Manipulating Hippocampal Place Cell Activity by Single-Cell Stimulation in Freely Moving Mice

Graphical Abstract

Highlights

- Juxtacellular stimulation of single hippocampal neurons in freely moving mice
- Stimulation in silent neurons can induce place fields
- Stimulation in single place cells can induce place field remapping

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In Brief

Place cells can serve as a readout of hippocampal memory. Diamantaki et al. show that the activity of single place cells can be rapidly modified by single-cell stimulation in freely moving mice. This finding provides insights into the cellular mechanisms that support the rapid reorganization of hippocampal place maps.

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Manipulating Hippocampal Place Cell Activity by Single-Cell Stimulation in Freely Moving Mice

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SUMMARY

Learning critically depends on the ability to rapidly form and store non-overlapping representations of the external world. In line with their postulated role in episodic memory, hippocampal place cells can undergo a rapid reorganization of their firing fields upon contextual manipulations. To explore the mechanisms underlying such global remapping, we juxtacellularly stimulated 42 hippocampal neurons in freely moving mice during spatial exploration. We found that evoking spike trains in silent neurons was sufficient for creating place fields, while in place cells, juxtacellular stimulation induced a rapid remapping of their place fields to the stimulus location. The occurrence of complex spikes was most predictive of place field plasticity. Our data thus indicate that plasticity-inducing stimuli are able to rapidly bias place cell activity, simultaneously suppressing existing place fields. We propose that such competitive place field dynamics could support the orthogonalization of the hippocampal map during global remapping.

INTRODUCTION

Neural circuits are thought to encode information via rapid and long-lasting modifications of synaptic weights. According to the Hebbian learning theory (Hebb, 1961), inputs that persistently take part in firing of a postsynaptic neuron become potentiated. This type of plasticity is referred to as input specific (or homosynaptic), because it critically depends on the near-simultaneous co-activation of pre- and postsynaptic neurons with specific temporal ordering rules (Markram et al., 1997; Abbott and Nelson, 2000; Bittner et al., 2017). Experimentally, these mechanisms have been extensively studied in the hippocampus, a brain region that has been strongly implicated in learning and memory. After the discovery of associative learning rules (Bliss and Lomo, 1973), it was found that the input activation should be strong and exceed a certain threshold to induce plastic changes (cooperativity rule) (McNaughton et al., 1978). Episodes of strong postsynaptic activity can also lead to concomitant weakening (or de-potentiation) of synapses that were not active during the induction, a process known as heterosynaptic plasticity (Lynch et al., 1977; Chistiakova et al., 2014). It has been shown that both forms of plasticity (homo- and heterosynaptic) can occur simultaneously on the same neuron (Volgushev et al., 1997; Lee et al., 2012; Chen et al., 2013), thus playing an important role in supporting synaptic competition (Miller, 1996; Elliott and Shadbolt, 2002; Finelli et al., 2008) and in preventing the saturation of synaptic weights (Kempter et al., 2001; Wu and Yamaguchi, 2006). Thus, the bidirectional regulation of synaptic weights via homo- and heterosynaptic plasticity mechanisms, operating on the same scale, is necessary for supporting learning within hippocampal circuits.

The seminal discovery of place cells (O’Keefe and Dostrovsky, 1971)—neurons that become active in a specific location of the environment visited by the animal—has provided fundamental insights into hippocampal function during natural behavior. During spatial exploration, the collective activity of place cells forms a map-like representation of the external space. These maps form rapidly during exploration of a novel environment (Hill, 1978; Wilson and McNaughton, 1993; Frank et al., 2004; Cohen et al., 2017) and remain stable over many consequent exposures to the same environment (Muller and Kubie, 1987; Frank et al., 2004; Dupret et al., 2010). However, when exposed to a different context, place cells have the capability of undergoing rapid reorganization of their firing fields so that a new spatial map is instantiated collectively (Muller and Kubie, 1987; Muller et al., 1991). By this process (known as global remapping), a large number of orthogonal maps can be created within the hippocampus (Alme et al., 2014; Rich et al., 2014) thus satisfying the high-capacity requirements of a memory network (Battaglia and Treves, 1998; Colgin et al., 2008).

