Hippocampal Place Fields Emerge upon Single-Cell Manipulation of Excitability During Behavior
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On the other hand, had the convict been found guilty of murder and had thus faced either the death sentence or life in prison without the possibility of parole, then future dangerousness would have lost its appeal as the defendant might have been incarcerated for life with no potential to reoffend. Further, judges were explicitly told that rehabilitation was not an alternative, as large-scale treatment has to date been ineffective for adult psychopaths. This eliminated a possible third option for those seeking to find a compromise between aggravation and mitigation. In future studies, the potential for effective treatment makes presentation of a third rehabilitative theory, with corresponding expert testimony, an attractive option for testing. The judges were also not presented with cross-examination, having only received the expert scientific testimony from either the defense or the prosecution.

Turning to limitations associated with the science, we focused exclusively on psychopathy, a diagnosis with much stigma. Thus, these results may not generalize to other psychiatric diagnoses associated with antisocial behavior (31, 32). Likewise, we based our account of the biomechanism of psychopathy on James Blair’s neurocognitive model (28). Changing this causal description might lead to different judgments (33). Finally, we combined psychiatric, genetic, and neurobiological science in constructing the expert testimony. Future research should examine the effects of separately introducing testimony on genetic penetrance and expression, neurodevelopment and plasticity, and probabilistic data indicating how much of the relative risk of developing the particular antisocial disorder can be attributed to the given biomechanism.

References and Notes
34. Answers are collapsed across eliciting question (mitigating versus. aggravating effect of evidence, legal responsibility, moral responsibility, free will, and sentencing). For verbatim examples of judges’ reasoning, see supplementary materials.

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Hippocampal Place Fields Emerge upon Single-Cell Manipulation of Excitability During Behavior
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The origin of the spatial receptive fields of hippocampal place cells has not been established. A hippocampal CA1 pyramidal cell receives thousands of synaptic inputs, mostly from other spatially tuned neurons; however, how the postsynaptic neuron’s cellular properties determine the response to these inputs during behavior is unknown. We discovered that, contrary to expectations from basic models of place cells and neuronal integration, a small, spatially uniform depolarization of the spatially untuned somatic membrane potential of a silent cell leads to the sudden and reversible emergence of a spatially tuned subthreshold response and place-field spiking. Such gating of inputs by postsynaptic neuronal excitability reveals a cellular mechanism for receptive field origin and may be critical for the formation of hippocampal memory representations.

The hippocampus plays a crucial role in the formation of long-term memories for facts and events in humans and for spatial learning in rodents (1). When a rodent explores an environment, spatial information is prominently represented in the spiking activity of a substantial, environment-specific subset of hippocampal pyramidal neurons. Each such “place cell” fires action potentials (APs) selectively whenever the animal is in a particular region—called the cell’s place field—within the environment (2), whereas the remaining neurons, called silent cells, fire few or no spikes (3). Similarly, subsets of human hippocampal neurons spike selectively for specific items or episodes over a background of low-firing rate cells (4). The establishment and stability of these stimulus-specific spiking responses are believed to be the neural basis of hippocampal-dependent learning and memory.

What is the origin of the spatially selective firing of place cells? Each pyramidal cell in hippocampal subregion CA1 receives excitatory inputs from other spatially tuned neurons (5, 6). Therefore, models have generally assumed that the critical factor is the environmental location where each input fires, with summation of these inputs (their firing rates times synaptic weights) followed by thresholding leading to various degrees of spatially selective output spiking or silence (7–11). Indeed, intracellular recordings have revealed that place cells have a region with clearly elevated somatic membrane potential (Vm)—i.e., a “hill”—under their place-field spiking (12–14), whereas silent cells have a flat, spatially uniform Vm (14).

However, another critical aspect of neuronal integration is the interaction of synaptic inputs with the membrane properties of the postsynaptic cell. Inputs can be strongly filtered or amplified (15, 16) before determining output spiking, yet such features have not been included in place cell models. With intracellular recording, place cells were, unexpectedly, also found to be more excitable than silent neurons; however, how the postsynaptic neuron’s cellular properties determine the response to these inputs during behavior is unknown. We discovered that, contrary to expectations from basic models of place cells and neuronal integration, a small, spatially uniform depolarization of the spatially untuned somatic membrane potential of a silent cell leads to the sudden and reversible emergence of a spatially tuned subthreshold response and place-field spiking. Such gating of inputs by postsynaptic neuronal excitability reveals a cellular mechanism for receptive field origin and may be critical for the formation of hippocampal memory representations.

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cells—even before the animal encountered the environment (14)—which suggested that cellular properties strongly influence the response to inputs during behavior.

