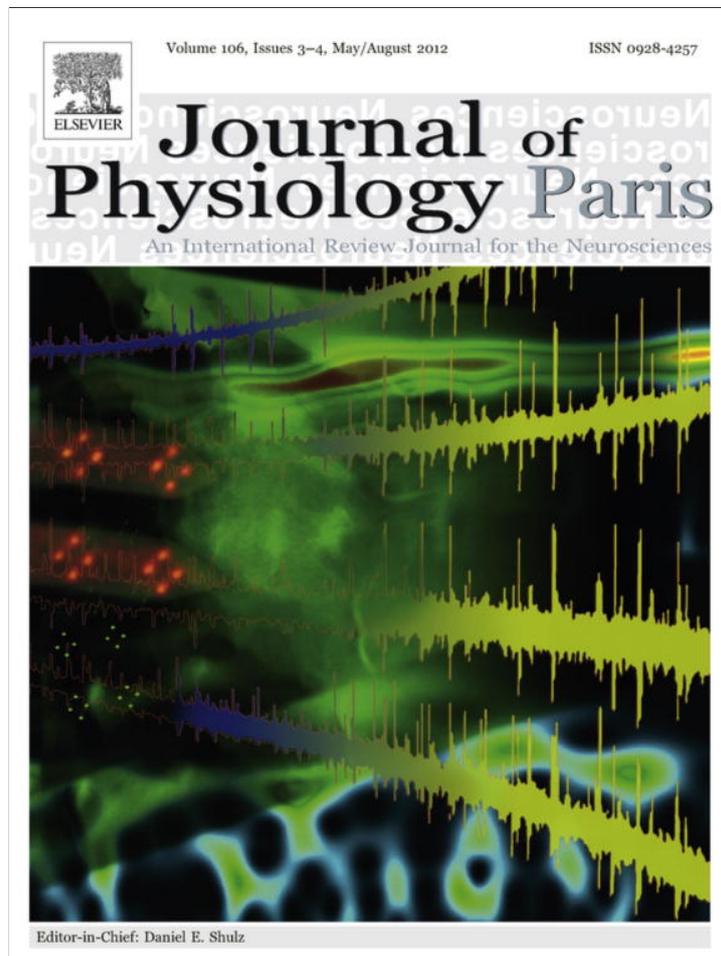


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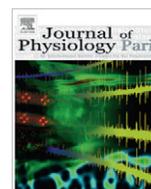
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Stability and variability of place cell activity during behavior: Functional implications for dynamic coding of spatial information

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ABSTRACT

In addition to their discharge strongly related to a rat's location in the environment, hippocampal place cells have recently been discovered to carry other more subtle signals. For instance, place cells exhibit overdispersion, i.e., a tendency to have highly variable firing rates across successive passes in the firing field, which may reflect the processing of different classes of cues. In addition, the place cell population tends to fire synchronously during specific phases of place navigation, presumably signaling the animal's arrival at the goal location, or to be reactivated during either sleep or wakefulness following exposure to a new environment, a process thought to be important for memory consolidation. Although these various phenomena are expressed at different timescales, it is very likely that they can occur at the same time during an animal's exposure to a spatial environment. The advantage of such simultaneous processing is that it permits the organism both to be aware of its own location in the environment, and to attend to other environmental features and to store multiple experiences. However its pitfall is that it may result in noisy signals that are difficult to decipher by output structures. Therefore the question is asked of how the information carried by each process can be disentangled. We provide some examples from recent research work showing that this problem is far from being trivial and we propose an explanatory framework in which place cell activity at different timescales could be viewed as a series of dynamic attractors nested within each other.

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1. Introduction

Our current understanding of the neural bases of memory in animals is based on the assumption that, in the absence of language, only behavior can give us information about the representations built during an organism's previous experiences. In some instances, the apparent ease and rapidity with which animals develop new behavioral solutions to encountered problems strongly suggests that insightful behavior results from the use of representations that can undergo internal manipulation so as to serve the organism's immediate needs. One peculiar instance of such flexible and reliable processing is provided by the ability of animals to form spatial representations, or maps, of their surroundings, which are used for navigation and other spatial behaviors. In addition to opening a window on complex cognitive processing, spatial cognitive maps have attracted much research for the last four decades because of the discovery of place cells. While they were looking for the behavioral discharge correlates

of neurons recorded from the hippocampus of freely moving rats, O'Keefe and Dostrovsky (1971) were struck by the strong positional selectivity of some of the cells; their firing was so strongly correlated with the rat's location in the environment that they were named "place cells". The discovery of place cells was an important step in understanding the neural basis of spatial processing since such cells provide ideal building blocks for implementing the capability to navigate. It is obvious that, for a rat to solve a spatial problem that requires a representation of the environmental layout, an initial requirement is to locate itself. It is only once self-localization is achieved that planning a path toward a potential goal is possible. Performance in the water maze navigation task, where the rat is demonstrably able to rapidly find a hidden platform using the array of available visual cues, is currently the prototypical illustrative example.

The idea that the hippocampus carries out fundamental computations involved in spatial navigation was proposed by O'Keefe and Nadel in 1978. In the years that followed, the theory received strong additional support from the discovery of other populations of cells that carry spatial signals. Such cells are found in the hippocampus proper but also in closely related structures (see Knierim, 2006 for a review). While the firing of hippocampal place cells is correlated with the location of a freely moving rat in its environment, the discharge of head direction cells, primarily found in

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the postsubiculum (Ranck, 1985) and the anterior and lateral dorsal thalamus (review in Taube, 2007), depends on the heading of the animal independently of its location. Furthermore, grid cells, which were documented for the first time in 2005 (Hafting et al., 2005), are found in the dorsocaudal medial entorhinal cortex, and are activated whenever the animal's position coincides with any vertex of a regular grid of equilateral triangles spanning the surface of the environment. Together, grid cells provide a directionally oriented, topographically organized neural map of the spatial environment. A common feature of place cells, head direction cells and grid cells, as well as of other cell populations with other more complex spatial activity (e.g., border cells: Savelli et al., 2008; Solstad et al., 2008, place \times direction cells: Cacucci et al., 2004; conjoint grid \times direction cells: Sargolini et al., 2006), is that their firing is primarily controlled by salient environmental cues (e.g., Cressant et al., 1997) and motion-related signals (e.g., Stackman et al., 2002) that together maintain coherent activity.

