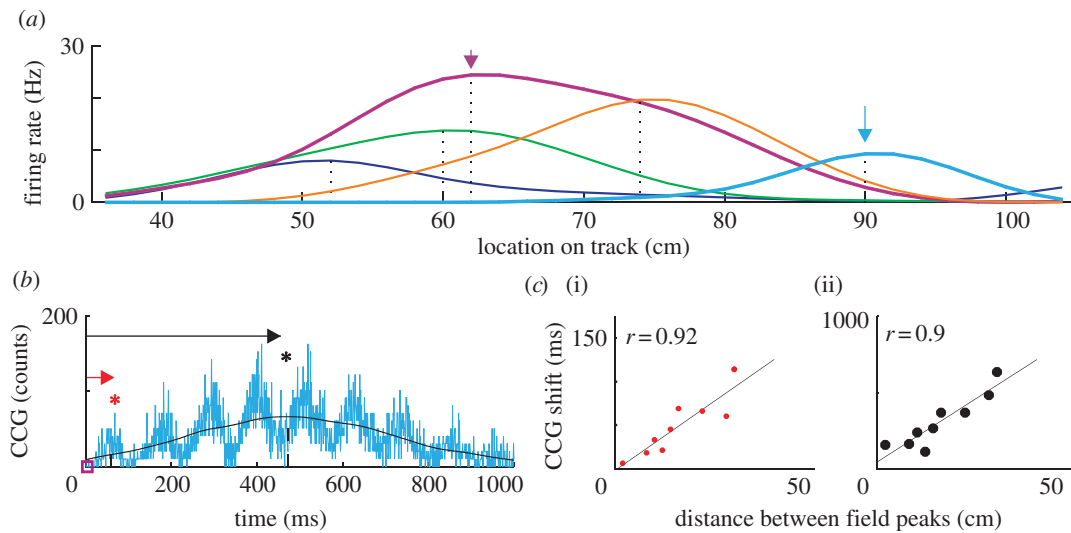
Figure 1. Representation of place cell sequences by temporal correlation at two timescales. (*a*) Encoding of sequential locations by individual place cells. Arrows mark Euclidian distance between two colour-coded locations, magenta and cyan. (*b*) Temporal correlation of the two cells marked in (*a*) assessed at two timescales by the temporal bias on the cross-correlogram (CCG) and measured by the red (compressed timescale) and black (real-time timescale) arrows. Asterisks mark the first (red) and absolute (black) maxima on the CCG. (*c*) Spatial distance between the five cells in (*a*) encoded at compressed ((i), red dots) and real-time ((ii), black dots) timescales during run. Reproduced from Dragoi & Buzsaki [15] with permission from Cell Press.

progressive accumulation of facts and experiences leading to knowledge. A diametrically opposed view led Plato [6] to propose 'ideal forms' that exist independent of the learner. During learning, the subject selects relevant information about the external world that gets assimilated into preconfigured mental schemata. Later on, Kant [7] argued that the concepts of space and time are not derived from experience but rather are its preconditions. To introduce these debates in the field of neuroscience and start looking for their answers, we first ask: what brain areas are implicated in the formation and expression of internally generated representations about the external world?

Located in the medial temporal lobe, the hippocampus is a brain area that has been intimately involved with multiple aspects of internally generated representations, primarily with the spatial–temporal ones. Bilateral removal of the hippocampus to alleviate untreatable epilepsy left patient H.M. with a severe form of anterograde amnesia [8], a case that first indicated the role of the hippocampus in the formation of new memories. Interestingly, the same patients that suffer from anterograde amnesia following bilateral hippocampal dysfunction are deficient in their ability to imagine new experiences [3,4,9], indicating that the same brain structure is necessary to internally represent past as well as future experiences. Furthermore, electrophysiological recordings of neuronal ensemble activity from the rodent hippocampus showed a similar pattern of temporal firing sequences during exploratory run and during subsequent periods of rapid eye movement sleep [10] which are associated with dreaming in human [11]. Finally, various anatomical and physiological deficits in the hippocampus have been reported in patients suffering from schizophrenia [12,13], a medical condition associated with abnormal forms of internally generated representations, such as delusions and hallucinations. Altogether, it appears that the hippocampus is a brain structure that is necessary for internally generated representations and, consequently, the study of the functional activity of ensembles of hippocampal cells could offer insight into the neuronal mechanisms underlying such representations.

