LETTER

Calci um transient prevalence across the dendritic arbour predicts place field properties

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Establishing the hippocampal cellular ensemble that represents an animal’s environment involves the emergence and disappearance of place fields in specific CA1 pyramidal neurons1–4, and the acquisition of different spatial firing properties across the active population5. While such firing flexibility and diversity have been linked to spatial memory, attention and task performance6–8, the cellular and network origin of these place cell features is unknown. Basic integrate-and-fire models of place firing propose that such features result solely from varying inputs to place cells9,10, but recent studies3,10 suggest instead that place cells themselves may play an active role through regenerative dendritic events. However, owing to the difficulty of performing functional recordings from place cell dendrites, no direct evidence of regenerative dendritic events exists, leaving any possible connection to place coding unknown. Using multi-plane two-photon calcium imaging of CA1 place cell somata, axons and dendrites in mice navigating a virtual environment, here we show that regenerative dendritic events do exist in place cells of behaving mice, and, surprisingly, their prevalence throughout the arbor is highly spatiotemporally variable. Furthermore, we show that the prevalence of such events predicts the spatial precision and persistence or disappearance of place fields. This suggests that the dynamics of spiking throughout the dendritic arbor may play a key role in forming the hippocampal representation of space.

CA1 pyramidal cell dendrites contain voltage-gated calcium and sodium channels along with NMDA (N-methyl-D-aspartate) receptors that allow them to produce nonlinear, regenerative (spiking) events. The spatial extent and site of generation of dendritic regenerative events can vary from widespread back-propagation of somatic action potentials (bAPs) into the arbour11–13 and multi-dendrite calcium spikes14,15, to more spatially heterogeneous processes such as partial bAP propagation14,15 and local spike generation16–17. Such events can provide amplification of synaptic input11–13 and the depolarization necessary for Hebbian plasticity induction15,16,19, both of which may be important for place field firing20. However, no measurements of regenerative dendritic activity in place cells have been made during behaviour, when network states affecting dendritic excitability are intact and relevant.

To study regenerative dendritic activity in the hippocampus during behaviour we co-acquired time-series movies through a chronic imaging window of calcium transients from dendrites, axons and somata of CA1 place cells sparsely labelled with a genetically-encoded calcium indicator21 (GCaMP6F) while head-restrained mice navigated a virtual linear track1,2 (Fig. 1a, b). One imaging plane was focused on the soma while the other was focused in the dendritic arbour, slicing through several branches. Many of the labelled neurons were identified as place cells by somatic calcium transient labelling occurring during traversals of the same track location (place field significance P < 0.05 from bootstrapping). Unless otherwise stated, our analysis focused only on these cells (33 place fields, 28 place cells, 19.3 ± 13.2 min per place cell imaging session, 8 mice), their basal arbours (170 total branches), their axon (visible in 3 place cells, 5 place fields), and on activity observed during place field traversals. The dendritic fields of view (~145 × 75 μm) on average contained 5 ± 3.5 (range, 2–18) basal arbour branches connected to the co-imaged place cell soma. The imaged branch sections had a mean length of 10 ± 3 μm (range, 3–23 μm), were positioned a mean of 74 ± 15% (range, 38–99%) of the distance along the dendritic length (from soma to dendrite tips), a mean of 2.8 ± 0.9 branch points (range, 1–6) and 130 ± 44 μm (range, 58–284 μm) from the soma, and a mean of 3.8 ± 2.0 branch points (range, 1–9) and 191 ± 83 μm (range, 20–440 μm) from each other. Our recordings of ~5 basal branches would typically represent

Figure 1 | Co-acquired time-series of CA1 place cell somata, dendrites and axons during virtual navigation. a, Two-photon microscopy with an electric lens (top) rapidly switches between two focal planes to generate co-acquired images of soma, dendrites and axon (bottom). b, Left, expanded view of place cell shown in a. The time-series was acquired while the mouse navigated a virtual linear track (right). c, Top, mouse position along linear track; bottom, fluorescence change over baseline (ΔF/F) traces from the soma (red), axon (brown) and dendrites (green, blue, cyan) of place cell shown in a during place field traversals (grey columns). Note the absence of detectable branch spikes during some somatic firing. Branch distance to soma and percent distance from soma to dendrite tip shown for each branch. *P < 0.001 from bootstrapping.

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about one-third of all basal dendritic branches at their branching depth (~2.8 branch points from the soma).