Therefore, the hippocampus and related structures appear to be at the core of a widespread neural network where spatial information is processed and coherently organized. For this processing to be useful, it seems at first glance that underlying neural activities need to be stable since their function is the coding of stable properties of space. Nevertheless, this view must be disputed as it is based on the false assumption that spatial cognitive maps constitute a static process that simply reflects environmental invariants. In fact, plasticity is a basic property of cognitive maps and there is a tremendous amount of literature showing why and how cognitive maps must be updated when necessary (e.g., Poucet (1993) for a review). In contrast, the apparent stability of place fields under constant conditions had led many researchers to see place cell firing as a phenomenon that maps the stability of the outside world onto a fixed neural representation within the hippocampus. While there is certainly a requirement for such stability, recent data have disclosed subtle variations in the hippocampal code that suggest that an appropriate description of how spatial information is carried by place cells must account for both constancy and variations in cell firing. In the present short review, we illustrate through a few selected examples why it is important for hippocampal place cells to be both stable and variable. We show that variability of place cell firing can be expressed at several timescales and we attempt to explain why it should be so. Lastly, we argue that the hippocampal place cell system provides a prototypical example of a brain system whose neural activity can be used to decipher the neural correlates of complex behaviors.

2. Brief description of properties of place cells

Place cell activity was described for the first time by O'Keefe and Dostrovsky (1971) who were monitoring the discharge of single pyramidal neurons in the CA1 and CA3 areas of the hippocampus while simultaneously following the location of a freely moving rat. Since this initial report, the place cell phenomenon has been confirmed by many experimenters (see reviews in Muller, 1996; Poucet and Benhamou, 1997). The cell-specific part of the environment in which a place cell is intensely active is called the "firing field". Firing fields are established very soon after the rat is exposed for the first time to a new environment (Hill, 1978; Wilson and McNaughton, 1993), and once established, their locations may be stationary for weeks or months (Muller et al., 1987; Thompson and Best, 1990). This stability is remarkable and, in fact, has been used as an index of how long-term memories can be formed at the neural level (see below). Even though place cell discharge may be modulated by non-spatial variables (review in Wiener, 1996), by the direction when on a linear track (McNaughton et al., 1983; Muller et al., 1994), or by the paths followed by the

rat (Markus et al., 1995), spatial location is by far the best and most consistent correlate of their activity.

The location-specific nature of place cell activity is possible only if the animal extracts information about its environment. Initial reports focused on the role of distal cues in the environment. O'Keefe and Conway (1978) were the first to demonstrate that distal cues exert a powerful influence on the location of place cell firing fields. Thus, rotating a set of cues that were placed some distance off the maze arms within a curtained "cue-controlled" environment produced equal rotation of the firing fields. Control by explicit cues is also seen when only a single landmark (a salient cue card attached to the wall of the recording cylinder) is present (Muller and Kubie, 1987). The implication is that the spatial firing of the cells is anchored to a reference frame provided by distal cues. In contrast, proximal object cues placed at the center of the recording cylinder are much less efficient (Cressant et al., 1997, 1999) although they can acquire stimulus control over firing fields under specific circumstances (Gothard et al., 1996). Even though external cues are determinant, self-motion information also may be important either in the absence of external cues (e.g., Save et al., 2000) or when such cues are unreliable (e.g., Jeffery and O'Keefe, 1999). To use self-motion information, the rat would update its position by tracking changes in position using signals derived from its own movement. The advantage of motion-related cues is that they allow ongoing calculation of the rat's position without external reference, thereby reducing attention to external cues. Nevertheless, the rat still occasionally has to re-calibrate its position to correct for errors and the most usual basis for such recalibration is visual information (e.g., Save et al., 1998).

3. Stability and variability at long timescales: Remapping

Although in constant surroundings place cell firing is usually very stable across minutes, hours, days or weeks, it can be markedly different while the rat explores a different environment. For example, the firing of place cells recorded as the rat explores a cylinder and a rectangular box is greatly changed between the two environments (Muller and Kubie, 1987). This "remapping" phenomenon suggests that each unique environment is represented by a distinct subset of hippocampal pyramidal cells; cells common to both subsets have different firing fields (Fig. 1). As a result, place cells collectively provide information about both the rat's current environment and the rat's location within the environment.

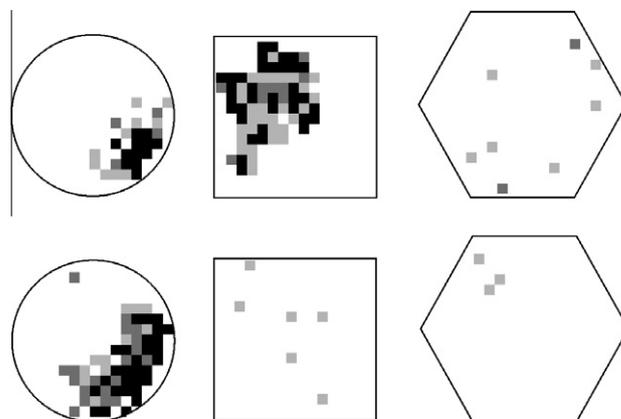


Fig. 1. Firing fields of two simultaneously recorded place cells in three distinct environments. In each map, locations in which no firing occurred during the 16-min recording session are white. The highest firing rate is coded as black, and intermediate rates are shown as light gray and dark gray from low to high. Both cells remapped their activity across the three environments. The first cell whose fields are shown on top fired on a circular arena and in a square box. The second cell (bottom) fired only in the circular arena (from Paz-Villagràn et al., 2004).

The dynamics of remapping is an important issue. While remapping is usually very rapid (Hill, 1978; Wilson and McNaughton, 1993), it can also take longer under some circumstances (Lever et al., 2002). Once remapping occurs however, the environment-specific firing patterns of place cells are generally observable immediately upon either passive placement (Muller et al., 1987) or active entrance of the rat into the recording box (Paz-Villagràn et al., 2004).