The capability of rapidly forming orthogonal representations is therefore crucial for memory and hippocampal function. Studies have shown that place field activity can emerge from silent neurons by manipulations of activity and/or excitability (Lee et al., 2012; Bittner et al., 2015, 2017; Diamantaki et al., 2016a) and that manipulations of upstream entorhinal inputs (Miao et al., 2015; Rueckemann et al., 2016; Kanter et al., 2017) or local place cell activity (Schoenenberger et al., 2016; Trouche et al., 2016) can induce hippocampal remapping. However, the cellular mechanisms underlying the rapid
reorganization of spatial activity in hippocampal place cells have remained largely unexplored.

Here we sought to address this question by employing juxtacellular stimulation of individual hippocampal neurons in the intact system, i.e., in freely moving mice engaged in spatial exploration. We provide evidence that juxtacellular stimulation in single place cells can lead to the rapid remapping of their place fields to the stimulus location. This input-based mechanism might support the rapid reorganization of the place map during global remapping.

RESULTS
Juxtacellular Recording Procedures in Freely Moving Mice
To record and stimulate single hippocampal neurons in freely moving mice, we adapted our juxtacellular procedures—developed and optimized in rats (Tang et al., 2014)—to mice. Animals were implanted with miniaturized components, including a head post, micromanipulator base, recording chamber, and connector (Figures 1A and 1B; Figures S1A and S1B), whose size and total weight (~1.4 g) were reduced to fit within the typical range of extracellular implants for mice (Jiang et al., 2017). Compared to the components previously used for rats (Tang et al., 2014; Diamantaki et al., 2016a, 2016b), the fully assembled recording implant contained a more compact micromanipulator-base assembly and a smaller head stage (Figures 1A and 1B; Figures S1A and S1B). During unrestrained behavior, the weight of the recording assembly was offset by a counterbalance system (see Supplemental Information for details).

We then employed juxtacellular recording procedures to monitor the activity of single neurons in the dorsal hippocampus (CA1 and CA3 subfields) while mice explored a familiar circular arena. Figures 1C–1H show two representative recordings from an identified CA1 pyramidal neuron (Figures 1C–1E) and an identified CA3 pyramidal cell (Figures 1F–1H), both of which displayed spatially localized spiking patterns (Figures 1D and 1G), a defining signature of place cell activity. Altogether, we recorded the activity of 87 hippocampal neurons during spatial exploration. In line with previous extracellular studies (Wilson and McNaughton, 1993; Lee et al., 2004; Leutgeb et al., 2004; Preston-Ferrer and Burgalossi, 2017), most of these active cells displayed spatially localized activity (~60%; 53 of 87 active neurons classified as place cells) (see details in Supplemental Information), and the firing fields of the place cell population evenly covered the available space (Figure 1I). All neurons included in the present study displayed low firing rates (<10 Hz; average firing rate = 2.33 ± 2.40 Hz; n = 87) and often fired short bursts of action potentials (referred to as complex spikes) (average burst index = 0.13 ± 0.12; n = 87)—features classically associated with principal cell identity (O’Keefe and Dostrovsky, 1971; Ranck, 1973). Cell identification by juxtacellular labeling confirmed these standard electrophysiological features.

Figure 1. Juxtacellular Recordings and Identification of Single Hippocampal Neurons in Freely Moving Mice
(A) Individual implant components that are either cemented to (head post, connector, recording chamber, and micromanipulator base) or mounted on (head stage, micromanipulator, glass pipette, and silver-wire recording electrode) the mouse’s head before recording. The respective weights of the custom-made components are indicated. Scale bar, 1 cm.
(B) Schematic drawing of the fully assembled recording implant on the animal’s head.
(C) Reconstruction of the dendritic morphology of a CA1 pyramidal neuron, recorded in a freely moving mouse (recording shown in D). Sr, stratum radiatum; Pyr, stratum pyramidale; So, stratum oriens; Slm, stratum lacunosum moleculare.
(D) Spike-trajectory plots (top) and rate maps (bottom) for the neuron shown in (C). Spontaneous spikes (red dots) and maximal firing rates are indicated.
(E) Representative high-pass filtered spike trace for the recordings shown in (D).
(F–H) Same as in (C)–(E) except for an identified CA3 pyramidal neuron.
(I) Color-coded distribution of place fields for all place cells (n = 53). Each row represents the normalized firing rates relative to the linearized 1D projection of the circular arena. Cells are ordered according to their place field position along the linearized trajectory.
Figure 2. Single-Cell Stimulation Procedures in Freely Moving Mice