During track traversals we often found significant calcium transients (detectable transients with <0.1% false positive error rates, indicated with an asterisk in figures; Methods) in the soma, axon (mean of 139 ± 26 μm from soma) and basal dendrites in the cell’s somatic place field (Fig. 1b, c; activity in these structures along the track but outside of the place field was rarely observed). Somatic calcium transients (Extended Data Fig. 1) were used as a surrogate measure of action potential firing \(^1\), and multiple lines of evidence (Methods) showed that somatic action potential firing occurred throughout nearly the entire somatic calcium-transient-defined place field. In cells in which we were able to record from the axon along with the soma and dendrites, we found that axonal transients co-occurred with somatic transients 100% of the time (130 transients; \(n = 4\) place cells; Supplementary Video 1). Because axonal calcium transients are tightly coupled to somatic firing, they provided an independent indicator of action potential firing (Methods). In dendrites of CA1 pyramidal neurons of navigating mice (not necessarily place cells), we observed calcium transients restricted to single spines, with no detectable shaft transient; however, we more frequently observed calcium transients invading all visible pixels of the recorded branch (both shaft and spines) that were larger in amplitude and spatial extent than single-spine transients. These transients were considered non-regenerative (excitatory input to a single spine) or regenerative (bAPs or dendritically generated spikes (dspikes) such as \(\mathrm{Na}^+\), NMDA and calcium spikes) depolarizations, respectively (Methods and Extended Data Fig. 2d, e), and we focused our analysis on the latter.

Here, we refer to these regenerative dendritic events as ‘branch spikes’ — events caused by either dspikes or bAPs or both. Furthermore, because single-spine transients are detectable under our recording conditions, we presume that our measurements are sensitive enough to detect most branch spiking, and therefore the absence of branch spiking additionally indicates that dspikes and bAPs probably did not occur.

The ability to measure spiking in both the soma and in multiple dendrites of CA1 neurons during navigation allowed us to investigate specifically whether somatic place field firing was associated with branch spiking. During many place field traversals with somatic firing, dendritic branch spikes were observed (often with onset latencies with respect to somatic firing, Fig. 2 and Extended Data Fig. 1d), providing the first direct evidence of their existence in place cells. Furthermore, from traversal-to-traversal, branch spiking was found to be highly spatially variable across the arbour. For example, in many place field traversals, all observed dendritic branches in our imaging field (representing a subset of all the cell’s branches) spiked along with the soma (Fig. 2a and Extended Data Figs 5 and 6). However, in some cases, only a subset of the observed branches displayed detectable spikes (Figs 1c, 2b and Extended Data Figs 3 and 4a). Finally, in many cases, none of the observed branches displayed detectable spikes during place field traversals while the soma (and axon) fired (Fig. 2c and Extended Data Figs 3–6). From 747 somatic place field transients (from all 28 place cells), 395 (52.9%) showed co-occurring branch spikes in all imaged branches while 154 (20.6%) showed at least one branch with and one branch without detectable spiking, and 198 somatic transients (26.5%) failed to show co-occurring detectable spikes in any of the imaged branches. Importantly, these three observation classes were often seen in the same place cell, but on different place field traversals (Fig. 2e, Extended Data Figs 3 and 4 and Supplementary Video 1).

Characterizing somato-dendritic events as one of these three observation classes did not depend on the recording distance of the dendritic imaging plane from the soma or the number of observed dendritic branches (Supplementary Information and Extended Data Fig. 5). Thus, recording from a subset of branches in a single dendritic imaging plane provides a reasonably accurate characterization of dendritic branch spiking throughout a large portion of the basal (and apical) arbour (Supplementary Information and Extended Data Figs 5 and 6), implying some level of cooperativity between the spiking in different branches (Extended Data Fig. 7).

A fourth class of observation was also made: branch spiking in the absence of detectable somatic spiking (Fig. 2d and Extended Data Fig. 4b), representing probable evidence of dspikes in place cells. These localized dspikes were rarely observed in the absence of somatic spiking (6 total in or around the mean somatic place field, during 8.3 recording hours; 2 other dspikes were observed outside of place fields or in non-place cells; Extended Data Fig. 2a–c, f). However, dspikes could contribute to more global branch spiking, making isolated dspikes difficult to detect.