Several forms of remapping have been documented. The most common, and first described, is global (or complete) remapping, in which firing activity of the whole subset of cells active in one environment is changed when the rat is introduced in another environment (Muller and Kubie, 1987). No consistent transformation of the firing patterns is apparent across place cells recorded in the two environments. Cells firing in both environments have fields that may be different in location, size, and shape and discharge rate while other cells may have fields in one apparatus but not in the other (Fig. 1). A special case of remapping, recently documented, is referred as to “rate remapping” (Leutgeb et al., 2005b). In rate remapping, place cell ensembles are affected as a unit by exposure to different environments. However, contrary to global remapping, rate remapping is best described as a strong change in cell discharge with no positional rearrangement of firing fields. The functional meaning of rate remapping, as well as the circumstances that induce it, is still poorly understood.

While global remapping is a consequence of an animal's exposure to a strongly modified environment, local (or partial) remapping is usually observed in situations in which only a fraction of the environment has been modified (see Muller et al., 1999 for a review). For example, local remapping occurs when objects are repositioned within a familiar arena (Lenck-Santini et al., 2005). In this situation, only the fields near the displaced objects are affected whereas fields away from the objects are unaltered. Interestingly, place cells failed to respond to object substitution, regardless of field location (Lenck-Santini et al., 2005). This dissociation is remarkable as both types of change, object repositioning and object substitution, induce strong re-exploration responses but hippocampal lesions alter such responses only following object repositioning (e.g., Save et al., 1992). This suggests that only the ability to recognize the spatial arrangement of objects in the arena depends on the stored hippocampal place cell representation.

Another instance of local remapping occurs when changes in the environment alter its topological structure and thus possible routes. In a recent study (Alvernhe et al., 2008), rats were trained to run back and forth between two locations in a maze. On specific sessions, a wall section of the maze was removed so as to open a shorter novel route within the otherwise familiar maze. Rats changed their behavior almost immediately to take the shortcut. Concomitantly, place cell discharge in the vicinity of the newly available shortcut was also altered (Fig. 2), but was much less affected further away. In a follow-up study (Alvernhe et al., 2011), rats were exposed to a Tolman-type detour problem in which a familiar path was blocked on specific sessions so as to force the rat to use a detour. Here again, rats rapidly and consistently chose the most appropriate route to the goal location and place cells displayed local remapping, i.e., firing fields in the vicinity of the barrier that blocked the familiar path were strongly affected. In addition, even though the overall pattern was very similar in the two studies, subtle differences in the response of CA1 and CA3 cells were found in the Alvernhe et al. (2008) shortcut study, which were not observed in the Alvernhe et al. (2011) detour study. Thus, CA3 fields away from the manipulated barrier were affected to a much greater extent in the shortcut study than in the detour study. In contrast, CA1 fields away from the barrier were unaltered in both experiments. In other words, CA3 cells had a unique response in the shortcut task since, contrary to CA1 cells, their fields were altered whether they were near or away from the removed barrier. Presumably, availability of a novel path and blocking of a familiar path are

not equivalent as they lead to different responses of CA3 place cells, pointing to a specific role of this region in the representation of spatial connectivity and sequences (see Alvernhe et al., 2011 for a discussion of this point). Nevertheless, these findings indicate that place cells code more than just the animal's spatial location and may provide additional information about the relationships between locations supporting possible routes within the environment.

Remapping, whether global or local, is a good instance of how the place cell system keeps its instantiated spatial representations up-to-date. To be useful for behavior, it is necessary that memory representations are in line with real world properties. Remapping reflects the process necessary for the brain to form new memories and to update old memories so that potentially important changes occurring in the environment are incorporated (see Poucet et al., 2000 for review). Since remapping is a memory process, it is not surprising that it is subject to the deleterious effects of treatments that impair memory. Recent work in genetically modified mice with impaired long-term potentiation (LTP) and in rats after pharmacological blockade of LTP has shown that, even though remapping can be induced by exposure of the animal to a novel environment, long-term stability of newly developed firing fields is seriously compromised (Kentros et al., 1998; Renaudineau et al., 2009; Rotenberg et al., 1996, 2000). In a similar vein, aging which also results in memory deficits is accompanied with both rigidity (i.e., resistance to change – Oler and Markus, 2000; Tanila et al., 1997; Wilson et al., 2003) and instability of the place cell representation (Barnes et al., 1997; Wilson et al., 2004; see below).

On a timescale that varies from a matter of minutes to several days or weeks, both stability and variability of the place cell representation are therefore required. Conceptually, these opposite requirements are reminiscent of computational processes commonly referred to as pattern completion and pattern separation. Pattern completion is the ability of the system to recall a stored representation in spite of a degraded sensory input. In contrast, pattern separation is the ability to make the stored representations of two overlapping input patterns more dissimilar so that different, though resembling experiences can be separately recalled. Although the dynamics of pattern completion and pattern separation may be different in hippocampal CA1 and CA3 (Lee et al., 2004; Leutgeb et al., 2004), these two processes are generally described as population responses in which activity of cell ensembles is convergent (e.g., Guzowski et al., 2004). Nevertheless, there are circumstances in which subsets of the cell ensembles may express different responses, as is the case for local remapping. The double rotation method, which consists of rotating separate sets of cues in opposite directions (e.g., Knierim, 2002; Shapiro et al., 1997), provides a prototypical illustration. As it results in a conflict between the two sets of cues, double rotation makes it possible to measure their respective influence by looking at the responses of individual place cells. For example, Shapiro et al. (1997) found that place cell firing is controlled by distal cues and floor cues in a flexible and hierarchical fashion. Most cells are influenced by the combined set of cues (i.e., their fields remapped after double rotation). For the remaining cells, distal cues prevailed over proximal cues. In another experiment, Renaudineau et al. (2007) examined how distal cues and proximal slender objects interact to control firing fields and found a different hierarchy. Although they also observed non-coherent responses with most fields influenced by the combined set of cues, proximal cues exerted a better control than distal cues. Thus the hierarchy of place cell responses is context-dependent rather than imposed by the sole class of cues being manipulated. More importantly, the results confirm that the system is highly opportunistic: it can deal with all available cues and can flexibly adapt to environmental changes. Previous authors have suggested that such features are conferred through the circuitry attractor properties (Knierim, 2002), which allow not only formation and stabilization of

