Untethered firing fields and intermittent silences: Why grid-cell discharge is so variable

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Abstract
Grid cells in medial entorhinal cortex are notoriously variable in their responses, despite the striking hexagonal arrangement of their spatial firing fields. Indeed, when the animal moves through a firing field, grid cells often fire much more vigorously than predicted or do not fire at all. The source of this trial-to-trial variability is not completely understood. By analyzing grid-cell spike trains from mice running in open arenas and on linear tracks, we characterize the phenomenon of "missed" firing fields using the statistical theory of zero inflation. We find that one major cause of grid-cell variability lies in the spatial representation itself: firing fields are not as strongly anchored to spatial location as the averaged grid suggests. In addition, grid fields from different cells drift together from trial to trial, regardless of whether the environment is real or virtual, or whether the animal moves in light or darkness. Spatial realignment across trials sharpens the grid representation, yielding firing fields that are more pronounced and significantly narrower. These findings indicate that ensembles of grid cells encode relative position more reliably than absolute position.

KEYWORDS
entorhinal cortex, excess variability, firing-field jitter and drift, grid cell, noise correlation, overdispersion, spatial navigation, trial-to-trial variability, tuning curve, zero inflation

1 INTRODUCTION

Path recall and path finding are crucial skills, yet the neurons that represent space in the mammalian brain are surprisingly variable in their discharge during spatial navigation, as first shown by Fenton and Muller (1998) for place cells. While grid cells in the medial entorhinal cortex (MEC), for instance, tend to fire at specific locations in space that map out a hexagonal grid (Figure 1a), close inspection of individual trajectories through a particular firing field (Figure 1b) reveals that a grid cell will often fire no spikes when the animal passes through the field; in other instances, the cell will fire many more spikes than expected from Poisson statistics. A grid cell's hexagonal spatial firing-rate map by itself does not capture these highly variable spike count statistics.

Hippocampal place cells, which have only a few isolated firing fields, also exhibit strongly fluctuating firing (Fenton & Muller, 1998). A number of explanations for place-cell spike-count variability have been proposed: neuronal sensitivity to task, action, or sensory variables that are unrelated to spatial location, changes in selective spatial attention (Fenton et al., 2010), flickering between multiple maps of space (Jezek, Henriksen, Treves, Moser, & Moser, 2011), or "knowledge-guided fluctuations" (Jackson & Redish, 2007; Kelemen & Fenton, 2016; Prerau, Lipton, Eichenbaum, & Eden, 2014). Another potential source of variability in neurons with spatial selectivity is error accumulation during path integration (Hardcastle, Ganguli, & Giocomo, 2015).

To study the origin of grid-cell variability, we analyze data from experiments in rats and mice moving in two-dimensional arenas and in...
mice on real and virtual linear tracks. We show that two distinct modes are necessary to explain the trial-to-trial variability of grid-cell activity. In one mode, cells fire stochastically when the animal is in a firing field; in the other mode, cells remain absolutely silent. In addition, grid cells’ firing fields, over time, drift in space, as seen across repeated experimental trials on the linear track. These findings provide a mechanistic explanation for the excess variability in grid-cell activity.

2 | RESULTS

2.1 | Grid cells are silent much more often than predicted by the firing-rate map

For spatially modulated neurons, such as place cells and grid cells, firing-rate maps allow one to calculate the expected number of spikes along any trajectory through the animal’s environment. The true number of spikes fired, however, will vary from run to run (Figure 1a,b), even if the animal takes the same path (Figure 2). To better understand this trial-to-trial variability, we analyzed multiple data sets (Domnisoru, Kinkhabwala, & Tank, 2013; Fyhn, Hafting, Treves, Moser, & Moser, 2007; Fyhn, Molden, Witter, Moser, & Moser, 2004; Pérez-Escobar et al., 2016; Sargolini et al., 2006; Stensola et al., 2012). By z-scoring the spike counts, we found that the observation by Fenton et al. (2010) on excess variability in hippocampal CA1 spike trains extends to recordings in MEC of rats and mice, as shown in Figure S1. The average z-score across all grid cells in rat was $\sigma_z^2 = 6.62 \pm 0.27 (n = 199)$, whereas mouse grid cells had a $\sigma_z^2 = 7.63 \pm 0.95 (n = 41)$. The difference of the average variability across species was not significant (Two-tailed Welch-test for equal population means: $w = 1.02, p = .31$).

To assess the spike-count statistics of MEC grid cells in mice at a more detailed level, we segmented mouse trajectories such that...
the expected number of spikes in each segment was the same (cf. Methods). To reach a fixed number of spikes, these trajectory segments covered time intervals of varying lengths. Such a segmentation requires no assumption that the firing fields have a grid-like structure, or even that distinct firing fields exist. We then constructed histograms of the spike counts on the trajectory segments.

If the spike-count statistics are determined solely by a time-varying firing rate, then the resulting distribution should be Poisson, for which the spike count variance is equal to the mean spike count (Figure 1c).

For grid cells recorded in two-dimensional arenas, only 5% (n = 138) had spike-count distributions that were consistent with Poisson spiking ($\chi^2$ test: $df = k - 2$, where $k$ is the number of categories with expected counts larger than 5, $p < 0.05$). Instead, these distributions were frequently bimodal and strongly skewed, as shown in Figure 1d,e. In fact, many times the spike count was zero; cells remained completely inactive much more frequently than expected from the Poisson null hypothesis.

Bimodal spike-count distributions can be described by mixture models, in which several distributions are combined. A particularly simple mixture, which is widely used outside of neuroscience (Greene, 1994; Lambert, 1992), invokes the concept of zero-inflation (ZI). For instance, a Geiger counter typically records a Poisson distribution of radioactive decay events. Now, if the Geiger counter intermittently fails, it would report an inflated number of zero radioactive events. Such a process would then be an example of ZI, which generally involves a secondary stochastic process.

