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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/345/6198/812/suppl/DC1
Materials and Methods
Figs. S1 to S5
Tables S1 and S2
References (*27*–*70*)

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PLACE CELLS

Large environments reveal the statistical structure governing hippocampal representations

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The rules governing the formation of spatial maps in the hippocampus have not been determined. We investigated the large-scale structure of place field activity by recording hippocampal neurons in rats exploring a previously unencountered 48-meter-long track. Single-cell and population activities were well described by a two-parameter stochastic model. Individual neurons had their own characteristic propensity for forming fields randomly along the track, with some cells expressing many fields and many exhibiting few or none. Because of the particular distribution of propensities across cells, the number of neurons with fields scaled logarithmically with track length over a wide, ethological range. These features constrain hippocampal memory mechanisms, may allow efficient encoding of environments and experiences of vastly different extents and durations, and could reflect general principles of population coding.

The hippocampus is involved in encoding long-term memories of items and events from daily life in humans (*1*) and spatial environments in rodents (*2*). Each item (*3*), experience (*4*), or environment (*5*–*7*) is represented by a subset of active neurons among an often much larger number of inactive neurons. For spatial representations, the active subset consists of place cells, each of which fires when the animal is at specific locations in an environment (called the place fields of that cell) (*8*). The inactive neurons, which fire few or no spikes throughout the environment, are called silent cells (*5*). When an animal encounters another environment, a different subset of neurons becomes active, and this difference is believed to be the basis by which spatial contexts are distinguished (*7*, *9*). Within a given environment, the fields of different cells together cover the space and are thought to provide a cognitive map enabling flexible navigation (*2*).

In environments typically used to study spatial firing (total track length <5 m, or open arenas <1 m^2), ~20 to 50% of pyramidal neurons from the dorsal CA1 subregion of the rat hippocampus are recruited to be place cells (*5*, *6*, *10*), and most have a single place field. Wild rats have home ranges typically up to 50 m across, sometimes extending to hundreds of meters (*11*); in larger laboratory environments (up to 18 m long or 3 m^2), more neurons are recruited to be place

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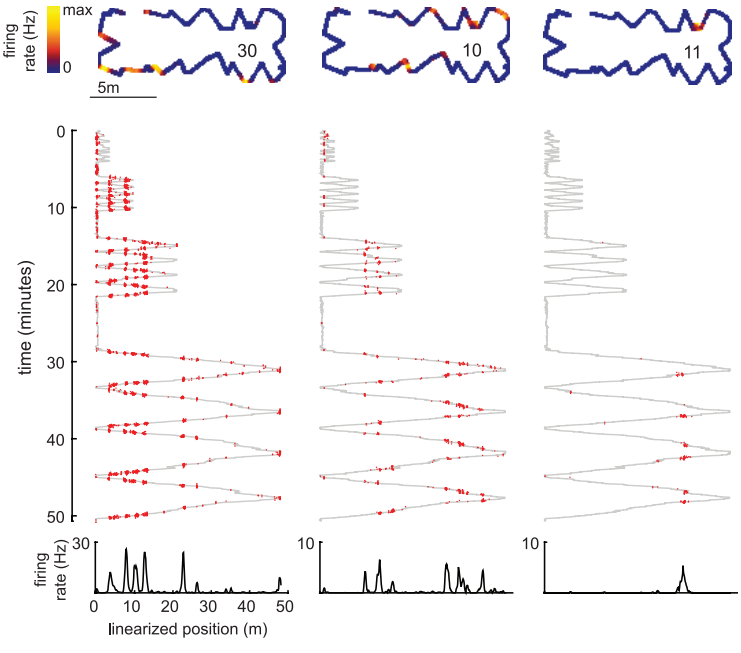

Fig. 1. Place cells form multiple peaks in large environments. From top to bottom, for three different neurons: firing rate on 48-m-long track, with peak rate noted; linearized position of animal (gray) and spikes (red); linearized firing rate. Spikes when an animal's speed was <5 cm/s are omitted.

cells, many cells have multiple fields, and place fields are wider (*12*–*14*).