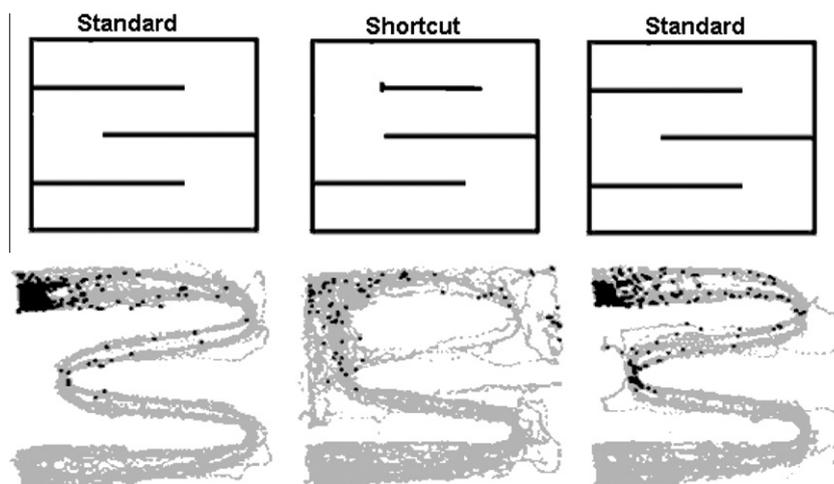


Fig. 2. Local discharge changes resulting from a structural modification of the maze. Following a recording session with the maze in its standard configuration, one wall is removed therefore allowing the rat to take a shortcut. The bottom panels show all the paths for the recording session, with black dots indicating the spikes from the neuron. The firing field near the removed wall is strongly affected during the shortcut session (from Alvernhe et al., 2008).

experience-specific representations, and their appropriate reinstatement at recall through pattern completion and pattern separation mechanisms, but also flexible updating following environmental changes. The balance between these processes is necessarily subtle as the system must be able both to store representations on the long-term and to update them when required.

4. Stability and variability at short timescales: Overdispersion

Firing fields as visualized in firing rate maps such as those shown in Fig. 1 are computed by accumulating cell activity for time periods ranging from a few minutes to one hour or more. Although very useful to catch immediately the location firing properties of place cells, such firing rate maps do not provide details about the fine structure of cell firing over short time periods. In fact, they even provide the false impression of a static process, in which each pass in the firing field location will result in a fixed number of action potentials that can be simply estimated from the averaged activity over the entire session. Fenton and Muller (1998) directly compared the number of action potentials expected from averaged activity with the number of action potentials actually observed across hundreds of passes through place cell firing fields. They found that activity of individual place cells was extremely variable from one run to another. This phenomenon referred to as “overdispersion” indicates in first approximation that place cell firing is less reliable than expected. Such overdispersion does not appear to result from any overt behavior of the animal, since the calculated variance of pairs of simultaneous recorded cells with overlapping fields was not correlated, thus implying that the processes responsible for the excess variance of each cell in a pair were independent. Furthermore, closer scrutiny of the factors likely to influence place cell firing (see Wiener, 1996 for a review) did not reveal any obvious link between overdispersion and the rat's behavior (e.g., running speed, head direction, etc.), hippocampal EEG state (e.g., ongoing theta cycle), or prominent sensory cues (which were kept constant across recordings). Although such variations for individual and independent cells may be incidental and have no consequence at the level of large cell assemblies, the question is nevertheless raised of their potential functional correlates.

In a follow-up study, Olypher et al. (2002) directly addressed this question by comparing overdispersion during navigation and during random foraging for food pellets to determine if subtle vari-

ations in place cell firing could be detected. They used a behavioral protocol called the place preference task (Rossier et al., 2000), which allows direct tagging of both types of behavioral episodes. In this task, each successful trial consists of two steps, one in which the rat follows a path oriented towards a goal zone (goal-directed navigation) and another in which the rat follows a seemingly random trajectory while looking for pellets (undirected foraging). Comparing passes through the field during foraging and goal approach, subtle differences were seen in several characteristics of CA1 place cell firing. The clearest change during navigation was an increase of firing reliability or, in other words, a decrease of overdispersion. The discharge rate was only marginally increased during navigation although cells fired more bursts than during foraging. The inference is that the positional signal of place cells is more robust during navigation than during foraging, as if the rat attends more to the current surroundings (Olypher et al., 2002). In a more general way, the existence of the overdispersion phenomenon reveals that the place cell representation could switch from one state to another, each state possibly corresponding to a different cognitive representation of the environment faced by the animal (Jackson and Redish, 2007). This is not to mean that, in a given state, all place cells are more (or less) active than expected since some cells may be tuned to one state whereas other cells may be tuned to another state. In other words, simply averaging activity at the population level fails to reveal the existence of such states.

That place cell activity can be modulated by a behaviorally silent attention-like process is further supported by a recent data meta-analysis (Fenton et al., 2010). The hypothesis was that overdispersion results from discharge fluctuations as spatial attention alternates between distal cues and local/self-motion cues. This hypothesis has three implications. First, preferential use of one cue class should decrease overdispersion; in other words, firing reliability would be increased because attentional switches are less frequent. Second, global, attention-like states can be decoded from ensemble discharge as a function of time. Ensemble activity would thus be separable into two states in which the spatial firing patterns and rates of individual cells differ substantially. Third, state-specific spike trains should predict current location better than observed state-independent spike trains. Therefore, identifying attention-like states should improve reconstructions of the rat's path from the discharge of ensembles of simultaneously recorded place cells.