In short, the statistical model of ZI works as follows: draw a Bernoulli variable for every sample with probability $\alpha$ to decide whether the spike count $s$ is set to zero or whether the count will be drawn from some standard spike-count distribution with expected value $\mu = h_s i \geq 0$. Under ZI, observing a spike count of zero can have two causes: the stochastic state corresponds to the ”zero regime” or the standard distribution produced a zero count. As a consequence, a grid cell might not fire at all even though the animal is at the center of a grid field for this cell. On the other hand, between firing fields, the firing rate will be close to zero, so the spike count will likely be zero, regardless of whether ZI is present.

Intermittent firing of grid cells also occurs when the animal runs on a linear track. Figure 2 shows the same grid cell recorded in two-dimensional and one-dimensional environments. Passages through a firing field in which, contrary to expectations, the cell failed to fire are highlighted by dashed black lines (Figure 2c,g). In both environments, the bin for zero spikes stands out in the spike-count histogram (Figure 2d,h).

The degree of ZI in the grid-cell spike count can be measured by an index $Z_{\text{Pois}}$, as introduced by Puig and Valero (2006):

$$Z_{\text{Pois}} = 1 + \ln(p_0) / \mu$$

where $\mu$ is the empirical mean spike count and $p_0$ is the frequency of observing zero counts.
This heuristic measure supposes that the null hypothesis for the spike-count statistics is Poisson. Given that the Poisson probability of observing zero spike counts is \( \exp(-\mu) \), the logarithm in the equation above is \( \ln(p_0) = -\mu \), and hence \( Z_{\text{idx}} = 0 \) for Poisson neurons. If there are more zeros, then \( Z_{\text{idx}} \) becomes positive.

One hundred and thirty one of 136 grid cells recorded by Pérez-Escobar et al. in the open field had a positive \( Z_{\text{idx}} \) (mean = 0.52 ± 0.01, which deviates significantly from zero based on a t-test: \( t = 44.66, p < 10^{-10}, N = 136 \)). The \( Z_{\text{idx}} \) is a sensitive, model-independent, empirical measure for the presence of ZI, which is calibrated against the Poisson null hypothesis. It makes no assumptions about the statistics of spiking (other than that the frequency of zero spikes should not be zero).

Given the finding of significant ZI, we specifically tested whether zero-inflated Poisson (ZIP) models describe the spike count data better than Poisson models. We fitted the Poisson and the ZIP model to the spike-count distributions and compared these models using a likelihood-ratio test. The likelihood-ratio test penalizes ZIP for having one more parameter than Poisson, namely the probability \( \alpha \) of being in the zero regime (see Supporting Information S1). Unlike \( Z_{\text{idx}} \), the probability \( \alpha \) is estimated using the maximum likelihood method and is specific to the underlying model for the spike count statistics. The ZIP model had a higher likelihood than the Poisson model for 52 of 65 pure grid cells (80%, \( p < .001, df = 1 \)) in the data set, and for 67 of the 76 grid cells with conjunctive speed, border or head direction tuning (88%, \( p < .001, df = 1 \)). The ZIP model is also a better match for most spatially modulated neurons that are not grid cells (69%, \( p < .001, df = 1 \)). To confirm the significance of these results, we numerically simulated inhomogeneous Poisson processes based on the animals’ trajectories through the firing rate maps. For these simulated data, we asked whether ZIP could accidentally have a higher likelihood than Poisson. ZIP, though, almost never had a higher likelihood—Poisson was preferred with \( p < .001, (df = 1) \) when the underlying statistics were truly Poisson.

We sought to rule out one trivial explanation for ZI. In rodents, the spike trains of spatially modulated cells in the entorhinal cortex and hippocampus are coupled to a 6–12 Hz theta rhythm. When the animal stops moving, the theta rhythm ceases, and cells reduce their rate of firing. To test whether pauses in the animal’s movement could explain pauses in grid cell spiking, we divided the data into segments corresponding to different speeds of the animal. Significant ZI was found in all speed ranges (Supplemental Figure S2A).

### 2.2 ZI on linear tracks is predicted by grid-cell behavior in open fields

In the experiments of Pérez-Escobar et al. (2016), mice were put on an 80 cm long linear track after the grid cells had first been recorded in a 70 × 70 cm² square box. The linear track experiments permit corroboration of ZI as a phenomenon in a context with less variation in the animal’s speeds and one less degree of freedom for movement. We, therefore, estimated the cells’ probability of being in the “zero-firing” state on the linear track and compared these estimates to ones derived from the open-field experiments. Indeed, cells that had a high probability \( \alpha \) of being in the “zero-firing” state in the open field tended to have a high value of \( \alpha \) on the linear track, too, independently of the running direction and light/darkness context of the track experiments (\( r = 0.40 \pm 0.04, p < .005 \), across all contexts, see Figure 3a for an example from a specific context). Figure S3 details

![Figure 3](https://example.com/figure3.png)

**Figure 3** In the experiments of Pérez-Escobar et al. (2016), mice first navigated in an open field (2D) before they ran back and forth on a linear track in light or darkness. a, The ZI parameter \( \alpha \) in 1D is predicted by its value measured in the preceding 2D session. The solid line depicts the linear regression for \( \alpha \) measured in context l2-right, rightward runs in the light (condition 2), against the value measured in the 2D arena (\( r = 0.40, p < .001 \)). b, The proportion of excess zero counts remains similar across contexts and running directions. In particular, runs in darkness lead to similar ZI measures as runs in light. The solid line depicts the linear regression for \( \alpha \) measured in l2-right (as in [a]) against \( \alpha \) measured in context d-left, corresponding to leftwards runs in the darkness (\( r = 0.46, p < .01 \)). This particular combination of contexts yielded the weakest correlation compared to other combinations of lighting context and running direction. The other comparisons are shown in Supplemental Figure S3.
the correlations in $\alpha$ on the linear track and the open field on a context-by-context basis.

The value of $\alpha$ on the linear track was also correlated across different running directions and light contexts (average linear correlation across all contexts $r = 0.68 \pm 0.03$, $p < .01$; Figure 3b). This shows the data with the weakest correlation of the six contexts, $r = 0.46$, $p < .01$.