(A) Representative high-pass filtered voltage trace (top) showing the activity of a single neuron in response to a pulse-entrainment stimulation protocol (current trace in red, bottom). The intensity of the 200 ms square current pulses was adjusted online to reach the threshold necessary to evoke action potentials (from the ninth pulse onward in this representative example). Right, high magnification showing entrainment of spiking activity by the current pulses. Asterisks indicate stimulus artifacts, truncated for display.

(B) Representative high-pass filtered voltage trace (top) showing an evoked spike train, which outlasted the square current pulse (current trace in red, bottom). Right, high magnification showing the presence of complex spikes. Asterisks indicate stimulus artifacts, truncated for display.

(C) Boxplots showing evoked average firing rates and total number of spikes for pulse entrainment (n = 60) and evoked action potential trains (n = 23). Whiskers represent a 1.5 interquartile range. Outliers are shown as crosses.

classification criteria in that all identified neurons for which morphology could be assessed (15 of 22 identified neurons) were classified as pyramidal cells (see details in Supplemental Information).

Juxtacellular recordings in mice displayed a higher degree of mechanical stability compared to recordings performed in rats (Tang et al., 2014). In multiple occasions, it was possible to maintain a juxtacellular recording from a single neuron while releasing the animal from head fixation and transferring it to the behavioral arena. Figures S1C and S1E show a representative example in which a recording from a hippocampal neuron, established under head fixation, could be maintained while the animal was released, lifted, and gently placed into the behavioral arena. During exploration, the neuron displayed place cell activity (Figure S1C). The higher mechanical stability of juxtacellular recordings in mice also made it possible to transfer animals from one arena to another while sequentially monitoring the activity of the same neuron. This is shown in the representative recording in Figures S1D and S1F, in which a hippocampal neuron, which was largely silent in a familiar circular arena (only 3 spikes in 80.4 s; average firing rate = 0.037 Hz), displayed spatially localized activity in a novel square environment (Figure S1D). At the end of the recording, the neuron was labeled and identified as a deep CA1 pyramidal neuron (data not shown).

Altogether, these data indicate that juxtacellular recording procedures can be employed for monitoring the activity of hippocampal neurons in freely moving mice with a high degree of mechanical stability.

Juxtacellular Stimulation of Single Hippocampal Neurons during Spatial Exploration

Next, we tested whether hippocampal representations in mice engaged in unrestrained natural behavior (i.e., spatial exploration) can be modified by single-cell manipulations of spiking activity. To this end, we employed standard juxtacellular stimulation procedures, referred to as nanostimulation by previous authors (Houweling and Brecht, 2008; Houweling et al., 2010; Doron et al., 2014; Stüttgen et al., 2017), in which squared current pulses are delivered to the recorded neuron to elicit spikes (Figure 2) (see Supplemental Information for details). In line with previous work (Houweling et al., 2010), when applied to cortical neurons under anesthesia, this stimulation protocol enabled parametric control of evoked action potential number and frequency (as in Houweling et al., 2010; Doron et al., 2014) (data not shown). However, the same protocol led to less consistent entrainment of spiking activity in hippocampal cells during unrestrained behavior, possibly due to intrinsic cell-type differences and/or more variable loose-seal configurations compared to more mechanically stable preparations. In most cases (39 of 62 stimulations), it was possible to entrain the activity of single hippocampal neurons in freely moving mice so that evoked spikes were largely confined to the stimulation pulses (Figure 2A); however, in some cases (23 of 62 stimulations), longer spike trains were triggered that outlasted the stimulation pulse (Figure 2B). These evoked spike trains often contained bursts of action potentials, which appeared as complex spikes associated to underlying dendritic plateau potentials (Epsztein et al., 2011; Bittner et al., 2015). We will refer to these events as evoked complex spikes.