How can one separate the role of cellular properties from inputs in the origin of place cell firing? One approach would be to test whether increasing excitability without altering synaptic inputs can convert a previously spatially untuned silent cell into a place cell. A straightforward way to increase excitability is to depolarize a neuron’s baseline $V_{m}$ by injecting a constant, i.e., spatially uniform, current into the soma and thus bias it toward spiking. Here, we used the whole-cell recording method to precisely manipulate the somatic $V_{m}$ in single CA1 pyramidal neurons while rats explored a novel environment, then measured the spatial distribution of subthreshold and spiking responses to see the effect on the integration of inputs.

We recorded 10 silent cells (Fig. 1A) in 10 rats (14, 17, 18) as they moved around an oval track (mean recording duration during behavior was 28 min), in four cases in both directions. Because place cells can have fields in a single direction in such environments, we treated the 14 directions separately. For each direction, animals first explored each location in the maze at least twice with no applied current (Fig. 1, B and C). The flat mean $V_{m}$ as a function of location (Fig. 1, C to E) (14) suggests that silent cells receive either few inputs or inputs whose overall tuning is spatially uniform. Alternatively, silent cells may receive substantial spatially tuned input, but their lower excitability severely limits or prevents propagation to the soma. It was surprising that the latter was the case. Depolarization of the somatic baseline $V_{m}$ by constant current injection immediately caused not only the appearance of a spiking place field (Fig. 1, B and C) but also an underlying subthreshold (i.e., excluding

![Fig. 1. Emergence of a spatially tuned subthreshold response and place field by a small depolarization of the somatic membrane potential ($V_{m}$).](image)

(A) Morphology of recorded CA1 pyramidal neuron. (B) Animal trajectory (gray), AP locations (red), and AP rate map in an “O”-shaped maze (inner wall not shown) during periods when the animal faced in the counterclockwise direction before (bottom) and after (top) injecting constant 83 pA current into soma. (C) $V_{m}$ (black) and AP rate (color) as a function of linearized location of animal around track in (B) for selected laps. Baseline $V_{m}$ (left), peak AP rate (right) for each lap. Animal movement direction (arrow). Large gaps in laps reflect changes in animal movement direction during lap or periods when experimenter adjusted current injection value. (D) $V_{m}$ (black) and mean subthreshold $V_{m}$ (color). (Inset) $V_{m}$ versus time corresponding to location marked by black bar. (E) Overlay of mean subthreshold $V_{m}$ from all laps (thin lines; red: 83 pA, blue: 0 pA). Thick lines: averages for each current level. Colors in (C) to (E) are matched.
APs and calcium spikes) $V_m$ hill (Fig. 1, D and E, red), both stable across laps. Of five directions (from five cells) in which a single current level was applied, a single spiking place field and spatially tuned subthreshold hill emerged in two cases (Fig. 1 and fig. S1): multiple, stable hills in one case and firing covering most of the maze in the other cases. This suggested that the number and size of place fields vary over a narrow voltage range.

Therefore, we asked whether, by applying different current levels across laps (five cells, nine directions), we could always create a single, narrow field, as expected in environments of this size. In four of five cells, narrow fields were produced in at least one direction, for a total of six such fields from five directions (one direction had two fields). For population analyses, we included these six fields plus the two from single-current population analyses, we included these six fields from four of five cells, narrow fields were produced in at least one direction, for a total of six such fields from five directions (one direction had two fields). For population analyses, we included these six fields plus the two from single-current-level experiments. Examples for which, at an intermediate level of depolarization, a single, narrow field was produced (red) are shown in Fig. 2 and fig. S2. Laps were ordered by baseline $V_m$ because this best predicted resulting subthreshold and spiking activity. With more depolarization, subthreshold and spiking responses broadened (orange). Field emergence depended on baseline $V_m$ not current injection itself, as illustrated in fig. S3.

For four fields, we returned to the original baseline $V_m$ (by returning to 0 pA) intermittently. In these cases, the field disappeared (Fig. 2A, laps 7 and 12, and fig. S4). Thus, field emergence was not simply experience-dependent. Also, the presence of the field for a few laps was apparently insufficient to induce plasticity that could then maintain the field without depolarization.

Within the (eventual) region of the created field, the amplitude of the hill (“peak – baseline” in Fig. 3A) as a function of baseline $V_m$ showed a sharp rise above a certain baseline $V_m$ value (Fig. 3B). For each field, we estimated the baseline $V_m$ at the midpoint of the rise ($V_{m,\text{gate}} = -56.6 \pm 1.0$ mV) then aligned the fields with respect to $V_{m,\text{gate}}$. The pooled result (Fig. 3C) showed a thresholdlike transition from a low to maximal amplitude hill within a ~1- to 3-mV range of baseline $V_m$ values, revealing striking sensitivity of a neuron to inputs around its own “threshold” value. This suggests that nonlinear voltage-dependent mechanisms underlie the generation of the subthreshold place field.