The ZI probability $\alpha$ did not differ between runs toward the right and the left end of the track (median = 0.13 ± 0.01 vs. 0.14 ± 0.01, Wilcoxon signed rank test, two-tailed: $U = 2,625$, $p = .09$, $n = 115$). Furthermore, whether the mouse ran in the dark or in the light had no effect on the strength of the ZI (Kruskal–Wallis test, $p > .1$).

These correlations exist across a range of time scales. On short time scales, motifs such as bursts or theta-rhythm modulated spiking might explain some part of ZI. While estimating the ZI probability time scales, motifs such as bursts or theta-rhythm modulated spiking (Figure S4B).

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These correlations exist across a range of time scales. On short time scales, motifs such as bursts or theta-rhythm modulated spiking might explain some part of ZI. While estimating the ZI probability from longer time windows yields lower values for $\alpha$, ZI is still significant on the time scale of seconds (Figure S4A). Indeed, the number of pauses on the linear track, measured on short time scales, is predicted by a cell's behavior in the open field on much longer time scales (Figure S4B).

The average firing rates did not correlate with the probability $\alpha$ of excess zeros (average Pearson $r = -0.05 \pm 0.01$, $p > .6$ for all light conditions and running directions on the linear track), even though the firing rates themselves were correlated across light conditions (average Pearson $r = 0.94 \pm 0.01$, $p < 10^{-10}$).

To check whether a grid cell's propensity to fire bursts of spikes correlates with the amount of ZI, we divided grid cells into bursty and non-bursty neurons as described by Latuske, Toader, and Allen (2015). The excess-zero probability $\alpha$ in the open field is similar for bursty and non-bursty grid cells ($\langle \alpha \rangle_{\text{bursty}} = 0.09 \pm 0.01$, $n = 40$, $\langle \alpha \rangle_{\text{non-bursty}} = 0.10 \pm 0.01$, $n = 97$). The difference was not significant (Kruskal–Wallis test for equal medians: $K = 0.88$, $p = .35$; t-test for equal means: $t = 0.80$, $p = .43$ and Mann–Whitney $U = 1,742$, $p = .175$). Taken together, neither the firing rate nor the burst behavior has a discernible relationship to a grid cell's ZI property. Conjunctive grid cells are tuned not only to the location of the animal, but are modulated by additional factors, such as speed or head direction. Such conjunctive tuning to multiple signal dimensions will cause neurons to fire more rarely if the different input streams interact in a multiplicative manner. We therefore tested whether cells that were previously labeled as conjunctive and were recorded both in the open field and on the linear track ($n = 115$) tended to have higher rates of ZI. The results are summarized in Table 1. Indeed, conjunctive neurons in the open field had higher scores for ZI.

### Table 1

Conjunctively tuned cells recorded in Pérez-Escobar et al. (2016), which respond not only to position, but also to speed or head direction, tended to exhibit more ZI

|                | Mean $\alpha$ open field | Mean $\alpha$ linear track |
|----------------|--------------------------|----------------------------|
| Grid conjunctive | 48 | 0.11 ± 0.01 | 0.14 ± 0.01 |
| Grid non-conjunctive | 67 | 0.16 ± 0.01 | 0.17 ± 0.01 |
| Spatial conjunctive | 42 | 0.14 ± 0.02 | 0.12 ± 0.01 |
| Spatial non-conjunctive | 50 | 0.17 ± 0.01 | 0.14 ± 0.01 |

Note: The table lists the average ZI probability $\alpha$ and its standard error for different classes of spatially modulated cells, which were recorded in the open field and the linear track. For the linear track data the average of $\alpha$ across all six experimental conditions (left/right running direction; 1/1/2/d lighting context) is displayed and for statistical testing all the $\alpha$ measurements were used. One hypothesis is that the difference in ZI between conjunctive and non-conjunctive cells should be less in 1D, as the head direction and speed vary less on the linear track; this expectation is borne out for grid cells. For grid cells and other spatially selective cells, we tested the likelihood that a randomly selected estimate of $\alpha$ from a conjunctive cell was larger than a randomly selected estimate from a non-conjunctive cell; specifically, the Mean–Whitney U-test asks whether one can reject the null hypothesis that this likelihood is 1/2. Levene tests for variance homogeneity showed no significant differences between the groups. On the linear track, grid cells had a U-statistic for conjunctive vs. non-conjunctive $\alpha$ of $U = 38,279$, $p = .001$; whereas in the open field $U = 753$, $p < .001$. In the open field, non- grid, but spatially modulated cells had significantly different $\alpha$ if they were conjunctive ($U = 760$, $p = .012$); on the linear track, though, the differences between conjunctive and non-conjunctive spatially modulated cells were not significant ($U = 29,034$, $p = .379$).

2.3 | Two sources of trial-to-trial variability: Shifted and missed firing fields

Previous reports indicate that the positions of firing fields are not fixed (Barry, Hayman, Burgess, & Jeffery, 2007; Hardcastle et al., 2015; Keinath, Epstein, & Balasubramanian, 2018). The data from Pérez-Escobar et al. (2016) confirmed this finding. Figure 4a, d displays a grid cell's spikes on single passages through two firing fields, which were recorded on the real linear track, revealing evident shifts from trial to trial (red, top row). Averaging across trials yields the usual estimate of the grid cell's firing rate as a function of position (middle row, blue). For comparison, we use the average firing rate to draw Poisson surrogate spike trains (bottom row, black). On each passage through a firing field, we compute the distance covered by the mouse from the first to the last spike within that field (shown as solid lines connecting the spikes in the raster plot of Figure 4a). At the single-trial level, the measured spike trains within a firing field tended to cover a shorter distance than the surrogate trains, even though the (trial-averaged) firing-rate map was identical (Figure 4b, d).