However, far less is understood about the organizing principles of hippocampal spatial maps. Basic questions remain with implications for the underlying mechanisms and proposed functions of hippocampal representations. When fields are formed, which cells do they come from?

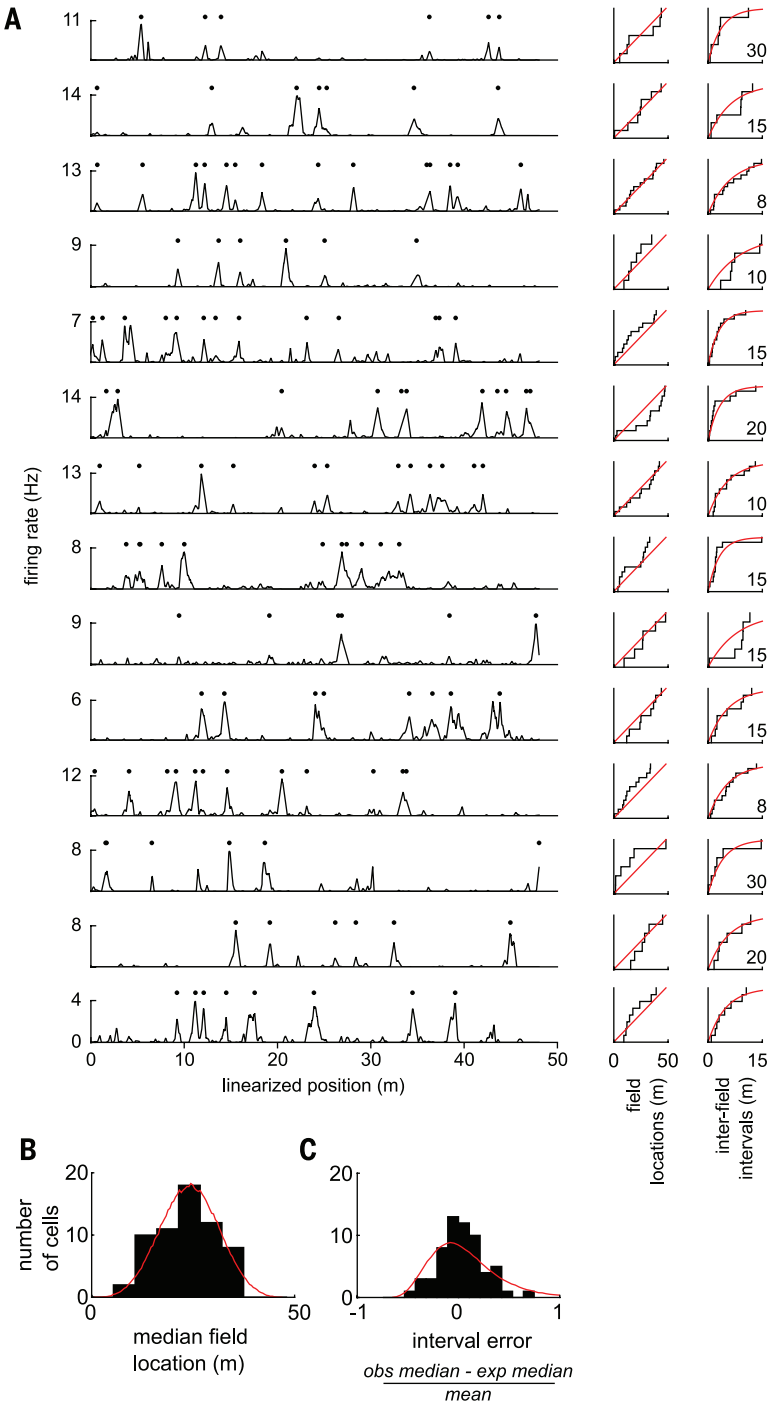

Fig. 2. Place field formation in individual cells is well described as a spatial Poisson process. (**A**) All cells with ≥6 place fields from a single animal; dots denote centers of detected fields. Cumulative distributions of field locations and interfield intervals are shown at the right (black), together with the uniform and exponential distributions expected for a Poisson process (red). (**B**) Distribution of median field location of all cells with ≥6 fields across animals (n = 61 cells from 5 rats) versus distribution expected for cells with uniformly distributed fields (red curve). (**C**) Distribution of deviation from exponential of median interfield interval (normalized by the mean interval) for all cells with ≥6 fields versus distribution expected for cells with exponentially distributed fields (red curve).