To test the above predictions, the discharge variance of place cells was compared in four different conditions. The task for two groups of “foraging” rats was to find food pellets randomly scattered into a cylindrical apparatus. For one of these two foraging groups, the cylinder was always stationary whereas for the other group the cylinder and floor were slowly rotated during alternating recording sessions but were stationary during interleaved sessions. The remaining two groups of “navigating” rats were trained in the place preference task (see above) in the cylinder under the same conditions as previously described (one stationary condition and one alternating between stationary and rotating states). For all groups only results from stationary sessions were analyzed. The conditions differed only by the factors that were explicitly manipulated by the experimenter (i.e., foraging vs. navigating and rotation vs. no rotation). In other words, sensory cues were kept as constant as possible between the foraging and navigating groups (in fact, the environments were physically the same in either stationary or rotating condition), and every effort was made to remove any possible unintended variation that could affect the results. Everything being equal, these four conditions permitted to dissect the separate influences of navigation and attention on overdispersion. The influence of attention itself could be estimated by comparing overdispersion in the two navigating groups since the rats trained in the stable cylinder could always identify the navigation goal using either local or distal cues, whereas rats trained in the rotating cylinder had been conditioned by arena rotation to preferentially attend to stationary distal cues for locating the navigation goal.

Comparison of these experimental conditions confirmed the above predictions. First, overdispersion is reduced during navigation relative to foraging. Preferential use of distal cues during navigation further decreases overdispersion. Second, ensemble discharge can be separated into two time-dependent attentional states during which firing of individual cells is substantially different. Lastly, decoding of rat's position from the discharge of cell ensembles (from 23 to 54 simultaneously recorded cells) is improved if attentional state is identified. Therefore place cell activity appears to be modulated by a behaviorally silent attention-like process that spontaneously switches between distinct ensemble place codes. This covert, dynamic attention-like process modulates cell discharge on a timescale of approximately 1 second. This implies that the place cell code dynamically represents spatial information in the immediate focus of attention. The assets of such dynamical coding are that it guarantees accurate self-localization while making permanently available attentional resources toward potentially important information. Nevertheless, it is important to realize that, although the Fenton et al.'s study used a procedure in which population activity was partitioned into two states, it is likely that additional states could have been revealed with larger recording ensembles, longer recording times and more complex behavioral manipulations.

5. Stability and variability at very short timescales: Replay, preplay and goal coding

When one looks at the typical firing rate map of a “good” place cell, one is struck by the sharpness and precision of its firing field. Very often, however, “out-of-field” discharge can be noticed in the firing rate map in the form of small patches of dispersed and low firing in locations outside the firing field. Although it is tempting to interpret such out-of-field firing as a consequence of a noisy discharge, other interpretations have recently been proposed. The recent demonstration of hippocampal replay during awake state provides such an alternative interpretation. During replay, hippocampal place cells that fired during exposure to an environment are orderly reactivated at a subsequent time so that the initial experience

is recapitulated over a very brief period of about 50–100 ms (Lee and Wilson, 2002; Nadasy et al., 1999; Skaggs and McNaughton, 1996, but see Quirk and Wilson, 1999). Although replay was initially observed during sleep periods (including REM states; Louie and Wilson, 2001) that followed initial exposure to an environment, it was recently documented to occur also during wakefulness (Foster and Wilson, 2006), and more specifically during an EEG state characterized by sharp waves and ripples (SWR). Such SWR occur either during slow wave sleep or during non-theta behaviors and result from the synchronous discharge of a large neuronal population in multiple hippocampal sites (Buzsáki, 1989). Because SWR bursts have been proposed to be initiated by neurons whose recurrent connectivity had been transiently potentiated during previous experiences, and because replay can be observed for recent events as well as for more remote experiences (Karlsson and Frank, 2009), it is widely accepted (at least by researchers working on the place cell system; Hennevin et al., 2007), that associated replay would reflect the operation of an off-line consolidation mechanism (e.g., Ego-Stengel and Wilson, 2010; Girardeau et al., 2009; Peyrache et al., 2009; review in Carr et al., 2011). Two recent experiments yield other interpretations however. In the first study, Gupta et al. (2010) demonstrated that replay does not occur more often for most recent or most frequent events compared to less recent or less frequent events, as would be predicted by the consolidation hypothesis in its strict version. Similarly, the existence of “preplay” (i.e., sequential activation of place cells for locations not yet experienced), recently reported by Dragoi and Tonegawa (2011), is also a finding difficult to reconcile with the consolidation hypothesis. Whatever its functional role, it is interesting to observe that, for obvious reasons of analysis, replay is studied in simple tasks requiring, for example, that the rat runs a straight alleyway such that the sequence of reactivation is straightforward to analyze. Thus, if the rat enters in slow wave sleep after such experience, or makes a pause at the end of the run (i.e., entering non-theta mode), the cells that just happened to be sequentially active during the unidirectional run are briefly reactivated and fire in forward order during slow-wave sleep (Lee and Wilson, 2002; Skaggs and McNaughton, 1996). Interestingly, replay during wakefulness can occur both in forward and reverse order. While reverse order replay occurs predominantly upon arrival at the reward site, forward order replay dominates as the animal is about to leave the reward site (Foster and Wilson, 2006; Diba and Buzsáki, 2007). Because these phenomena are observed in simple, one-dimensional runways, a crucial question is whether they also occur in less structured and more natural two-dimensional environments, such as open fields, which are associated with complex and variable paths which do not result in consistent sequences of place cell activity (see Kloosterman and Wilson, 2010, for preliminary data on these topics).

In addition to replay and preplay, place cells can also display two other interesting phenomena. Johnson and Redish (2007) recorded from neural ensembles from the CA3 region as rats were running on a multiple T-maze alternation task. They found that place cells were transiently activated at the choice-point (as the rat was about to make a decision) in such a way that the location reconstructed from the neural ensemble swept forward, first down one path and then the other. Very similar to preplay, estimated representations were coherent and preferentially swept ahead of the animal rather than behind the animal. Presumably, such transient activities at the choice-point are therefore more likely to represent future possibilities than recently traveled paths, as if the rat was assessing the two alternatives choices (i.e., turning right vs. turning left). These data suggest that the hippocampus does not represent space as a static computation, but rather that hippocampal spatial processing is a dynamic process likely regulated by cognitive mechanisms.