These shifts should have an intracellular correlate, given that the firing fields occur in conjunction with long-lasting ramps of depolarization; Figure 5 shows the spatial activity patterns for a mouse grid cell recorded intracellularly (Domnisoru et al., 2013). Both the low-pass filtered intracellular voltage (Figure 5a), named “ramp voltage” in Domnisoru et al. (2013) and the firing rate (Figure 5b) are highly variable from trial to trial. We now computed the centers-of-mass of the largest voltage peak in each trial, and used these to align the trials according to the center-of-mass of the largest voltage peak (Figure 5c, cf. “Single-cell trial alignment” in Materials and methods). This undid the effect of positional jitter of the firing fields (Figure 5d). Alignment sharpened the profile of the average voltage ramps (Figure 5e) and the firing fields (Figure 5f).
Narrower fields with higher firing rates, reduced variability, and increased information in the spike trains are also found after realignment of extracellularly recorded grid cells (Pérez-Escobar et al., 2016), as shown in Figure S5. Domnisoru et al. also observed events in which a grid cell fired no spikes during a passage through a grid field, which were called missed fields (see Supplemental Figure 22 in Domnisoru et al. (2013)). Under Poisson statistics, such events should be rare. Close examination of the intracellular recordings reveals trial-to-trial...
variations in the average membrane potential relative to the spiking threshold. These variations become more evident once the traces have been aligned (Figure 5c). When the ramp amplitude is too small, the grid cell fails to fire during a field passage.

2.4 Variability: Field positions versus field-to-field distances

The grid-cell population is thought to support distance estimation in addition to encoding the actual physical location of an animal (Huhn, Somogyva, Kiss, & Érdi, 2009). We wanted to test whether distinct fields of the same cell maintain their relative distances as the firing fields shift from trial to trial.

We quantified the variability in the relative distances by selecting cells that had at least two well-defined and well-separated firing fields (cf. Methods). For these cells, we computed the spatial autocorrelations of the firing rates on each trial. We defined the grid cell’s spatial period on a trial-by-trial basis as the position of the first maximum in the autocorrelation. For the spatial period to be well-defined, the height of the local maximum in the Pearson correlation (which is normalized to lie between −1 and +1) had to lie at least 0.5 above the surrounding minima and occur at a spatial lag larger than 4.8 cm (equivalent to two spatial bins). Given that some fields might be missed on some trials, we furthermore insisted that an autocorrelation peak matching these criteria be present on at least 25% of the trials.

There is a simple prediction for the variance $\sigma_{ptp}^2$ in the spatial period across trials. If each firing-field shifts its position independently across trials, then $\sigma_{ptp}^2 = 2\sigma_{shift}^2$, provided that the peak-to-peak distances are large compared to the magnitude of typical shifts. Figure 6 plots $\sigma_{ptp}$ against $\sigma_{shift}$. On average, in 67 ± 4% of the cells, the variance $\sigma_{ptp}^2$ was smaller than expected from the null hypothesis of random jitter (see Table 3). One example of a simultaneous recording is shown in Figure 7. For these neurons (marked by orange points in Figure 6), $\sigma_{ptp}$ was more than two times as large as $\sigma_{shift}$. Thus, the position of the fields was less consistent than the first peak in the spatial autocorrelation.

A cell with a high value of $\sigma_{ptp}$ in one light or running condition tended to also have a high value of $\sigma_{ptp}$ under other conditions (average...
correlation of $\sigma_{ptp}$ across conditions was $h_{r} = 0.53 \pm 0.03$, all correlations were significant (at level .01) after Bonferroni correction for N = 15 tests.

2.5 Independence versus coherence of firing-field shifts across grid cells

Next, we sought to distinguish two possible scenarios that could give rise to drifts in the firing fields: noise at the single-cell level or a population-level drift in the internal representation of the animal’s location. In the second scenario, fields shift across the whole population of spatially tuned neurons in a coherent fashion, so that the fluctuations in activity will be shared across the population as correlated noise. For this purpose, we studied simultaneous recordings from spatially modulated cells in the data from Pérez-Escobar et al. (2016). Figure 7a shows an example of five simultaneously recorded cells, two of which were classified as grid cells. Each cell had firing fields whose position varied across trials.

We were able to undo the trial-by-trial displacements in Figure 7a by positing that the fields shifted coherently across cells. After concatenating the spike trains of the five cells on each trial, we computed the cross-correlation thereof to the first trial, which was used as the reference. The location of the peak in this cross-correlation determined the joint shift to be applied to the five cells’ spike trains – this peak occurred at different spatial offsets from trial to trial (Figure 7b). Figure 7c shows the firing rates for the five cells after applying these identical spatial shifts on such a trial-by-trial basis. Strikingly, the population-wide alignment sharpened the firing-field profiles (Figure 7d), as was true for the alignment of trials on a single-cell basis (Figure 5). Once again, but now on a population-wide basis, alignment permits the recovery of more spatial information from the MEC population of neurons. Moreover, the distance between the firing fields of two cells within the same trial was less variable than the positions of the fields across trials.

We then decided to assess the coherence in the field drift quantitatively. To do so, we followed a multi-step procedure. First,
the rate maps for each cell were normalized to have the same peak firing rate, in order to eliminate trends in the firing rate over time. We then aligned the trial-averaged rate maps so that the average spatial phase of the grid-pattern was the same across cells. This procedure, illustrated in Figure S7, preserves relative drifts of the firing fields, if such are present. Then, we compared the Pearson correlations of the firing rate maps across cells for simultaneous trials to the correlation for randomly shuffled trials. If the firing fields jointly drift, then the Pearson correlation will be higher for the original than for shuffled trials. The results were deemed to be statistically significant for p values below 0.05/(n_tets*n_cells) (Bonferroni correction for multiple testing).

We ran this analysis for runs toward the right and left end of the track under the three different lighting conditions used by Pérez-Escobar et al. (2016), which they had labeled l1 for light condition 1, l2 for light condition 2 (with a different pattern of lighted stripes on the apparatus) and d for darkness. The correlation analysis revealed a joint component of field position drift across all six contexts (Figure S8A). In 41 out of 44 recordings of multiple cells, coherent drifting was detected in at least two contexts. In total, 3,238 cell pairs were considered. Pairs with significant coherent drift in all six contexts (5%) showed up 106 times more often than expected for independent drift.