We then employed these stimulation procedures for evoking spikes in hippocampal neurons while animals were freely exploring a familiar circular arena. Stimulation-evoked spiking activity parameters (e.g., average firing rates and total number of spikes) (Figure 2C) varied across stimulations during both pulse entrainment (evoked firing rates, median = 29.5 Hz, interquartile range = 23.2 Hz; total number of spikes, median = 44, interquartile range = 54) and evoked action potential (AP) trains (average firing rates, median = 22.5 Hz, interquartile range = 25.1 Hz; total number of spikes, median = 66, interquartile range = 202). In line with observations from freely moving rats (Diamantaki et al., 2016a), we found that juxtacellular stimulation was able to prime the rapid appearance of
place fields in previously silent cells. This is shown in the representative recording in Figures 3A and 3B, in which juxtcacellular stimulation of a silent neuron was sufficient for eliciting spatially localized activity at the stimulus location. Altogether, 22 silent neurons were stimulated at randomly chosen locations in freely moving mice, and in ~32% of them (7 of 22), spatial activity could be induced by juxtcacellular stimulation (see additional examples in Figure 3C). Following stimulation, spontaneous activity at the stimulus location appeared rapidly (average latency = 55.6 ± 53.0 s) and often persisted until the end of the recordings (Figure 3B). This indicates that in line with previous evidence (Lee et al., 2012; Bittner et al., 2015; Diamantaki et al., 2016a), single-cell stimulation in silent hippocampal neurons can be sufficient for inducing the rapid appearance of place activity during unrestrained natural behavior.

Next, we tested the effect of out-of-field stimulations in single place cells. To this end, we evoked spikes outside place fields by juxtcacellular stimulation (n = 20 stimulated neurons) (Figure 4) at an average distance of 46.5 ± 8.9 cm from the original place field. We found that in a consistent fraction of the stimulated cells (~45%; 9 of 20) place activity could be rapidly modified by juxtcacellular stimulation. In most cases (n = 7), juxtcacellular stimulation induced a remapping of the place field to the stimulus location (Figures 4A and 4B). That is, the original field disappeared (or became considerable weaker), while a new activity cluster emerged at the stimulus location (see also cell identifier [id] 25 and cell id38 in Figure 4C). In two other cases, we observed the appearance of an additional field (see cell id14 in Figure 4C). To quantify stimulation effects, we computed pixel-by-pixel correlations between rate maps before and those after stimulation. Rate-map correlations were bimodally distributed (Figure 4D), with the remapping group displaying low correlations (<0.05; n = 7) and the no-effect cells displaying high correlations (>0.62; n = 13), the exception being the two neurons in which an additional field was induced, which retained relatively high correlations (0.64 and 0.62) due to the persistence of the original place field (arrow in Figure 4D). At the population level, including all stimulated place cells (n = 20), single-cell stimulation resulted in a significant decrease of activity within the original place field (before, 8.3 ± 8.7 Hz; after, 5.9 ± 8.07 Hz; p = 0.02; Wilcoxon signed-rank test), while an increase was observed at the stimulus location (before, 0.09 ± 0.15 Hz; after, 0.99 ± 1.65 Hz; p = 0.009; Wilcoxon signed-rank test) (Figure 4E). Average firing rates before and after stimulation were not significantly different (before, 1.7 ± 1.3 Hz; after, 2.0 ± 2.0 Hz; p = 0.55; Wilcoxon signed-rank test), indicating that single-cell stimulation induced a redistribution of spatial firing rather than a global change in activity levels.

As for the induction of place fields in silent neurons (Figure 3), modifications of place activity were also fast (average latency, 99.3 ± 142.9 s) and often persisted until the end of the recording (Figure 4B). In one case, in which we could test the same neuron in the circular arena, in a square maze, and then back to the circular arena (Figure S2), we observed that the induced place field was still expressed on the second exposure to the circular arena (Figure S2D). However, in general, the limited recording durations (344 ± 485 s) and total number of laps (13.8 ± 11.2) prevented rigorous assessment of long-term effects of juxtcacellular stimulation.