Place cells exhibited different degrees and patterns of branch-spiking heterogeneity. As a measure of this heterogeneity we calculated the prevalence of branch spiking (fraction of branches with detectable branch spikes) during each place field traversal, defined as branch-spike prevalence (BSP, see Methods for calculation). Figure 3 shows a place field with low average BSP (the average BSP across all place field traversals, Fig. 3a), one with moderate average BSP (Fig. 3b), and one with consistent somato-dendritic unison (high average BSP, Fig. 3c). Further, we observed that average BSP could differ significantly between different place fields of the same cell and that in-field average BSP was significantly greater than out-of-field BSP (Supplementary Information, Extended Data Fig. 8). Together, these results demonstrate that average BSP varies between different place cells and place fields and is not solely determined by cellular properties, such as the general degree of excitability, but is also synaptic-input specific.
The above observations demonstrate spatiotemporal variability in the regenerative dendritic events that are widely believed to provide amplification of synaptic input and the depolarization necessary for Hebbian plasticity (defining plasticity 'windows'). Many possible mechanisms could generate our observed patterns of somatic action potential firing and branch spiking: (1) bAP-induced branch spiking could be spatially and temporally modulated\(^\text{24,25}\) by inhibition, synaptic boosting or sodium channel inactivation; (2) clustered synaptic input could generate branch spiking\(^\text{24,25,26}\) in the form of widespread calcium spikes and/or more local dspikes\(^\text{24,25,26}\); or (3) dspikes and bAPs could co-occur. However, regardless of spike initiation site(s), the known involvement of branch spiking in plasticity and input amplification suggests that differences between place cells and their firing fields may be related to BSP.

To investigate the relationship between branch spiking and place field firing, we looked at two features of place fields previously linked to plasticity and input amplification suggests that differences between place cells and their firing fields may be related to BSP.

We found a significant correlation between a place field's average BSP and its spatial precision index (defined in Methods; Fig. 3a–c; Spearman's rank correlation coefficient: \(P = 0.0038; \rho = 0.6442\); significant positive linear slope within 95% confidence bounds; 26 place fields). The nine fields with the largest average BSP were also the most precise, indicating that average BSP can be used to predict precision. Notably, when we compared a place field's somatic firing intensity (integral of somatic firing over each traversal) to its spatial precision, little to no correlation was observed (Fig. 3c; Spearman's rank correlation coefficient: \(P = 0.01; \rho = 0.29\); linear slope not significantly positive). Thus, average BSP, but not somatic firing intensity, is a predictor of a place field's spatial precision.

We next assessed the relationship between average BSP and place field stability (Fig. 3d–f) by monitoring somatic and dendritic activity in the same cells over the course of 2 days. Place field average BSP was measured on day 1 and then the same cell was imaged the next day to determine whether it had the same somatic place field (Fig. 3d). We classified place fields that persisted to day 2 as stable place fields and those that disappeared by day 2 as transitory place fields (Fig. 3e). Stable fields had significantly greater average BSP than transitory fields (Fig. 3f; \(0.83 \pm 0.06 \text{ versus } 0.37 \pm 0.07\); \(t\)-test, \(P = 0.0006\)). When the somatic firing intensity of transitory and stable place fields was compared no significant difference was observed (Fig. 3f; \(0.374 \pm 0.036 \text{ versus } 0.368 \pm 0.057\); \(t\)-test, \(P = 0.92\)). This indicates that average BSP, but not somatic firing...
intensity, is a predictor of the long-term stability of a place cell’s place field. Together, the above results indicate that place field spatial precision, persistence and disappearance can be predicted based on the prevalence of regenerative events in place cell dendrites, but not based on somatic firing alone (precision and stability were also positively correlated, Supplementary Information and Extended Data Fig. 9).

Branch spikes can act to amplify synaptic input (through dspskies) to drive somatic firing and can also provide the post-synaptic signal required for Hebbian plasticity. In this context, our observation that BSP is variable implies that spatially heterogeneous and temporally variable input amplification and synaptic plasticity have a role in place field precision and stability. Somewhat paradoxically, however, increased branch spiking did not strongly correlate with an increased average number of somatic action potentials during place field traversals (Extended Data Fig. 10), and fields associated with more ‘open plasticity windows’ (more branch spiking possibly associated with greater plasticity) were actually more stable and precise.