For grid-cell pairs and conjunctive-grid-cell pairs, higher ratios of consistent field displacement were observed than for non-grid spatial-cell pairs, see Table 2 and Figure S8B for a comparison of the fractions of significant common shifts in pure-grid-cell pairs and other spatially modulated cell pairs. In some recordings, neither cell in a pair


2.6 | No evidence for error accumulation in grid cells recorded on linear tracks

Hardcastle et al. (2015) report that grid fields drift in open fields as path-integration errors accumulate. The amount of drift increases with the distance to the boundary and the time since the last boundary contact. Whenever the animal encounters a wall, these authors argue that the drift is reset to zero.

To test whether grid fields on the linear track are also subject to cumulative drift, we analyzed the jitter in the position of individual firing fields, treating runs toward the left and right end of the track separately. If drift accumulates until it is corrected by encountering a boundary, then the jitter should be greatest for the fields farthest from the most recently visited end. We used data from 28 grid fields that were reliably detected in both left and right runs and under all light conditions on the track (l1, l2, and d). Fields on the two end platforms were not considered. The boundary-driven error-correction hypothesis predicts that the size of the jitter grows with distance ran on the track. Therefore, we computed a linear regression between field position and jitter width for both running directions. Jitter width and field locations were measured as described in the Methods. No significant correlations were found between the magnitude of the jitter and the distance from the most recent boundary reached by the animal, however. Error accumulation would also predict that jitter causes the firing fields to become wider in the right half of the track for rightward runs, and in the left half for leftward runs. We therefore computed the difference in the jitter in left- and rightward runs for firing fields present in both directions. Under all conditions, the null hypothesis (identical jitter for both running directions) could not be rejected, based on a one-sided Mann-Whitney-U-test. For the three light contexts, this test yielded: (l1, fields in the left half (L), Mann-Whitney-U: \( U = 178, \ p = .94; \) l1, right half of track (R): \( U = 239, \ p = .429; \) l2-L: \( U = 74, \ p = .96; \) l2-R: \( U = 143, \ p = .51; \) d-L: \( U = 90, \ p = .99; \) d-R: \( U = 119, \ p = .16). The median jitter-width was around 3.5 cm in each condition, compared to an average field-width of 6.7 cm. Again, we found no indication of error accumulation on the linear track. Not even in the dark, when the mice would most likely path-integrate, did there seem to be significant error accumulation; it cannot be ruled out, though, that other sensory cues were present on the apparatus that calibrated the field positions. It is also conceivable that error accumulation over the timespan of a few seconds is too small to be measurable in these experiments.

2.7 | Trial alignment reduces variability

We hypothesized that alignment would make the spike-count statistics more Poisson-like and reduce the amount of ZI toward a small positive level determined by “missed-field” events. We fit a linear-nonlinear-Poisson (LNP) model to the spike trains of each cell, based on the animal’s position as the covariate, before and after alignment across trials (for details see Figure S9). For every cell, we then compared the two fits using a likelihood ratio test. We penalized the aligned fits for having more free parameters; each trial’s shift was treated as an additional parameter.

Based on a likelihood-ratio test, in 368 out of 475 cells, the alignment improved the match of the spike-train statistics to an LNP model (\( p < .001). Surprisingly, not all of the cells that were better fit by an LNP model after alignment met the criteria of Pérez-Escobar et al. (2016) for spatially modulated cells: only 256 of the 368 cells were spatially modulated, classified either as border cells (\( n = 23), grid cells (\( n = 116) or other spatial cells (\( n = 117). Only 33 spatially modulated cells did not significantly improve their fit to an LNP model under alignment.

To avoid bias, we estimated the shifts from the cross correlations across trials, not from a maximum-likelihood procedure to optimize the likelihood of the LNP model. Indeed, in some cases, alignment reduced the likelihood of the LNP model (\( n = 96). We then fit zero-inflated variants of the LNP model as described in Giles (2010). After alignment, the maximum-likelihood estimate of the ZI probability \( \alpha \) dropped in value by 54–70% (Wilcoxon tests, \( p < .001) for all six settings, \( N = 61). Despite the drop, \( \alpha \) did not vanish after alignment in most cases. More precisely, in only 8% of the cases did \( \alpha \) drop to a value smaller than 0.01 after alignment, see Figure S6. We concluded that not all unexpected firing pauses can be explained by firing fields shifting along the track.

While the shifts are not correlated across running directions, the overall amount of shift \( \sigma_{\text{shift}} \) of individual grid cells was highly correlated across light contexts (l1-l2, left: Pearson correlation coefficient...
FIGURE 8  Coherence of the state transitions across the five simultaneously recorded cells shown in Figure 7. Spike trains were first jointly aligned across all cells to counteract the coherent firing field drift. The phenomenon of zero-inflated spike counts still existed after alignment. a: Probability of the zero-state based on the expected spike counts \( n_i(t) \) and the average zero-state probability \( \alpha_i \) for each cell (cf. SI). Expected spike counts were taken from the jointly aligned trial averages, measured in 200 ms long time windows. b: For comparison, the estimated firing rate for each time point, using the trial averaged tuning curves after joint-alignment. c: For each of the jointly aligned cells, we estimated the time-resolved firing rate and the ZI parameter \( \alpha \) from an LNP model (cf. SI). With these parameters, we then simulated 40 independent, surrogate ZIP models for the five cells. By comparing the real data to the surrogates, we asked whether the zero-state transitions were more highly correlated across cells than expected by chance. To be deemed significantly correlated, the real correlation value had to be greater than the 95% percentile of the simulated correlations (marked by red stars).

2.8  |  Coherence of the “zero-firing” state across cells

Firing field displacements contribute to the observed phenomenon of zero-inflation, as was seen by the drop in the ZI probability \( \alpha \) after alignment. Nevertheless, some degree of ZI is preserved. For the data set of simultaneously recorded cells shown in Figure 5, we asked whether the probability of being in the “zero-firing” state is correlated across these cells, not just before alignment, but after alignment.