Lastly, we asked whether evoked spike-train parameters could be used to predict stimulation effects. In line with previous work (Bittner et al., 2015), we found that in 11 of 16 cells in which juxtcacellular stimulation induced a place field (Figure 3) or place field remapping (Figure 4), complex spikes were observed. This proportion was significantly higher than in neurons without stimulation effects (3 of 26; p = 0.0004; Fisher’s exact test). To confirm this observation, we used regularized logistic regression with recursive feature elimination (see Supplemental Information) and found that the presence of complex spikes within evoked spike trains was most predictive of a stimulation effect (Figure S3). This observation strengthens the view that evoked complex spikes are key plasticity-inducing events that can
bias spatial activity—both in silent and in place cells—during spatial exploration.

**DISCUSSION**

In the present work, we show that juxtacellular stimulation of single hippocampal neurons can be sufficient for biasing neuronal output to the stimulus location. In line with previous evidence from head-fixed animals (Bittner et al., 2015) and freely moving animals (Diamantaki et al., 2016a), we show that spatially localized suprathreshold activation can recruit silent hippocampal neurons into the coding population. Overall, the probability of inducing place fields by juxtacellular stimulation in silent pyramidal neurons was relatively low (≈32%). Although stimulation efficiencies could be higher in a novel environment (Diamantaki et al., 2016a), this was most likely due to the large variability in the evoked activity parameters (Figure 2C). Based on correlative evidence (Figure S3) and previous work (Bittner et al., 2015, 2017), we envision the possibility of precisely controlling the occurrence of complex spikes by juxtacellular stimulation resulting in higher efficiency in creating place fields (Figure 3) or inducing place field remapping (Figure 4) during unrestrained behavior.

Place fields can be virtually induced at any location visited by the animal (Figures 3 and 4), which indirectly suggests that place cells might receive a range of spatially tuned inputs, spanning the entire available space. This hypothesis is in line with intracellular studies (Lee et al., 2012; Bittner et al., 2015) and imaging studies (C. Domnisoru and D.W. Tank, 2017, Soc. Neurosci., abstract) that point to a broad distribution of input tuning in individual place cells. Such a random functional connectivity scheme would confer a high degree of flexibility in neural coding, enabling place cells to rapidly tune their output to changing subsets of potentiated inputs.

The most important finding of this study is perhaps the observation that individual place cells can undergo fast remapping in response to single-cell stimulation (Figure 4). Even under conditions in which the hippocampal map is thought to be most stable (i.e., in a familiar environment), the firing location of individual place cells can be dynamically biased by suprathreshold activation. Previous work has shown that hippocampal remapping can be triggered by manipulations of upstream inputs (Miao et al., 2015; Rueckemann et al., 2016; Kanter et al., 2017) and can occur in response to optogenetic-mediated inhibition of place cell activity (Schoenenberger et al., 2016; Trouche et al., 2016). Our data add to this work by showing that strong spatially localized stimuli are able to rapidly switch place field location in individual place cells. Mechanistically, this is consistent with a stimulation-induced potentiation of the spatial inputs active around the stimulus location (via homosynaptic plasticity) (Bittner et al., 2015, 2017) and a concomitant depotentiation of place-related activity (via heterosynaptic plasticity). This fast form of place field plasticity appears to be ideally suited for the instantiation of novel spatial maps during global remapping by ensuring that the emergence of novel place fields is accompanied by a concomitant weakening of the previous activity patterns. Such a mechanism would be particularly suited under conditions in which existing representations have to be flexibly

![Figure 4. Out-of-Field Juxtacellular Stimulation of Hippocampal Place Cells Can Modify Spatial Tuning](image-url)
adapted to changing behavioral or contextual contingencies (e.g., Fyhn et al., 2002; Anderson and Jeffery, 2003; Dupret et al., 2010; Spiers et al., 2015). We envision that a new set of upstream inputs, if sufficiently strong to drive dendritic plateau potentials, could be sufficient for resetting place cell output and ensuring the rapid emergence of a new representation. Thus, the output of hippocampal neurons might be determined by the competitive interaction between inputs' strengths via a winner-takes-all mechanism.