2. Internal representation of past and future spatial experiences in the hippocampus

Individual hippocampal pyramidal cells are active at specific locations along the trajectory of an animal, and thus are called place cells [14]. Given that most place cells have unimodal spatial tuning curves (i.e. single place fields), the sequence of an ensemble of place cells depicts the trajectory of the animal in real time (figure 1*a*; [15,16]). Euclidian spatial distances between any two locations along the trajectory of the animal can be derived by multiplying the velocity of the animal and the relative timing between the firing spikes of any two place cells with place field centres in the respective two locations, as measured by the temporal bias (temporal shift from zero) of the maximum peak of the cross-correlation between the spikes of the two place cells (figure 1*b*, black arrow) [15]. Owing to the oscillatory nature of the place cell spiking activity in the theta band (7–11 Hz), the cross-correlation between any two place cells active during run is also oscillatory and displays multiple peaks in the time domain (figure 1*b*). Interestingly, the temporal bias of the maximum peak of the cross-correlogram (figure 1*b*, black arrow) correlates with the temporal bias of the nearest-to-zero peak of the same cross-correlogram (figure 1*b*, red arrow), which occurs at a one order of magnitude faster timescale [15]. Thus, spatial distance can be represented online in time at two different timescales, one being the real-time timescale as derived from the velocity of the animal movement through the physical space (i.e. temporal bias of the maximum peak; figure 1*c*(i)) while the other is temporally compressed 8–16 times (temporal bias of the closest-to-zero peak; figure 1*c*(ii)) [15]. We propose that an animal model of internal representation of the external space is the compressed temporal sequence of place cell activity in the rodent hippocampus as represented by the closest-to-zero temporal bias on the cross-correlogram during run. This compressed representation occurs online as the animal moves through the spatial environment [15–18] and is dependent on the synaptic weights within the hippocampal network [19,20].

A similar form of compressed temporal sequence of place cell firing has been repeatedly shown to occur offline, during the sleep period following the spatial experience [21–24], particularly in association with sharp-wave ripples in the CA1 area of the hippocampus. The detection of such temporal sequences during sleep was greatly facilitated by the property of hippocampal pyramidal cells to synchronously fire in 'frames' of activity [23] flanked by short epochs of neuronal silence [23–25]. As this type of compressed representation was initially recorded during a sleep session following the spatial experience, it was considered to represent a reactivation or replay of the previously experienced activity [22]. This finding gave experimental support to the previously formulated two-stage model of memory formation [26]. According to this model, memory formation occurs in two stages, the encoding stage and the consolidation stage. First, novel information is encoded in the place cell activity associated with theta oscillation in the CA1 area of the hippocampus during exploratory behaviour [26,27]. Second, the encoded information is consolidated and transferred to neocortical areas for long-term storage during epochs of increased synchrony when reactivation/replay was believed to occur in association with sharp-wave ripples in the CA1 [28,29]. Subsequent studies have shown that such replay events also occur during brief periods of awake resting states [24,25,30–34]. More importantly, the existence of the offline activity structured into compressed temporal sequences creates an opportunity for experimentally testing a long-standing debate: prior to a new spatial experience, is the hippocampal network *tabula rasa* or is it a preconfigured network?

Most of the studies focusing on the offline hippocampal replay of the previous run activity used experienced animals and did not thoroughly investigate the activity of the hippocampal network prior to the run experience [21,25,31]. The remaining part of the studies on replay investigated the offline neuronal activity prior to the run experience, but only prior to runs on already visited (i.e. familiar) spaces in experienced animals. In addition, the latter studies either based their analysis on the activity of pairs of cells [35–37], which is not sensitive enough to detect extended sequences [22,24], or have insufficiently sampled spiking events during the sleep or rest epochs preceding the run experience [21–23,25,31]. In order to detect significantly correlated temporal sequences using spatial template matching [22] or Bayesian decoding [33] analysis of spiking events during sleep/rest a good coverage of the spatial environment by place cells is needed, whereas extended sleep periods are required to elicit sufficient spiking event 'frames', as discussed before [24]. Most importantly, all of these studies focused only on the activity of pyramidal cells that were active as place cells during the previous spatial experience, and in addition described the existence of significant replay events in no more than 50% of the total spiking events that could be detected during hippocampal frames of activity, in sleep or rest.