In Figure 8a, we compute the probability of a cell being in the “zero-firing” state, given a ZIP model for the spike-count statistics. The Bayesian estimate of the “zero-firing” probability in each 200 ms long time window requires two parameters: (a) the cell’s firing rate in that time window, averaged over aligned trials; and (b) the zero-state probability \( \alpha \) for that particular cell, as estimated from the entire experiment. This probability is particularly high when, contrary to expectations, a cell does not fire even when the firing rate predicts it should. This probability is not correlated with the time-dependent firing rate itself (Figure 8b).

To show that the “zero-firing” state is more strongly correlated across cells than would be predicted by chance, we drew independent ZIP surrogate spike trains for each of the five cells. Figure 8c marks the cases with asterisks in which the true correlations are significantly stronger than expected by chance.

2.9  |  Trial-to-trial displacement of firing fields induces noise correlations

We found that the spatial tuning of MEC cells changed from trial to trial, but did so jointly across cells. When firing fields shift together, cells with overlapping fields will exhibit correlated changes in their firing rates. In short, coherent shifts result in noise correlations. We therefore asked whether firing-field shifts could explain the noise correlations across cells at a quantitative level. For this purpose, we employed statistical models of cell ensembles. We created five artificial cells with multiple firing fields on a simulated linear track to mimic the experiments of Pérez-Escobar et al. (2016). For each cell, the fields represented a random slice through a two-dimensional hexagonal grid (Pröll et al., 2018; Yoon et al., 2013). The firing fields were modeled by von Mises tuning curves with a concentration parameter \( \kappa = 2.1 \), as suggested in Herz, Mathis, and Stemmler (2017) and a maximal firing rate of 12.5 Hz. Both the spatial phase (in the range from \(-30\) to \(+30\) cm) and the period of the lattice (10, 14, or 19.6 cm) were chosen randomly for every cell. We drew 100 such ensembles of five cells. Fields drifted from trial to trial by anywhere from 0 to 0.4 cm. Finally, we generated Poisson spikes based on the displaced tuning. Each ensemble was simulated five times for \( N_{\text{trials}} = 100 \) trials.

Noise correlations were computed as

\[
\rho_{ij} = \frac{1}{N_{\text{trials}} N_{\text{bins}}} \sum_{x,y} \frac{n_{x,y} \left( f_{ijk} - \mu_{ij} \right) \left( f_{ijk} - \mu_{ij} \right)}{\sigma_{x,i} \sigma_{y,j}}
\]

(2)

where \( f_{ijk} \) denotes the firing rate of a cell \( i \) in the spatial bin \( x \) on trial \( k \) and \( \mu_{ij} \) is the trial-averaged firing rate of cell \( i \) in bin \( x \). Figure 9b plots the noise correlation against the spatial offset of the firing fields.
shared trial-to-trial variations in the spatial phases increase noise correlations between otherwise independent Poisson grid cells. Firing-rate profiles for model cells were simulated as slices through 2D grids. The correlations are plotted against the tuning offset measured from the spatial cross-correlation between cells. a, Noise correlations in a Poisson simulation with static tuning curves across trials. b, Poisson simulation with jointly displaced tuning curves on individual trials across cells. c, Noise correlations measured from experimental grid-cell data (linear track, $N = 138$, data shown for runs to right end of the track from all light conditions).

DISCUSSION

In this study, a detailed analysis of the trial-to-trial variability in the responses of mouse grid cells revealed new insight into their coding properties: roughly half of the grid-cell excess variability can be explained as a result of the grid-cell population’s shifting representation of space. Despite such shifts, the peak-to-peak separation of firing fields is largely preserved. In many instances, we were able to realign repeated trials and recover spatial information in the firing-rate map, which revealed firing fields that had been partially “buried in the noise.”

Various authors have sought to explain the origins of neural variability; for a review, see Renart and Machens (2014). For instance, a conjunctive (mixed) tuning of neurons to additional sensory, task, or state variables unrelated to spatial location will increase neuronal variability. Hardcastle, Maheswaranathan, Ganguli, and Giocomo (2017) find that some grid cells are jointly tuned to combinations of place, head-direction, and speed. In our analysis, conjunctive location- and head-direction tuned cells were, in fact, more variable than “pure” grid cells. Such conjunctive tuning can coexist with persistent variations in a cell’s grid field properties from field to field, which would allow grid cells to convey additional spatial or contextual information; in particular, the peak firing rate varies across fields (Diehl, Hon, Leutgeb, & Leutgeb, 2017; Dunn, Wennberg, Huang, & Roudi, 2017; Ismakov, Barak, Jeffery, & Derdikman, 2017).

Yet conjunctive tuning only provides a partial explanation for the excess variability exhibited by grid cells. Other phenomena, such as variations in the sub-threshold voltage or firing threshold, intrinsic bursting behavior, or other non-stationarities must play a role. We focused on two factors: changes in the firing state and shifting field positions from trial to trial.

The failure of a grid cell to discharge in a firing field is corroborated by calcium imaging studies of entorhinal cortex (Gu et al., 2018; Heys, Rangarajan, & Dombeck, 2014; Low, Gu, & Tank, 2014). Interpersed among trials with vigorous calcium dye responses, one will generally find traces with no response. Such behavior is consistent with a fluctuating spike threshold, which led us to model grid-cell discharge using a particularly simple version of a Hidden Markov Model (Gat, Tishby, & Abeles, 1997): a ZIP process. Cells thus had two states: a silent state and an active state. In the intracellular data on grid cells (Domnisoru et al., 2013) that we reanalyzed, the silent state was associated with lower sub-threshold membrane potentials. The transitions between the silent and active state as the mice ran on the linear track...
could simply reflect natural fluctuations in the membrane potential. In addition, a silent state might correspond to the firing field’s position transiently shifting away from the track. As we observed field shifts parallel to the track’s direction from trial to trial, it is reasonable to suppose that fields also drift in the transverse direction.