In summary, we show that much like place cell remapping under natural conditions, juxtacellular stimulation can promote a rapid switch of place field location in single neurons. This cell-autonomous mechanism constrains current models of hippocampal remapping in that a transient redistribution of input strengths, rather than a global reorganization of inputs, might be sufficient for biasing the spatial output of hippocampal neurons. Methodologically, we show that juxtacellular techniques can also be employed in freely moving mice (Figure 1), offering the possibility of combining single-cell identification and stimulation with mouse genetics. This single-cell approach complements current virtual reality-based methods, by making it possible to probe the plasticity rules of spatial representations during natural multisensory-guided spatial behaviors.

**EXPERIMENTAL PROCEDURES**

**Animals**

All experimental procedures were performed according to the German guidelines on animal welfare under the supervision of local ethics committees. Surgery and implantation on wild-type C57BL/6J mice (males, >2 months old; Charles River) were performed following previously published procedures (Tang et al., 2014).

**Juxtacellular Recordings**

Juxtacellular recordings, signal acquisition and processing, and animal tracking were essentially performed as previously described (Tang et al., 2014; Diamantaki et al., 2016a), as were juxtacellular stimulation of single neurons (referred to as nanostimulation) (Houweling and Brecht, 2008; Houweling et al., 2010; Doron et al., 2014) and single-cell labeling (Pinault, 1996; Preston-Ferrer et al., 2016).

**Statistical Analysis**

Statistical significance was assessed by Wilcoxon signed-rank test with 95% confidence intervals. Logistic regression classification with L2 regularization was performed using the glmnet toolbox for Python. All data are presented as mean ± SD unless indicated otherwise.

Detailed methods can be found in Supplemental Information.

**SUPPLEMENTAL INFORMATION**

Supplemental Information includes STAR Methods and three figures and can be found with this article online at https://doi.org/10.1016/j.celrep.2018.03.031.

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**AUTHOR CONTRIBUTIONS**

A.B. and P.P.-F. conceived, designed, and supervised the study. A.B., M.D., and S.C. performed experiments. M.D., K.N., R.Z., and S.C. analyzed data. P.P.-F. analyzed anatomical data. S.L. and P.B. performed the classification analysis. A.B. wrote the manuscript, with input from all authors.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.

**REFERENCES**

Abbott, L.F., and Nelson, S.B. (2000). Synaptic plasticity: taming the beast. Nat. Neurosci. 3 (Suppl.), 1178–1183.

Alme, C.B., Miao, C., Jezek, K., Treves, A., Moser, E.I., and Moser, M.-B. (2014). Place cells in the hippocampus: eleven maps for eleven rooms. Proc. Natl. Acad. Sci. USA 111, 18428–18435.

Anderson, M.I., and Jeffery, K.J. (2003). Heterogeneous modulation of place cell firing by changes in context. J. Neurosci. 23, 8827–8835.

Battaglia, F.P., and Treves, A. (1998). Stable and rapid recurrent processing in realistic autoassociative memories. Neural Comput. 10, 431–450.

Bittner, K.C., Grienberger, C., Vaidya, S.P., Milstein, A.D., Macklin, J.J., Suh, J., Tonegawa, S., and Magee, J.C. (2015). Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. Nat. Neurosci. 18, 1133–1142.

Bittner, K.C., Milstein, A.D., Grienberger, C., Romani, S., and Magee, J.C. (2017). Behavioral time scale synaptic plasticity underlies CA1 place fields. Science 357, 1033–1036.

Bliss, T.V., and Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232, 331–356.

Chen, J.-Y., Lonjers, P., Lee, C., Chistiakova, M., Volgushev, M., and Bazhenov, M. (2013). Heterosynaptic plasticity prevents runaway synaptic dynamics. J. Neurosci. 33, 15915–15929.

Chistiakova, M., Bannon, N.M., Bazhenov, M., and Volgushev, M. (2014). Heterosynaptic plasticity: multiple mechanisms and multiple roles. Neuroscientist 20, 483–498.

Cohen, J.D., Bolstad, M., and Lee, A.K. (2017). Experience-dependent shaping of hippocampal CA1 intracellular activity in novel and familiar environments. eLife 6, e23040.

Colgin, L.L., Moser, E.I., and Moser, M.-B. (2008). Understanding memory through hippocampal remapping. Trends Neurosci. 31, 469–477.