However, a more comprehensive look at all temporal sequences during sleep and rest (marked here with small letters) with respect to the place cell sequences (capitalized letters) recorded during run on a track (e.g. A-B-C-D-E; letters depict individual cells) will detect: (i) a subset of correlated temporal sequences (e.g. a-b-c-d-e; same place cells, same order of firing), and (ii) an equally large subset of uncorrelated sequences contributed by the same cells (e.g. e-b-c-a-d; same place cells, different order) but also (iii) a

significant subset of temporal sequences contributed by the 'silent' cells [38,39] that are active during sleep or rest, but not while the animals explore the track (e.g. f-g-h-i-j, silent cells only; c-f-g-h-a-i, mix of place cells and silent cells). Within this overall distribution of temporal sequences, the subset of replay events represents a minority. Indeed, recent more conservative estimations of the incidence of replay events out of the total number of events detected using both silent and place cells report that about 15% of all detected events during sleep or rest are representations of the recent run experience [24,33]. This rather low percentage raises several questions. Why is the hippocampal network devoting 85% of its energy and time during sleep and rest to an activity that has little to do with the recent spatial experience of the animal or with the memory of the recently encoded information? Is it the case that the remaining, non-replay temporal sequences rather reflect the default organization of the hippocampal formation into sequential cellular assemblies [40]? Finally, in experimentally naive animals, is the order in which hippocampal cells fire during the sleep or rests epochs that precede a novel spatial experience predictive or correlated with the order in which they will fire as place cells during the experience? An affirmative answer will demonstrate that the brain of experimentally naive animals is not *tabula rasa*.

3. Distinct preplay of multiple novel spatial experiences in the hippocampus

In a recent set of experiments, we investigated whether temporally structured activity exists in the hippocampal network of experimentally naive animals during sleep and rest and whether the temporal pattern of that activity is predictive or correlated with the pattern of cellular activation during repeated runs on a novel linear track [24,41]. Prior to our experiments, the dominant model of hippocampal place cell ensemble activity had postulated that place cell firing order is established for the first time during the exploration to encode the spatial experience, and is subsequently replayed during sleep or rest perhaps to enable the consolidation of the encoded experience [26,27,32,35]. In contrast with this view, we found that during a significant proportion (approx. 10%) of awake resting epochs, the temporal order of firing of a mix of silent cells and previously active place cells was predictive of their future order of firing as place cells on a novel linear track [24]. We called this novel phenomenon preplay [24,41] because the predictive temporal sequences preceded the matching place cell sequences on the novel track. The preplay sequences were not a replay of the recent activity because the order in which the previously active place cells fired on the novel track was different from the order in which they had fired during the previous exploration of the familiar track, and the preplay sequences were not correlated with the place cell sequences active on the familiar track [24]. The preplay sequences occur prior to the exploration of novel spaces and in that respect they are different from the forward replay sequences that occur in anticipation of runs in already visited, familiar linear [25] and two-dimensional spaces [42].