We checked several possible sources for the emergence of the hill. First, hills did not require the generation of somatic APs. Laps with baseline $V_m$ within the transition range displayed a clear subthreshold hill without APs (Fig. 3D). Also, the ascending slope of a hill could begin before any spiking in the field in the first lap with current injection (Fig. 1D, inset).

Was there a small, preexisting hill at the eventual location of the field that was amplified by depolarization? No, the mean in-field and out-of-field $V_m$ in the initial 0 pA laps did not differ across the population (difference = 0.03 ± 0.05 mV, $P = 0.49$) (Fig. 3E) or for individual fields (fig. S5).

Alternatively, the field could emerge from a location with no difference in mean $V_m$ but an elevated input resistance ($R_N$) (due to decreased excitatory and inhibitory input), which would depolarize more than regions with lower $R_N$ in response to a constant current. In this case, the initial appearance of the hill could be independent of voltage-gated mechanisms. However, for two of the three fields we could test, there was no evidence of this ($P = 0.24, P = 0.47$).

We then checked whether the subthreshold response emerged from regions with larger fluctuations in $V_m$ (but no difference in mean $V_m$). Neither the standard deviation ($P = 0.25$) (Fig. 3E), nor gamma (25 to 100 Hz) band power ($P = 0.63$), nor right tail of the distribution (fig. S6) of $V_m$ were initially different inside versus outside the eventual field location. We examined the prominent theta (4 to 10 Hz) band in more detail. Theta power was higher within the field for laps with fields ($P = 0.01$) (Fig. 4, A and B) ($\chi^2(2)$, but, again, not in the initial 0 pA laps ($P = 0.89$) (fig. S7 and Fig. 4B). Rather, theta power varied with $V_m$ and not location per se (i.e., the power-$V_m$ relation did not differ inside and outside the field) (Fig. 4C and fig. S8).

Therefore, there was no obvious indication of where the field would eventually emerge. When it did emerge, the subthreshold response could remain elevated for an extended period (4.8 ± 0.5 s) while the animal remained in the field (Fig. 1D, inset, and Fig. 4A).

In two recordings of place, as opposed to silent cells, we suppressed spiking with hyperpolarizing current. In one case, the original subthreshold hill disappeared (fig. S9), which provides further evidence that place fields may not originate from passive summation of synaptic input in novel environments.

Although any spatial information in the hippocampus must ultimately come from external inputs (5, 19–21), these findings directly demonstrate that nonspatial, cellular factors can play a decisive role in how neurons respond to inputs during behavior. In particular, most CA1 pyramidal cells receive spatially tuned synaptic input that, in silent cells, does

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**Fig. 2.** Tuning of subthreshold response and place field as a function of the somatic baseline $V_m$ level. (A) $V_m$ (black) and AP rate (color) for individual laps ordered by baseline $V_m$ (left). Peak AP rate (right). Current injected (rightmost). (B) Mean subthreshold $V_m$ of each lap (thin lines), average for each group of laps (thick lines). Spatially tuned subthreshold response and place field emerge at intermediate (red) $V_m$ levels.
Fig. 3. Sudden emergence of a spatially tuned sub-threshold response with increasing somatic baseline $V_m$. (A) Two laps from Fig. 2A with similar baseline $V_m$. Peak ($V_p$) and baseline ($V_b$) of mean subthreshold $V_m$ of subthreshold response as function of baseline $V_m$ for Fig. 2 neuron. Baseline "$V_m,\text{gate}$" (dashed line) giving maximal difference of mean amplitude between groups above and below that level. Laps in (A) (filled circles). (B) Amplitude (peak - baseline) of subthreshold response versus baseline $V_m$ for Fig. 2 neuron. Baseline "$V_m,\text{gate}$" (dashed line) giving maximal difference of mean amplitude between groups above and below that level. Laps in (A) (filled circles). (C) Normalized subthreshold response amplitude versus baseline $V_m$, aligned by $V_m,\text{gate}$ and pooled across fields (n = 7, different symbols for each field). Sigmoid fit (red). (D) Examples of subthreshold hills without APs (horizontal bars: eventual field locations). (E) Difference between mean and standard deviation of $V_m$ inside and outside location of eventual field in initial 0 pA laps (n = 8 fields).

Fig. 4. Theta frequency power depends on mean somatic $V_m$. (A) $V_m$ (top), spectrogram (middle), and instantaneous power in 4 to 10 Hz band (bottom) versus time for Fig. 2A lap 5. Inside of place field (box). (Above) Expanded $V_m$ dynamics inside and outside the field. (B) Ratios of mean theta power inside versus outside location of (eventual) field for initial 0 pA and place field laps (n = 8 fields). (C) Theta power as a function of mean $V_m$ inside (filled) and outside (open) (eventual) field for Fig. 2 neuron. Linear regression for open circles (black line).
not propagate to the soma to yield place-field activity. However, a spatially uniform signal that slightly depolarizes the soma can reveal this input. This gating of inputs, as opposed to just outputs, by somatic $V_m$ constitutes a novel mechanism for receptive fields. It also implies that integration of multiple inputs is gated by somatic $V_m$ (fig. S10).