In a similar way, Hok et al. (2007) examined place cell activity while rats solved a continuous place navigation task in which they

had to wait at an unmarked goal location to receive a food pellet. They found that, in addition to having widely distributed firing fields, place cells also discharged selectively while the hungry rat was waiting at the goal location (Fig. 3). The exact meaning of this synchronous activity of a large fraction of place cells is not entirely clear. It may reflect either the rat's expectancy that it is located correctly at the goal, the rat's anticipation of an upcoming reward, or even future foraging behavior. However, it strongly suggests the existence of a dual spatial coding scheme by the same cell population. Therefore, the findings show that, in addition to providing a geometric representation of the current environment, place cells carry signals that may be relevant to the rat's past, current or future behavior. Thus, their firing may recapitulate sequences of recently traversed locations (replay), simulate possible choices and therefore guide the rat's decision, or reflect expectancies as to goal locations.

A common feature of all of the above-mentioned processes is that they rely on transient activity levels compared to the usually more robust location-related place cell discharge. In other words, the spikes that contribute to the coding of the different aspects of ongoing, past or future behavior are generally rare. In addition, they may be embedded in more sustained activity or, on the contrary, they may appear as sporadic and highly variable discharge within an otherwise rather silent background state. As stated in the introduction of this section, spatial firing rate maps look noisy, and deciphering the meaning of such "noise" requires appropriate analytical tools that permit the extraction of regularities within the stream of neural activity.

6. Integrating firing variability at different timescales

The data reviewed in the previous sections suggest that the timescale used for analysis of place cell activity is important in capturing distinct facets of their functioning, and therefore of their potential coding role. At long timescales place cells identify the rat's current environment and signal the rat's location within that environment while at very short timescales they appear to provide either retrospective or prospective information useful for the rat's immediate behavior. At intermediate timescales, place cell discharge may reflect the rat attending to distinct sets of cues. A remarkable and consistent observation is the apparent unreliability of the discharge that carries this information. For example, the peri-event histogram in Fig. 3 does not reflect the trial-to-trial variability in firing that can be seen in the corresponding raster diagram. We argue that, in spite of this variability at the single neuron level, the system properties at population level might provide consistent information. Thus, the rat's placement at the goal location in the Hok et al.'s study (2007) is signaled by synchronous activity of a large fraction of place cells even though discharge may appear sporadic for each individual neuron of the population (Fig. 3). In the same way, attending to diverse cue sets is supported by ensembles of cells tuned to either distal or local cues and not by individual neurons.

Since all these features are supported by subsets of cells from the same population, namely place cells, the question is raised of how they are integrated and coordinated during behavior. For example, there is no reason for the place cell attentional states revealed by overdispersion to be interrupted during replay, preplay or decision making. Similarly global remapping must leave time and processing resources for other phenomena to develop. In other words, the separation between these seemingly independent processes is artificial as it is caused by the "empirical lens" used by the experimenter to target a given process.

Recent work on place cell stability in old rats further supports the idea that these phenomena with different timescales are indeed interacting with each other (Hok et al., 2010). In this study, the

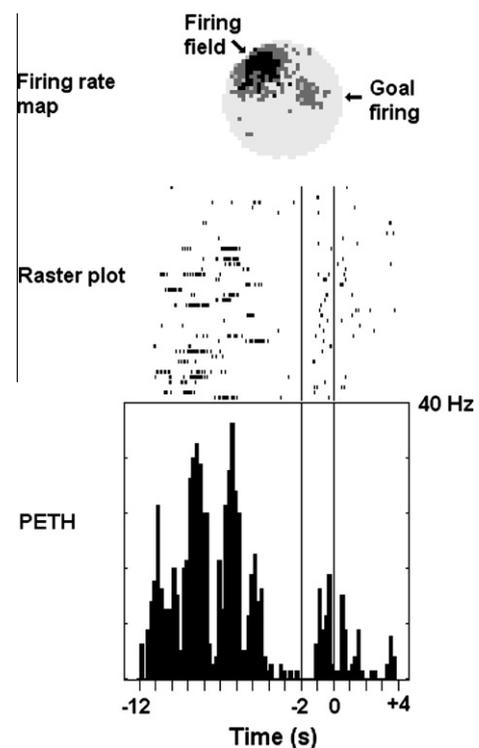


Fig. 3. Firing rate map, raster plot and peri-event histogram (PETH) of a place cell recorded in the continuous spatial navigation task. Locations in which no firing occurred during the whole recording session are white. The highest firing rate is coded as black, and intermediate rates are shown as gray. The cell had a well-localized firing field in the northwest quadrant of the circular arena. It also fired a few action potentials as the rat was at the goal location. The raster plot and PETH show this goal-related firing just before release of the reward at time '0'. The data on which this figure is based are drawn from Hok et al., 2007.

authors examined the hippocampal spatial representations in a rat model of cognitive aging characterized by heterogeneous abilities in memory tasks. The working memory capacity of old rats was first assessed in a delayed non-matching-to-sample task, and the firing patterns of hippocampal CA1 pyramidal cells were then recorded as the rats explored a familiar square arena ($64 \times 64 \times 25$ cm high) while performing a pellet-chasing task. As previously described by Barnes et al. (1997), place cells in some of the memory-impaired rats showed a spontaneous tendency to remap from one session to the other, despite the high level of familiarity with the environment. In the Hok et al. (2010)'s study like in Barnes et al. (1997), remapping occurs when between-session place-field correlations fell below an arbitrary cut-off of $r = 0.5$. The main result of this study is that remapping rats tend to exhibit less overdispersion than rats that have stable hippocampal representations (Fig. 4). These differences in the degree of variance could not be explained on the basis of changes in the firing regime as the two groups show a similar average frequency (1.05 ± 0.05 Hz (stable rats) versus 1.12 ± 0.05 Hz (remapping rats); Mann-Whitney U test, $Z = 1.49$, *ns*). Although no synaptic loss can be detected at the CA1 synapse in old rats contrary to what is seen in the dentate gyrus and CA3 (Smith et al., 2000), a decrease in postsynaptic density of certain synapses might explain a loss in firing variability (Nicholson et al., 2004; Geinisman, 1993; Olypher et al., 2002). Therefore, whether overdispersion is constitutively altered in aged rats or is modulated as a consequence of the remapping process remains to be elucidated. This finding suggests nonetheless that a global phenomenon such as remapping can encompass more subtle events that take place on smaller timescales.