Were grid cells to integrate time since trial onset, not spatial distance, one would also measure apparent field drifts (Eichenbaum et al., 2016; Kraus et al., 2015; Tsao et al., 2018). As the animal’s speed is fairly constant on the linear track, grid-cell firing will show the same regularities in time as in space. However, if grid cells encode time, trial-to-trial speed variations would lead to a rescaling of the grid fields measured in space. All fields would move either closer together or further apart. Moreover, fields should become larger or smaller, depending on speed. We found no evidence for such effects in the data sets we analyzed. De Almeida, Idiart, Villavicencio, and Lisman (2012) observe that grid-cell spiking falls into two modes: either the cell fires on an inbound trajectory and not when leaving the field, or vice versa. In the interpretation of these authors, grid cells switch between prediction and retrospection. Moreover, simultaneously recorded grid cells are likely to operate in the same mode—either prediction or retrospection. Correlated field displacement reflecting an uncertainty or error in the absolute position estimate could lead to similar effects, though in one shift direction, the fields would be active behind the animal’s current position, whereas in the other direction, fields would be active ahead of it.

For the majority of mouse grid-cell recordings in darkness, the firing fields, measured in terms of absolute positions, are no longer discernible in the averaged firing-rate map (Chen, Manson, Cacucci, & Wills, 2016; Pérez-Escobar et al., 2016). Nevertheless, when one measures the spatial autocorrelation over short time intervals, a dominant length scale emerges, which deviates only slightly from the one observed in light. This observation is consistent with the hypothesis that the firing fields continually shift, but in a manner that maintains the relative distance between firing fields. Our analysis shows that not only grid cells, but also other spatially modulated cells exhibit such shifts. Such coherent firing-field drifts are compatible with continuous-attractor models of grid-cell firing (Burak & Fiete, 2009). These models envision a hexagonal bump-attractor state in a recurrent neural network; the state moves coherently across the network in response to a velocity signal. Any source of noise, barring some form of recalibration of the firing-rate map, will lead to coordinated drifts in the measured firing fields.

But the question remains why firing fields on the linear track shift not only in darkness, but also when lights are on and visual landmarks could anchor the firing-rate map. In the grid-cell recordings we analyzed, the mice never needed to pay attention to visual cues during traversals of the linear track. Little is known about the modulation of entorhinal grid cells by attention, though the presence of goals can change the grid pattern (Boccara, Nardin, Stella, O, & Csicsvari, 2019; Bray, 2019; Butler, Hardcastle, & Giocomo, 2019). In the absence of an explicitly spatial task for the animals, it is hard to say whether firing pauses in grid cells and coherent firing field drift have behavioral consequences. We can only speculate that mice should be better at tasks that require them to estimate relative distances, rather than tasks that require them to locate objects in absolute coordinates.

Much more is known about the role of attention on place and time cells in hippocampus. In fact, place fields in mice are often unstable unless the mice are explicitly engaged in a spatial task (Kentros, Agnihotri, Streeter, Hawkins, & Kandel, 2004; Muzzio, Kentros, & Kandel, 2009); in long-term experiments, only 15% of place fields are stable over several days (Ziv et al., 2013). The set of active hippocampal cells changes over the time-scale of minutes (Mau et al., 2018); in addition, multiple spatial and temporal representations alternate on time-scales of several tens of milliseconds to seconds (Kelemen & Fenton, 2016). Kinsky et al. find that the hippocampal map in mice rotates coherently when the arena is rotated, but not necessarily in the same direction as the external rotation (Kinsky, Sullivan, Mao, Hasselmo, & Eichenbaum, 2018). These map rotations explain some of the place-field instability. Head-direction and grid cells presumably rotate their representations in concert with hippocampal cells.

Rats, however, seem to have stable grid-cell representations, even when the animals are forced to reorient (Weiss et al., 2017). There could well be species-specific differences in the amount of drift grid fields exhibit, even on the time-scale of minutes that affect measures of variability. It is conceivable, as well, that drift accumulates more in mice than in rats. Accumulated drift would manifest itself in the long-term loss of place-field stability for mice; rats, on the other hand, might pay more attention to distal visual and spatial geometry cues that help maintain the hippocampal map in register over longer time periods. We note, though, that both rat and mouse grid cells exhibit similar amounts of excess variability (Figure 5I). Thus, minor shifts in the firing fields and pauses in firing might already explain much of the excess variability.

Computational models propose that grid cells give rise to place fields (Rolls, Stringer, & Elliot, 2006; Solstad, Moser, & Eidevoll, 2006). So it is not surprising that CA1 and CA3 place fields shift, too (Lee & Knierim, 2007; Mehta & McNaughton, 1997; Roth, Yu, Rao, & Knierim, 2012). Given the reciprocal connections between hippocampus and entorhinal cortex (Marozzi, Ginzberg, Alenda, & Jeffery, 2015), an unanswered question is whether the MEC grid-field drift drives hippocampal place-field shifts, or vice versa. Models of the entorhinal-hippocampal interaction might permit quantitative predictions of how much “noise” is transferred from one area to the other, and how much of the apparent noise is due to correlated shifts in the spatial maps (Monsalve-Mercado & Leibold, 2017; Rolls et al., 2006).

While we found that grid-cell discharge is highly variable in both 1D and 2D environments, we have only established a direct link between firing-field dynamics and variability for the linear-track recordings. Several approaches have been used to measure the dynamics of grid spatial phases and single grid-field locations in 2D recordings in the open field: For example, Hardcastle et al. (2015) suggest a “spike-distance metric” to compare inbound and outbound spiking on firing-field crossings. Krupic, Bauza, Burton, and O’Keefe (2018) and Hägglund, Mærreaunet, Moser, and Moser (2019) use flow maps to study the dynamics of grid fields in response to changing the shape of the arena. Such attempts are fraught with difficulties, however. Grid cells often fire at low rates, even at the center of a firing field. As a consequence, the firing fields only become
apparent after the animal’s trajectory has passed through each location multiple times. Moreover, unlike in experiments on virtual linear tracks, recording from animals foraging in 2D arenas does not permit dividing the data into well-defined “trials.” Nevertheless, stochastic mixture models could reveal whether the encoding of space is static or not. As drifting firing fields provide a generative model of grid-cell variability, one can fit such models to spike-count data and thereby deduce the range and variance of the field shifts, even if it is impossible to measure the shifts directly. Therefore, further research into variability could give us insight into the dynamics of two-dimensional firing fields. Moreover, understanding how the excess variability in grid-cell discharge arises will allow future studies to address how the nervous system might compensate for this variability.