Place fields are the units of spatial representation in CA1, and their distribution among cells determines how they code for location. Will every cell become a place cell if the environment is large enough? If all cells became place cells, the specificity of active subsets would disappear, requiring other mechanisms for retrieving the appropriate spatial context from memory.

To investigate such questions, we used a very large maze and quantified two key aspects of hippocampal maps—which cells fire and where they fire—as they were was being established in five rats. We recorded 253 putative pyramidal cells from dorsal CA1 (fig. S1) in the rats as they explored a 48-m-long track (fig. S2). The track and room were both entirely novel to the animal. To test whether there was a limit to recruitment, we challenged the representational capacities of the hippocampus by progressively extending the track in stages and making locations along the track as distinct as possible. In each epoch, an animal traversed the current total length of track three to five times, and between epochs it was confined to the original start location while the track was extended. Total track lengths in the four epochs were 3, 10, 22, and 48 m. Although animals traversed the entire available track during each epoch, we restricted analysis to periods when the animal explored the additional novel sections of track introduced in each epoch; this enabled us to focus on the initial recruitment of cells and fields. To ensure accurate counts of silent cells, we only analyzed neurons that could be isolated in sleep periods flanking behavioral periods (*5*, *6*).

In each new section of track, existing place cells formed additional fields and new place cells were recruited from the pool of silent cells (*12*) (Fig. 1 and figs. S3 to S5). The multiple fields of individual cells appeared to be irregularly spaced over the track (Fig. 2A). The simplest model of place field formation is that the locations of the fields of each cell follow a spatial Poisson process; that is, the locations are random and described only by a certain average rate. For cells with ≥6 fields (61/253), neither the spatial distributions of fields nor interfield interval distributions differed from the Poisson model (Anderson-Darling test, 0/61 cells with $P < 0.05$, adjusted for false discovery rate), where they are uniform and exponential, respectively (Fig. 2; see fig. S6 for cells with <6 fields).

We asked whether a correspondingly simple model could describe the population as a whole (Fig. 3A). Specifically, did each cell have the same Poisson rate of field formation? This model would capture the qualitative behavior observed as environments increase in size, i.e., additional fields are formed and previously silent cells are recruited to be place cells. Quantitatively, this model makes certain predictions. First, the observed number of fields per cell would follow a Poisson distribution. Second, the distribution of the location of each cell's field that is closest to the start of the track (called the recruitment curve, as it shows the fraction of the population that is recruited to be place cells as the track lengthens)

would follow an exponential distribution. However, the fits of both distributions to the data were poor (Fig. 3, B and C), indicating that such a model does not describe hippocampal population representations in novel environments.

Instead, the observed number of fields per cell was overdispersed relative to the equal-rate Poisson model (Fig. 3B and fig. S7A), indicating significant differences in the spatial rate of field formation between cells. That is, a few neurons had many fields, whereas many more than expected had few or no fields. The recruitment of neurons into the representation reached only ~65% at 48 m (range 46 to 77%, fig. S7B), greatly undershooting the equal-rate Poisson prediction. To see whether the ~35% of cells that remained silent were capable of forming fields at all, we later exposed the animal to a second novel environment and found that some of these cells formed clear place fields (fig. S8).