One of the major difficulties highlighted by the results on overdispersion and place field stability is that coding at one timescale may interfere, and hence produce a noisy signal, with coding at

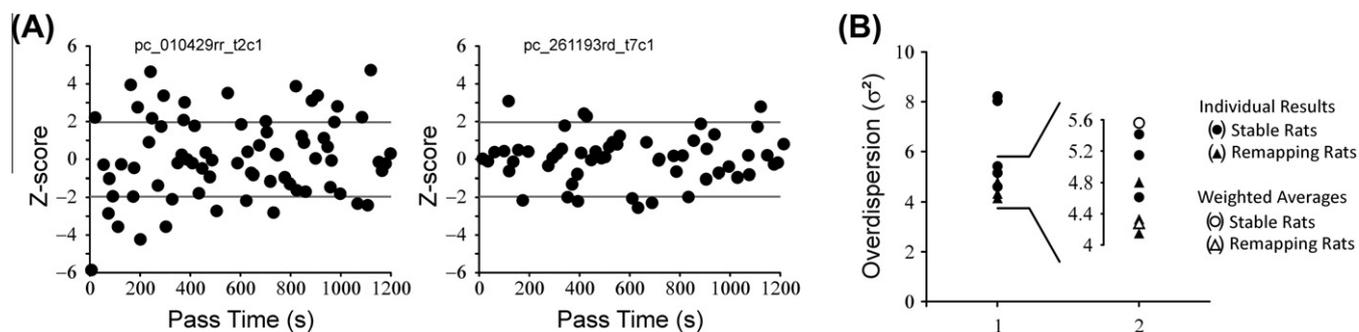


Fig. 4. Rats with unstable hippocampal representations show weaker place cell firing variability. (A, left) Plot of the time series of Z-scores for the observed firing on all passes through the center of the field of one place cell recorded for 1200 s in one stable rat. The gray lines indicate the 0.05 probability tails of the normal distribution ($Z \leq 1.96$ and $Z \geq 1.96$). As described previously (Fenton and Muller, 1998), high negative and positive Z-scores alternate over the whole recording time. (right) Plot of the time series of Z-scores obtained for one place cell recorded in a remapping rat. Note that these values lie almost exclusively within the 95% confidence interval. (B) Distribution of eight individual variance scores in stable and remapping rats (1; close-up in 2). Note that remapping rats' distributions yield lower values, significantly different when comparing weighted averages (empty symbols; $\sigma^2 = 5.53$, $\mu = 0.04$, $N_{\text{passes}} = 10,012$ (stable rats) versus $\sigma^2 = 4.31$, $\mu = 0.03$, $N_{\text{passes}} = 7718$ (remapping rats); Levene's test for equality of variances, $W = 52.7$, $p < 0.001$).

another timescale. Although understanding place cell firing at different timescales is a challenging issue, we argue that it is even more difficult to understand how the different coding mechanisms supported by place cell activity are related to each other and to reconcile their functioning into a single time-independent conceptual framework. Fig. 5 provides an empirical illustration of this temporal overlapping problem. A rat's place cell is recorded as the animal is exploring a circular arena for 16 min. The resulting cumulative activity of the cell is shown in Fig. 5A, which features the existence of a crescent-shaped firing field near the apparatus wall. One single pass of the rat in the field lasting about 2 s is superimposed on the firing rate map in Fig. 5B (small black squares denote the rat's location as the cell is firing action potentials). The same spike data of this particular path are also displayed on the timescale shown in Fig. 5C. The local field potential was simultaneously recorded. When appropriately high-pass band-filtered, the LFP reveals several occurrences of high-frequency oscillations (Fig. 5D) putatively associated with replay. In other words, within the same period of about 2 s, the place cell system is engaged in both signaling the rat's location and replaying past information. To keep it simple, we illustrate a situation in which temporal overlapping is limited to two coding schemes. Nevertheless, there may well be more complex instances in which, for example, location-specific firing occurs simultaneously with both replay-like events and greater-than-expected firing (overdispersion). The problem is how information can be decoded from the "noisy" state generated by temporal overlapping of several putative coding schemes occurring

simultaneously in the same spatio-temporal dimension. We provide below a tentative explanatory framework, which has no other purpose than to stimulate interest and discussion.

We assume that the place cell population acts as a dynamical system. What we mean here is that place cell activity can suddenly change and converge towards stable states, or attractors. A good example of such dynamical coding is provided by the Wills et al.'s study (2005) in which rats were exposed repeatedly to a square and circular environment. Exposure to a new environment whose shape was neither a pure square or a pure circle, but an intermediate polygon, revealed that place cells abruptly and simultaneously switched between representations of either the square or the circle. Thus learning the novel environment initially relied on a dynamic population code in which place cell activity suddenly changed towards stable states built during previous experience (see Leutgeb et al., 2005a however). Presumably, continued exposure to the novel environment would result in the creation of a new stable state (Poucet and Save, 2005). A dynamical system can be described as a trajectory in a transition (or phase) space. The temporal parameters used to describe the trajectory are crucial. It is likely that major state transitions involving a large fraction of cells can be captured at very low time resolutions. In contrast, more subtle and punctual changes are observed only if finer time resolutions are used. We imagine therefore that, much as the geometric shape of a landscape can be described as fractals (i.e., can be split into parts that are reduced-size copies of the whole; Mandelbrot, 1982), the dynamical trajectory that describes the properties of place cell activity at different