These results are the opposite of those expected from standard models of cortical receptive fields (22, 23) and place cells (7–11). In these models, a neuron receives more excitatory synaptic input in response to the preferred stimulus, and this input is passively summed then compared with the AP threshold. Silent cells would have spatially tuned somatic $V_m$ hills of various amplitudes that do not reach threshold, and somatic depolarization would reduce the driving force and, thus, hill amplitude (23).

At the other extreme is a model in which synaptic inputs are uniformly distributed in stimulus space, and the neuron selectively amplifies a subset of them. This possibility is supported by recent in vivo work in visual cortex showing that input signals coding for multiple stimulus orientations are present in each neuron, regardless of its output tuning (24), and in vitro work showing that particular dendrites can propagate inputs to the soma more effectively than others (25) via dendritic spiking (15, 16, 25, 26).

Our results strongly support such nonlinear dendritic amplification mechanisms, regardless of whether synaptic inputs are uniformly distributed. In particular, in vitro work has shown that depolarizing the somatic (27, 28) or dendritic (29) $V_m$, can gate inputs in a thresholdlike manner. The lack of a hill or increased fluctuations at resting $V_m$ makes unlikely a purely somatic locus of amplification. Rather, somatic depolarization may (i) shift the dendritic $V_m$ closer to the activation range of voltage-gated conductances or deactivate hyperpolarization-activated currents (increasing $R_S$ locally), and thus amplify spatially tuned responses and trigger dendritic spikes, or (ii) simply push the peak response in the dendrite above the dendritic spike threshold. Or instead, depolarization may act to let already existing dendritic spikes propagate to the soma (29).

These findings have important implications for place cells, spatial memory, and hippocampal-dependent memory in general. In novel environments, inhibitory neuron activity drops (30), which could depolarize the somatic baseline $V_m$ of a silent cell and produce place fields (30, 31) without requiring synaptic plasticity. Neuron modulation could also depolarize or lower the threshold baseline $V_{m,\text{gate}}$ described here. Furthermore, already existing place cells could be those neurons whose $V_{m,\text{gate}}$ is below their baseline $V_m$. That is, (baseline $V_m - V_{m,\text{gate}}$) could reflect intrinsic excitability, with depolarization compensating for lower excitability in silent cells. Alternatively, place cell inputs could differ or be arranged differently on the dendritic tree, although this would not easily explain preexposure differences in excitability (14). Finally, the explicit demonstration that most CA1 pyramidal neurons, even originally silent ones, can be place cells in a given maze suggests that the role of CA1 is not only to create spatial tuning, but to choose which subset of neurons should be active within a specific environment. The exclusively input-based models of place cells (7–11) could work as described but with an independent, excitability-based “AND” gate added. The distribution of excitability levels across the population would then determine which cells would represent a new item or environment in memory (14, 32). Moreover, the gating machinery would be a potential locus of plasticity for long-term storage (25–29).

References and Notes

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Neural Representations of Location Composed of Spatially Periodic Bands
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The mammalian hippocampal formation provides neuronal representations of environmental location, but the underlying mechanisms are poorly understood. Here, we report a class of cells whose spatially periodic firing patterns are composed of plane waves (or bands) drawn from a discrete set of orientations and wavelengths. The majority of cells recorded in parasebulcular and medial entorhinal cortices of freely moving rats belonged to this class and included grid cells, an important subset that corresponds to three bands at 60° orientations and has the most stable firing pattern. Occasional changes between hexagonal and nonhexagonal patterns imply a common underlying mechanism. Our results indicate a Fourier-like spatial analysis underlying neuronal representations of location, and suggest that path integration is performed by integrating displacement along a restricted set of directions.

Grid cells represent the animal’s location by firing in a hexagonally symmetric array of locations covering the entire environment (1). These cells are found in the medial entorhinal cortex (mEC) (1, 2) and in pre- and parasubiculum (PaS) (2). This spatially periodic firing may provide the spatial metric for the hippocampal cognitive map (3–6). The hexagonal symmetry raises important questions: Is this an entirely unique pattern or one end of a continuum? Is this pattern required for spatial representation, or does it reflect properties such as stability (7) or coding efficiency (8)? We recorded 351 cells from superficial layers (II and III) of the medial part of dorsocaudal mEC (five implants) and adjacent PaS (two implants) in seven adult male rats (fig. S1) while they foraged for food in a square enclosure (1.69 m²). Many of these showed the regular hexagonal