We next asked whether the differing propensity of cells to form fields across the population could be described by a particular distribution. The number of fields per cell was well fit with a negative binomial distribution (Fig. 3B, parameters r, p = 0.57, 0.14), which can arise if each cell is an independent Poisson process with its rate drawn from a gamma distribution (fig. S9). Moreover, the recruitment curve under such a gamma-Poisson model would follow a Lomax, or Pareto type II (power law), distribution. The predicted recruitment curve matched the observed one well (Fig. 3C; Kolmogorov-Smirnov statistic = 0.05, P = 0.48). The curve shows logarithmic-like recruitment over spatial scales spanning several orders of magnitude, including the range of distances traveled by wild rats (*11*), and its extrapolation predicts 90% recruitment at ~500 m.

We examined additional properties of the distribution of fields. As expected from independent Poisson processes, overall field density was uniform over the environment (Fig. 3D; Kolmogorov-Smirnov statistic = 0.03, P = 0.36) and was uninfluenced by local track features or running speed (fig. S10), field propensities were stationary across the track (fig. S11), and field locations were uncorrelated between pairs of cells (fig. S12).

Memorylessness—being invariant with respect to the starting point or history—is a defining property of Poisson processes. We thus chose evenly spaced points on the track, ignored whether or not cells had been recruited before that point, and then determined the subsequent recruitment curve for the remainder of the track. These memoryless recruitment curves had the same shape regardless of the starting point (Fig. 3E and fig. S13).

The uniform field density at the single-cell and population levels, exponential interfield spacing, good match to the predicted recruitment curve, stable propensity distribution, uncorrelated field locations across cells, memorylessness of recruitment, and uncorrelated spatial and nonspatial field properties (fig. S14) demonstrate that the gamma-Poisson model is a good statistical description of place field formation in a novel environment. Different criteria for place field detection did not change the results (fig. S15). Although the gamma-Poisson model was sufficient to explain the recruitment of cells and fields under our experimental conditions, other studies have shown increased field density around goals (*15*) and changing recruitment over time (*10*, *16*), indicating that other factors can modulate field propensity.