4 | MATERIALS AND METHODS

4.1 | Data sources

We analyzed multiple data sets (Domnisoru et al., 2013; Fyhn et al., 2004; Fyhn et al., 2007; Pérez-Escobar et al., 2016; Sargolini et al., 2006; Stensola et al., 2012), focusing on tetrode recordings from Pérez-Escobar et al. (2016) and whole-cell data from Domnisoru et al. (2013).

The tetrode recordings from Pérez-Escobar et al. (2016) are available at https://datadryad.org/resource/doi:10.5061/dryad.c261c. The data set contains recordings of entorhinal neurons from male wild-type C57BL mice. From among these neurons grid cells were identified by letting mice run in a 70 cm × 70 cm arena (Pérez-Escobar et al., 2016). The mice were then put on a 80 cm × 5.6 cm linear track. Positions were projected onto the long axis of the linear track. For our analysis, coordinates were measured from the center of the track. Each trial yielded a trajectory segment that extends ≥30 cm from the track’s midpoint; we discarded data within 10 cm of the ends of the track. To eliminate the animal’s running direction as a potential factor contributing to the trial-to-trial variability (Pröll et al., 2018), we split the data into runs toward the right and the left end of the track.

Whole-cell data from Domnisoru et al. (2013) were kindly provided by Cristina Domnisoru and David Tank. In these virtual-reality experiments, male wild-type C57BL mice were head-fixed and ran only in one direction. To start a new trial the animal was reset within the virtual-reality environment. The data consisted of 27 grid-cells recordings. Three cells were excluded from the analysis because they had a low number of trials (n < 10) or low firing rate (f < 0.5 Hz).

4.2 | Calculation of firing-rate maps

We estimated a spatially discretized 2D firing-rate map \( F_{x,y} \) for each cell by counting the number of spikes in \( 2.4 \times 2.4 \) cm\(^2\) bins and dividing this number by the total time the animal spent in the spatial bin. In 1D, spikes and trajectory points were binned for each trial. For the real linear track, we used a bin size of 2.4 cm, and 8 cm for the VR data. These different bin sizes were used as mice ran faster in VR, as described in (Domnisoru et al., 2013), and the VR tracks were longer than the real tracks. The ratio of spike count to dwell time in each bin yielded an estimate of the spatial firing rate for individual trials. The firing-rate map was then calculated as the trial-averaged firing rate.

4.3 | Spike-count distributions

To study the discharge variability, we discretized the trajectory \((x_t, y_t)\) (or, in 1D, \([x_t]\)) in steps of \( \Delta t = 20 \) ms and discarded trajectory points for which the rate \( F(t) < F_{\text{min}} = 5 \) Hz. Next, trajectory segments were chosen such that the expected number of spikes \( n = \sum F_{x,y} \cdot \Delta t \), was \( n = 5 \), unless otherwise stated. The actually measured number of spikes on such trajectory segments yielded a spike-count distribution, which was compared with the predicted spike count. The constraint \( F(t) \geq 5 \) Hz induced no statistically significant change in the count distributions for any of the 106 cells, but it restricted the duration of single trajectory segments to less than 1 s.

4.4 | Field detection and jitter on linear tracks

To identify and follow individual firing fields across trials, we first detected peaks in the tuning curves. A peak was defined as a local maximum whenever the difference to the next closest local minimum was larger than 20% of the global maximum. The region between the two adjacent minima was defined as a firing field; regions outside these areas were not considered further. Each peak marked one firing field. Next, for each peak we computed

\[
\langle x_{\text{field}} \rangle = \frac{\sum_i f_i x_i}{\sum_i f_i}
\]

\[
\langle x_{\text{field}} \rangle^2 = \frac{\sum_i f_i (x_i - \langle x_{\text{field}} \rangle)^2}{\sum_i f_i}
\]

where \( x_i \) are the bin centers and \( f_i \) is the firing rate on each trial. The field centers and widths were computed for each individual trial using the formulae above. If a cell did not spike as a field was crossed, then the corresponding firing field was undefined on that particular trial.

This approach assigns the field location to the “center-of-mass” of the firing field, rather than the trial-by-trial peak in the firing rate. The distance between field locations from one trial to the next trial can vary, with the limitation that these positions cannot fall outside the field boundaries (demarcated by the two local minima surrounding each trial-averaged peak), nor occur at the track boundaries, which correspond to positions more distant than 30 cm away from the center of the track. A firing field was considered to be reliable whenever it was identified on left and right runs and the distance between the respective field boundaries was larger than 9.6 cm (4 bins).
4.5 | Single-cell trial alignment

To align the spatial firing-rate profiles across trials, we first detected the location that elicited the largest number of spikes for each trial. We then computed the firing rate’s centers-of-mass in a window of ±7 bins around the detected peak. The firing rate-maps were then shifted to bring these centers-of-mass into alignment, while zero-paddling the maps as necessary. The evaluation of this alignment procedure using a LNP model is illustrated in Figure S9.

4.6 | Software

All analyses were performed in the Python scripting language (Python Software Foundation, Python Language Reference, version 3.4, available at http://www.python.org) including the packages numpy (version 1.14.3), scipy (version 1.0.1), and sklearn (version 0.19.1).

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

This study was designed by J.N., M.S., and A.V.M.H. and carried out by J.N. The manuscript was jointly written by J.N., A.V.M.H., and M.S.

DATA AVAILABILITY STATEMENT

All data are publically available (we reanalyze the data from experiments performed in other laboratories, which were generously made available).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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