Diamantaki, M., Frey, M., Preston-Ferrer, P., and Burgalossi, A. (2016a). Priming spatial activity by single-cell stimulation in the dentate gyrus of freely moving rats. Curr. Biol. 26, 536–541.

Diamantaki, M., Frey, M., Berens, P., Preston-Ferrer, P., and Burgalossi, A. (2016b). Sparse activity of identified dentate granule cells during spatial exploration. eLife 5, e20252.

Doron, G., von Hemmending, M., Schlattmann, P., Houweling, A.R., and Brecht, M. (2014). Spiking irregularity and frequency modulate the behavioral report of single-neuron stimulation. Neuron 81, 653–663.

Dupret, D., O’Neill, J., Pleydell-Bouverie, B., and Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. Nat. Neurosci. 13, 995–1002.
Miller, K.D. (1996). Synaptic economics: competition and cooperation in synaptic plasticity. Neuron 17, 371–374.
Muller, R.U., and Kubie, J.L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. 7, 1951–1968.
Muller, R.U., Kubie, J.L., Bostock, E., Taube, J., and Quirk, G. (1991). Spatial firing correlates of neurons in the hippocampal formation of freely moving rats. In Brain and Space, J. Paillart, ed. (Oxford University Press), pp. 296–333.
O’Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 34, 171–175.
Pinaud, D. (1996). A novel single-cell staining procedure performed in vivo under electrophysiological control: morpho-functional features of juxtacellularly labeled thalamic cells and other central neurons with biocytin or Neurobiotin. J. Neurosci. Methods 65, 113–136.

Preston-Ferrer, P., and Burgalossi, A. (2017). Linking neuronal structure to function in rodent hippocampus: a methodological perspective. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2732-7

Preston-Ferrer, P., Coletta, S., Frey, M., and Burgalossi, A. (2016). Anatomical organization of presubicular head-direction circuits. eLife 5.

Ranck, J.B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. Exp. Neurol. 41, 461–531.

Rich, P.D., Liaw, H.-P., and Lee, A.K. (2014). Place cells. Large environments reveal the statistical structure governing hippocampal representations. Science 345, 814–817.

Rueckemann, J.W., DiMauro, A.J., Rangel, L.M., Han, X., Boydens, E.S., and Eichenbaum, H. (2016). Transient optogenetic inactivation of the medial entorhinal cortex biases the active population of hippocampal neurons. Hippocampus 26, 246–260.

Schoenberger, P., O’Neill, J., and Csicsvari, J. (2018). Activity-dependent plasticity of hippocampal place maps. Nat. Commun. 7, 11824.

Spiers, H.J., Hayman, R.M., Jovalekic, A., Marozzi, E., and Jeffery, K.J. (2015). Place field repetition and purely local remapping in a multicompartiment environment. Cereb. Cortex 25, 10–25.

Stüttgen, M.C., Nonkes, L.J.P., Geis, H.R.A.P., Tiesinga, P.H., and Houweling, A.R. (2017). Temporally precise control of single-neuron spiking by juxtacellular nanostimulation. J. Neurophysiol. 117, 1363–1378.

Tang, Q., Brecht, M., and Burgalossi, A. (2014). Juxtacellular recording and morphological identification of single neurons in freely moving rats. Nat. Protoc. 9, 2369–2381.

Trouche, S., Perestenko, P.V., van de Ven, G.M., Bratley, C.T., McNamara, C.G., Campo-Urriza, N., Black, S.L., Reijmers, L.G., and Dupret, D. (2016). Recoding a cocaine-place memory engrain to a neutral engrain in the hippocampus. Nat. Neurosci. 19, 564–567.

Volgushev, M., Voronin, L.L., Chistiakova, M., and Singer, W. (1997). Relations between long-term synaptic modifications and paired-pulse interactions in the rat neocortex. Eur. J. Neurosci. 9, 1656–1665.

Wilson, M.A., and McNaughton, B.L. (1993). Dynamics of the hippocampal ensemble code for space. Science 261, 1055–1058.

Wu, Z., and Yamaguchi, Y. (2006). Conserving total synaptic weight ensures one-trial sequence learning of place fields in the hippocampus. Neural Netw. 19, 547–563.