The preplay sequences occurred more frequently during resting periods in the spatial locations adjacent to the novel track compared with the more remote locations [24]. This
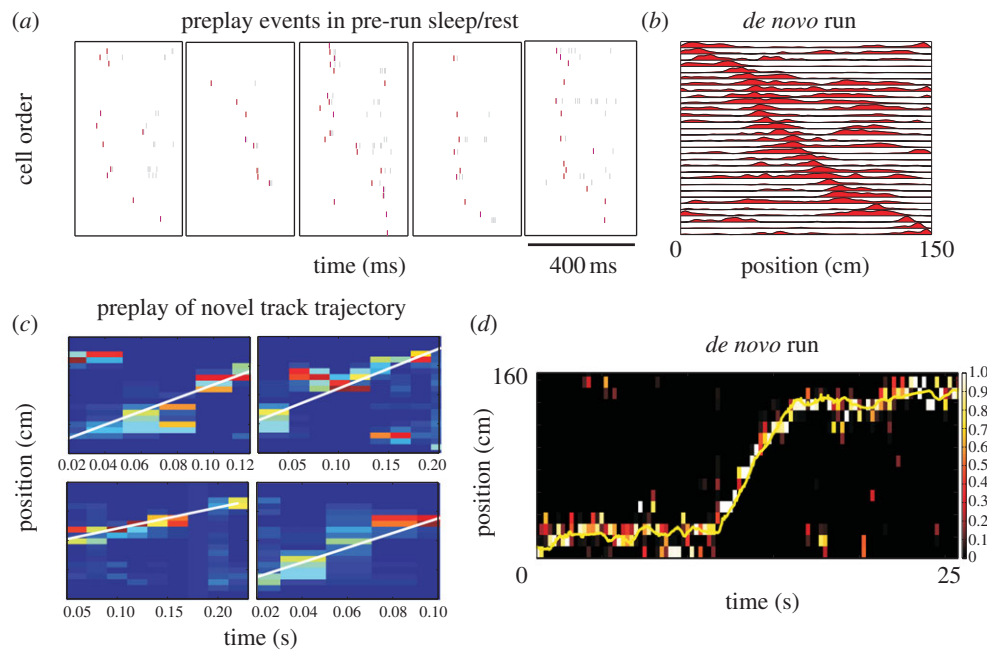
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Figure 2. Examples of preplay (*a*) of a future novel place cell sequence (*b*) using template matching method and of preplay (*c*) of a future novel spatial trajectory (*d*) using Bayesian decoding method in the sleeping rat. Reproduced with permission from Dragoi & Tonegawa [41].

indicates that in the awake resting state, the external cues from the environment as well as factors internal to the animal (i.e. planning, imagining) modulate which specific cell assembly sequences are active at given times and locations [24]. A recent study [42] using experienced rats showed that an animal's intention to reach a known nearby goal location is associated with a number of temporal sequences that, when decoded, depict future paths ending in that familiar goal location. As the goal location was daily assigned to one of the 36 possible goal locations on the familiar two-dimensional arena, the spiking events depicting the paths specifically ending in that location represented a relatively small, though significant, proportion out of all possible temporal sequences recorded in the hippocampus during that session (2–3%) [42]. As in our initial study [24] the awake resting preplay was associated with animals' prior exposure to part of the experimental apparatus (i.e. room context and the familiar track) and possibly with undetermined visual access to the area of the future trajectory, it was not entirely clear whether the prior experience on the familiar track was necessary for preplay to occur.

In order to address this necessity issue, we recently recorded 1–2 h of sleep/rest from naive rats (figure 2*a*) before they had any visual or physical access to a linear track [41]. Subsequently, the naive animals ran for the very first time on a linear track and the newly established place cell sequences (figure 2*b*) were correlated with the temporal sequences fired during the preceding sleep/rest session (figure 2*a*). Intriguingly, we found significant preplay sequences (figure 2*a*,*c*) for the future place cell sequences (figure 2*b*) and future spatial trajectories (figure 2*d*) on the novel track in 7–10% of all spiking events recorded during the preceding sleep in the naive rats [41]. This result demonstrates that the hippocampal network, and likely the remaining brain, is not *tabula rasa* in the naive animals (figure 3*a*) but it is preconfigured by default into sequentially active cellular assemblies (figure 3*b*), possibly as a result of previous, spatially unstructured experiences. This indicates that a

novel spatial experience does not 'instruct' a blank hippocampal network as previously thought (figure 3*a*), but rather 'selects' an ensemble of cells whose preconfigured sequential activation is associated with a given spatial experience (figure 3*c*). The specific external cues from the environment and factors internal to the animal (e.g. imagining) active at the time of the spatial experience likely contribute to the selection of the specific ensemble of cells. It is not entirely clear whether the preconfigured sequences originate from preconfigured maps or, conversely, neurons have an inherent temporal bias in between them that might influence place map formation. Given the similar range of proportions for the 'putatively intended' preplay events during awake rest [24,42] in experienced animals and the preplay events during sleep/rest [24,41] in naive animals, it is not entirely clear whether in the two experimental conditions (i.e. awake rest and sleep) we are detecting a neuronal organization that goes beyond the default preconfigured architecture of the hippocampal network.