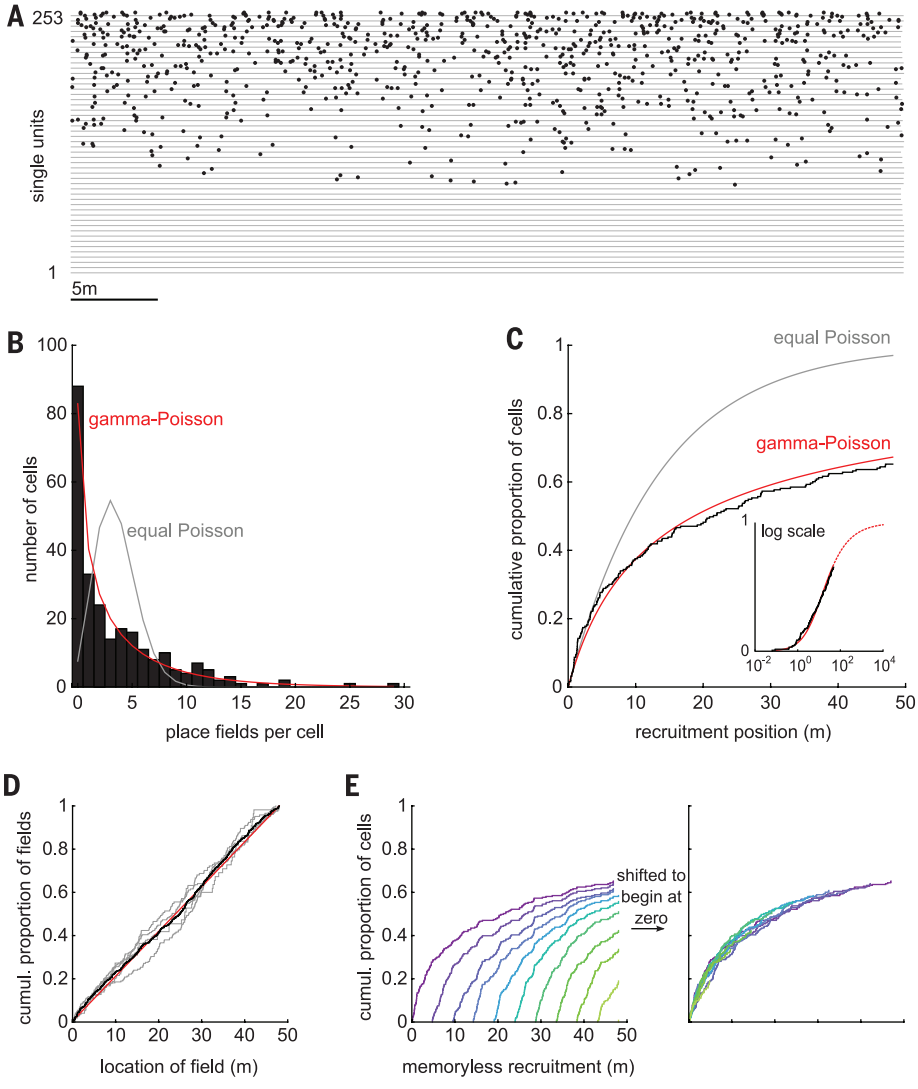

Fig. 3. Statistical, population-level model of the formation of hippocampal spatial representations. (**A**) Place field locations of all 253 recorded neurons. Lines show extent of the track every 5 cells. Cells sorted by number of fields. (**B**) Number of place fields per cell. Distribution assuming each cell has equal Poisson rate (given by the mean number of fields per cell) of forming place fields per unit length (gray). Fit of negative binomial distribution (red), which results from gamma-distributed Poisson rates (i.e., gamma-distributed field propensities). (**C**) Recruitment curve, derived from location of field closest to start (0 m) for each cell, representing the proportion of place cells in the entire population as function of track size. Predictions of equal-rate Poisson (gray) and gamma-Poisson (red) models, each using parameters estimated from (B). (**D**) Distribution of all fields across animals (black) along track versus constant-density uniform distribution (red). Individual animals (gray). (**E**) Memoryless recruitment curves constructed by starting at a point along track and then calculating subsequent recruitment regardless of activity in previous length of track. Same curves shifted to allow comparison of shapes (right).

Our attempt to challenge the representational capacity of the hippocampus revealed neither a hard limit to recruitment nor completely random recruitment. Instead, a skewed distribution of field propensities across the population led to logarithmic-like recruitment over a wide range of ethologically relevant distances. What causes place cells to fire has been the subject of intense investigation for decades; this finding adds another dimension to that question: What causes a cell to have a particular rate of expressing place fields?

Two distinct mechanisms can give rise to the observed gamma-Poisson process (*17*): (i) preexisting differences between cells (*18*), or (ii) a