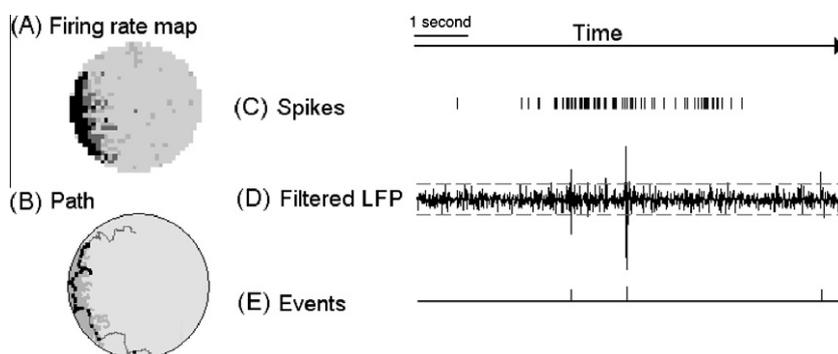


Fig. 5. Illustration of the temporal overlapping problem. The functional correlates of a single place cell are illustrated through three distinct analytical lenses. The cell has a firing field in the portion of the circular arena located at about 9 o'clock (A). A few seconds of this cell's firing are shown as the rat traverses the field location (B), thus resulting in elevated firing (C). During the same period, the LFP recording (D) features the occurrence of high-frequency events. The LFP signal is high-pass filtered (150–250 Hz) so that only rapid oscillations can be seen (i.e., low fluctuations such as theta rhythm are not visible). High-frequency events result from simultaneous activation of a population of cells, which or may not be associated with replay-like events (E). The problem is how information can be decoded from the "noisy" state generated by temporal overlapping of several putative coding schemes occurring simultaneously in the same spatio-temporal dimension.

timescales would resemble a set of nested attractors that reflect the different timescales of variability (Fig. 6). In other words, the global path in the space of phase transitions would combine a variety of spatially distinct paths, and the exact mechanism under scrutiny would depend on the resolution used for path analysis in transition space. Although it is not explanatory of how attractors are created, this speculation would account for how they do not interact with each other, i.e., how phase transitions at one timescale do not interfere under normal conditions with phase transitions at another timescale (Fig. 6). The simplest illustration of this process is the recruitment of a subset of pyramidal cells acting as place cells for a given environment, with each place cell being active only when the rat is in its place field. In this situation, phase transitions from a cell being transiently silent to being transiently active depend only on the rat's location, which itself results from the rat's motion and therefore the hippocampal theta rhythm. A more complex scheme is provided by the situation in which a place cell is active in its firing field while replay-like firing of other cells occurs simultaneously (Fig. 5). Here, phase transitions may depend on both the rat's location and brain state (e.g., theta vs LIA, different levels of ACh, etc.). Thus, the hypothesis of nested attractors likely relies on the properties of hippocampal state, which is characterized by the predominance of a variety of rhythmic activities in well-separated frequency bands that could serve as the substrate for different types of coding.

7. Conclusion

In this brief review of functional properties of place cell firing, we summarized current evidence that, in addition to their prominent stable location-specific correlates, place cells carry more subtle and variable information through the temporally precise discharge of subsets of hippocampal cells. Thus, both stability

and variability are important properties of hippocampal place cell discharge. While stability allows for the coding of stable properties of space, we speculate that variability might endow the hippocampal place cell system with the flexibility required to keep the map up-to-date and reliable, two conditions that are necessary for the occurrence of map-based behavior. We therefore are convinced that the study of hippocampal neural activity provides the ideal window to decipher the neural correlates of complex cognitive processing. Although we have focused our review on the temporal modulation of hippocampal place cell activity, and therefore on the associated complex behaviors that occur in space, the computational role of the dynamical activities that are observed in the hippocampus can be extended to all kinds of processing involving relational coding (Eichenbaum et al., 1999). Interestingly, it is only relatively recently that the most subtle features of hippocampal place cell activity were uncovered. The reason is largely methodological in that decoding the detailed information carried by place cells required sophisticated *in vivo* recording techniques. Such techniques had to yield the ability to record large numbers of well-discriminated neurons, and to provide the analysis tools to decode the information from these neurons. The development of tetrode recordings in the mid-90's coupled with increased recording capacity and powerful mathematical tools was the condition for the emergence of a new generation of data analyses that has permitted to address the fine structure of spike trains emitted by place cells. There is little doubt that the constant evolution of analytical tools and of recording methods will greatly help researchers better understand the computing tasks endorsed by these amazing little neuronal processors.

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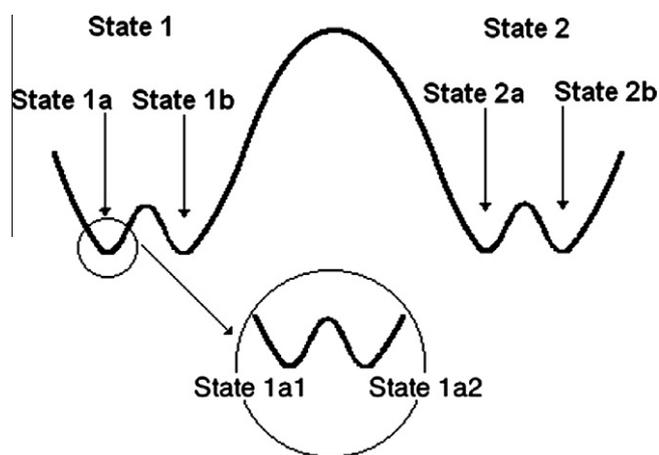


Fig. 6. Illustration of the hypothesis of nested attractors. Because place cell firing reflects simultaneous processing of different features in the spatial domain, there must be a mechanism to avoid noisy states. In this scenario, coherence of place cell firing is maintained through nested attractors. For instance, State 1 may represent the state of the hippocampal place cell system when the rat is in a cylinder environment while State 2 may represent hippocampal state when the rat is in a square arena. State 1a may represent hippocampal state when the rat is at the firing field location of the cylinder shown in Fig. 5 while State 1b could correspond to a different field location (i.e., to the activity of a different subset of place cells active in the cylinder). Looking at place cell activity at an even shorter timescale (i.e., zooming on State 1a), States 1a1 and 1a2 would correspond to different replay activities triggered by both the current rat's location in the field and the exact trajectory that led it to this location. Note that similar scenarios can be proposed for other timescales and types of place cell activity. For example, we could imagine that States 1a and 1b and States 2a and 2b represent attending to local and distal cues in each environment respectively.

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