The preconfigured hippocampal network during sleep/rest was able to preplay multiple, distinct, parallel spatial experiences as early as 6–8 h before the actual spatial experiences would occur [41]. Using three individual tracks connected in a letter 'U' shape, we were able to show the existence of three separate clusters of temporal sequences that individually preplayed each of the three tracks with very high specificity, 90% on a pair of novel tracks [41]. The basic unit that uniquely encoded each of the tracks was represented by the sequence of place cells on each track, rather than the identity of individual place cells, 90% of which were shared between the individual tracks. The hippocampal architecture was known to support the formation of novel individual place cells in any novel environment [27,43–46]. However, it was previously not known whether the place cell sequences on a novel track are created *de novo* during the experience [22,36,47] or whether and to what extent the naive hippocampal network was preconfigured into sequential cellular assemblies (i.e. Hebbian phase sequences) that could rapidly be used to encode future novel spatial
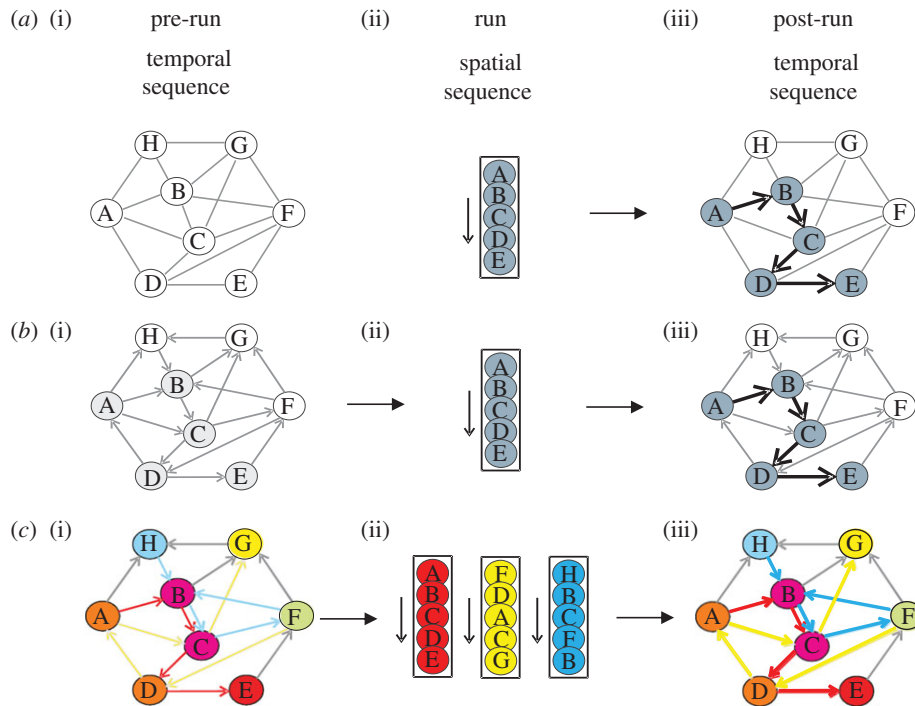
Figure 3. Temporal order diagrams emphasizing order of firing of hippocampal cells during the sleep/rest epochs preceding (i) and following (iii) a *de novo* run session on a linear track (ii). (*a*) Earlier interpretations of externally driven hippocampal network emphasizing the lack of temporal sequences during pre-run sleep and the predominant replay of the recent experience during post-run sleep. (*b*) Internally driven temporal sequences during pre-run (preplay) and post-run sleep. (*c*) Selection of specific preplay sequences during run from a repertoire of temporal sequences existing in the preconfigured hippocampal network during pre-run sleep. Circled letters represent individual cells; arrows represent order of firing on individual tracks. Colours mark cells specifically active during run on individual tracks (red, yellow and blue) or on a combination of tracks (remaining colours).