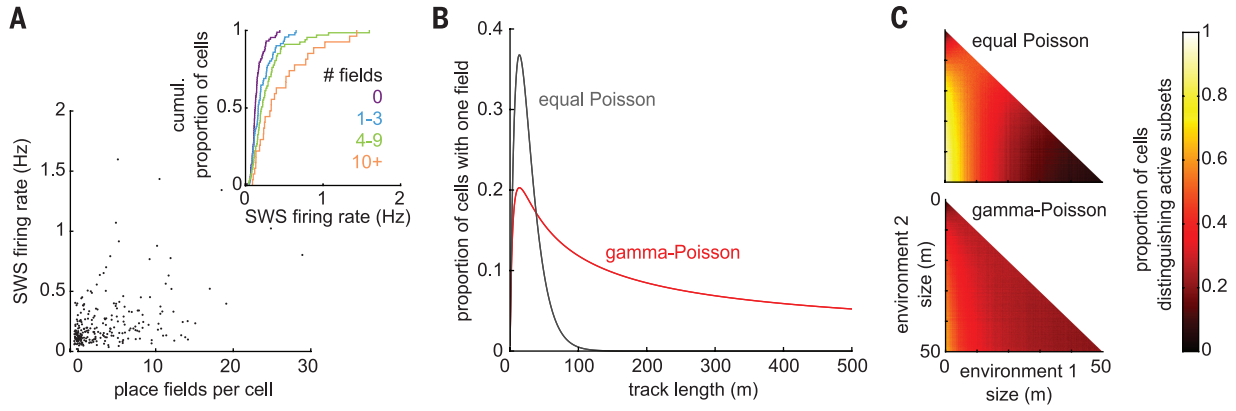

Fig. 4. Origin and coding implications of the distribution of field propensities. (**A**) Firing rates in slow-wave sleep (SWS) before exploration were correlated with subsequent number of fields per cell on track (jitter added for visualization). SWS firing rates separated into groups by number of fields (inset). (**B**) Proportion of cells with exactly one place field as a function of environment size under equal-rate Poisson and gamma-distributed models of field propensities. (**C**) Simulation of the expected proportion of neurons that are place cells in one environment and silent in another for environments of different sizes under the two models.

cumulative advantage mechanism during exploration (e.g., Polya-Eggenberger urn). Firing rates in slow-wave sleep (SWS) before the animal had experienced the maze were moderately correlated with the subsequent number of fields per cell (Fig. 4A; $r = 0.45$, $P < 10^{-13}$); this finding provides evidence that preexisting differences contribute to field propensities but does not rule out possible additional cumulative advantage mechanisms.

Preexisting differences between cells could result from differences in cellular excitability or network inputs. Future place cells are more excitable than future silent cells before exploration (*19*), and artificially increasing the excitability of silent cells can convert them to place cells (*20*), thereby linking preexisting intrinsic differences (*21*) with field propensity. Fixed cellular or network differences likely underlie the moderate variation in field propensity (*22*, *23*) (fig. S16) with anatomical location.

Place fields are ultimately derived from spatial information originating from external sensory or self-motion sources. Preexisting differences, whether cellular or network-based, could act as an additional element in existing models of place field origin (*24*–*26*) by modifying responses to spatial inputs (*20*). The gamma distribution of field propensities we observed provides a specific constraint on mechanisms and models of place cell firing. The link between preexisting differences and field propensity could also account for preplay of novel environments (*27*), as well as correlated firing rates (*28*) and correlated field propensities (fig. S17) across multiple environments.

What functions might a range of field propensities serve? Equal rates of random field formation would maximize the network's ability to uniquely encode distinct places. But with the observed gamma-distributed propensities, the proportion of cells with single fields would remain at ~5 to 10% over a wide range of environment sizes, potentially enabling a simple readout of location (Fig. 4B). Furthermore, equal propensities would lead to difficulties in distinguishing environments based on their active subsets, because large-enough environments would recruit all cells. Instead, the observed distribution of propensities allows environments with a wider range of sizes to be distinguished based on their active subsets, even if one assumes each cell's propensity to be permanently fixed (Fig. 4C and fig. S18). These features may also operate alongside the dorsoventrally modulated range of CA3 field sizes (*14*) to efficiently encode differently sized environments.

Loglike recruitment has been seen in motor (*29*) and sensory (*30*) systems, which suggests that it may be a general feature of neural population coding, along with other functions of skewed distributions (*28*). In the hippocampus, it could underlie a Weber-like perception of space. The quantitative description of spatial representations provides new insight into how the hippocampus may handle capacity for multiple items as well as single, extended experiences, and may have implications for representations and memory formation (*31*) in other systems.

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SUPPLEMENTARY MATERIALS

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Supplementary Text
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Large environments reveal the statistical structure governing hippocampal representations

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Nerve cells displaying extra large spaces

Rats use brain cells called "place" cells to figure out where they are. Rich *et al.* used mazes or tracks many meters long —the size of rats' ranges in the wild—to investigate how rats represent a very large environment or extended experience in their brain. As novel environments became larger and larger, the rats' brains recruited new place cells. However, no matter how large the environment became, some cells always remained silent, perhaps as a reserve for other environments yet to be visited.

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