experiences [24,41]. We further estimated the capacity of the naive hippocampal network that we recorded during sleep/rest to preplay future novel experiences of similar complexity and distinctiveness. We propose that at least 15 novel linear tracks could be separately encoded by the sets of sequential cellular assemblies as recorded during the preceding sleep/rest state [41]. This does not mean that during an animal's entire lifetime, the hippocampus can only encode 15 different spatial experiences. Rather, just like in the case of working memory that can actively hold 7 ± 2 items at a time [48,49], the 15 experiences refer to the number of linear trajectories that can be simultaneously preplayed with 90% specificity by the recorded group of neurons (up to 55 neurons/animal) in the current spatial context [50]. If more neurons are recorded simultaneously and larger overlaps are allowed between the decoded spatial experiences, and if multiple spatial contexts are considered, then one would expect a higher capacity for the hippocampal network to encode multiple spatial experiences. However, as very low percentages of individually significant preplay events may not reach an overall significant incidence level under those conditions, the practical experimental demonstration of large hippocampal network capacities might technically face a detectability limit.

4. Selection of preconfigured pre-representations: functional significance of preplay

Before the preplay phenomenon was described in the hippocampus, the existing models of neuronal ensemble organization across different animal behaviours and brain states and

their role in processing different stages of memory formation were largely focusing on the encoding part and on the subsequent sleep/rest period [22,26,51,52]. It has been assumed that in experienced rats prior to a new spatial experience, the activity of the hippocampal network was noisy and did not exhibit any form of organization in sequential cellular assemblies, particularly if no run on a familiar or novel track occurred in the past 24 h [22,53]. However, a single run session on a novel or familiar track was considered sufficient to instruct the CA1 network of the hippocampus to repeatedly fire in unique spatial–temporal sequences during run, in association with theta oscillations (figure 3*a*). This sequential activity was repeatedly shown to be replayed in compressed temporal sequences during the sleep or resting period following the run, for 1–2 h, possibly owing to an increase in the firing rate of the previously active place cells [54,55]. It was hypothesized that this replay process facilitated memory consolidation as well as the transfer of the encoded information to neocortical brain areas during the postrun sleep, particularly during epochs of synchronous hippocampal ripples and neocortical spindles [26,28]. By contrast, the demonstration of preplay sequences indicated that the hippocampal network of naive mice and rats was preconfigured before the novel experience and further argued that the firing sequences on the novel track were not entirely created *de novo* in response to the external stimuli (figure 3*b*) [24,34,39]. Instead, the internal neuronal dynamics during resting and sleep organized the hippocampal cellular assemblies into temporal sequences that contributed to the encoding of the novel experience occurring in the future. Furthermore, the existence of distinct preplay sequences for multiple novel spatial experiences indicated that the place cell

sequence of a novel spatial experience is determined, in part, by an online selection of a subset of cellular firing sequences from a larger repertoire of pre-existing temporal firing sequences in the hippocampal cellular assembly network which become rapidly bound to the novel experience (figure 3c) [41]. Conceptually, this indicates that novel stimuli from the external world select from their pre-representations rather than construct *de novo* our internal representations of the world.

What could be the functional significance of a preconfigured hippocampal network? Both episodic memory and imagining are sequential processes embedded in the spatial–temporal continuum. The existence of temporally compressed neuronal sequences that are independent of the recent experience of the animal could support its ability to mentally travel into its past as well as into the future, a sophisticated process that may underlie higher cognitive functions like memory recollection [8,56,57], navigational planning [42,58,59], imagining [3,4,9],

cognitive map formation [58,60] and schema-based rapid learning [61,62]. Recent work that demonstrated that mice and rats are able to successfully navigate in virtual environments [63–67] reinforces the idea that rodents are capable of generating internal representations. A hippocampal network that is preconfigured by default could also accelerate the encoding of novel spatial information into the hippocampus, a brain area known to support rapid animal learning [68] and spatial memory [69–71]. The preconfigured network of the hippocampus could be supported by the highly autoassociative nature of the neuronal communications in the area CA3 which are passed onto downstream area CA1. Anatomical support for the cellular assemblies [15,19,40] generation in neocortical networks has been recently reported in the rat [72].

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