It is somewhat puzzling then how synaptic plasticity and amplification mechanisms might be used by place cells to develop their representations of space. A ‘winner-takes-all’ scenario incorporating synaptic Hebbian potentiation and somatic firing homeostasis provides a possible answer. Previous models examined spatially imprecise place fields generated by different combinations of synaptic input, each with different spatial tuning. The combinations which happened to overlap more (in space and time) generated greater post-synaptic responses and more Hebbian potentiation of the contributing inputs. This increased the effectiveness of the potentiated inputs to drive somatic firing relative to other inputs with non-overlapping spatial tuning. A repetition of this process caused the cell to respond mainly to the subset of strong inputs with spatial tuning overlap, leading to more precise place field firing. The increased effective drive to the cell caused by the potentiated inputs then triggered a homeostatic mechanism that lowered overall cellular excitability (through synaptic or intrinsic excitability renormalization). This increased the contribution from the strong inputs (in relation to the weak inputs) in driving somatic firing, thus further increasing spatial precision, but maintaining the average firing rate of the place cell.

Assuming that branch spikes represent the postsynaptic responses that signal Hebbian potentiation, our observation of increased spatial precision of somatic firing with greater average BSP fits with the above model. Also, the sets of surviving, stronger synapses in the model would be expected to persist longer in time, consistent with our observation of greater field stability with increased average BSP. The use of a somatic action potential firing homeostasis mechanism also explains the weak relationship observed between BSP and action potential firing, with the implication that firing may be driven more by regenerative dendritic activity in high average BSP fields, and less in low average BSP fields. Furthermore, given the above scenario, in silent cells, strong sets of clustered synapses formed through potentiation in different environments may be partially activated in the animal’s current environment, but just below dspike threshold and therefore sensitive to small changes in somatic depolarization, as recently observed.

In the context of synaptic plasticity (see Supplementary Information for further discussion), while our methods do not directly reveal if branch spikes induce long-term potentiation, long-term depression or no weight change, the above model implies that in place fields, branch spiking potentiates synapses, is the result of previous potentiation, and/or maintains the strength of previously potentiated synapses through positive feedback. Our measurements demonstrate multiple levels of dissociation between action potential firing and the mechanisms widely believed to signal dendritic plasticity, providing the first clues regarding the spatial and temporal scales at which associative Hebbian learning rules may operate in a behaving animal performing a task known to engage integration and plasticity in the cells being studied. One implication is that the process by which place cells orchestrate plasticity signals (dendritic branch spiking) may be variably, rather than consistently, linked to their mode of information transmission (the somato-axonal action potential).

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to D.D. (d-dombeck@northwestern.edu).
METHODS

Mouse surgery, virtual reality, and behaviour training. All experiments were approved by the Northwestern University Animal Care and Use Committee. Male C57BL/6 mice (postnatal day ~70) were anaesthetized (~1–2% isoflurane) and a small (~0.5–1.0 mm) craniotomy was made over the hippocampus (1.8 mm lateral, 2.4 mm caudal of Bregma). For single-cell dendritic imaging a low titre Cre virus (AAV2/1–CamKII–Cre, 1.5 × 10^10 GC ml^-1, all virus from University of Pennsylvania Vector Core) was injected (1 injection of ~30 nl at a depth of ~1.250 µm below the dura surface using a bevelled glass micropipette, ~1–2 ML before bevelling) in combination with a high titre of flexed–GCaMP6f virus (AAV1–Syn–flex–GCaMP6f, 1.4 × 10^10 GC ml^-1) leading to expression of GCaMP6f (ref. 21) in a sparse CA1 pyramidal neuron population. For population imaging (Extended Data Fig. 9), dense labelling was performed the same as sparse except AAV1–Syn–GCaMP6f (1.5 × 10^10 GC ml^-1) was injected. Mouse water scheduling began the next day (0.8–1.0 ml per day) followed either the next day or ~7 days later by a hippocampal window and head-plate implantation surgery (as described in ref. 1), for population or single-cell dendritic imaging respectively. Training in a 1.8-m virtual linear track (one ~40–60 min session per mouse per day) began ~7 days after window implantation and continued until mice routinely ran back and forth along the linear track to achieve a high reward rate (~2 rewards per minute); rewards consisted of water (4 µl) delivered as described previously22. Once this criterion was reached (~7–14 days of virtual reality training), place cell imaging commenced and was repeated daily for ~1–4 weeks. During the imaging sessions included in our analysis, mice received an average of 4.4 ± 1.1 rewards per min. GCaMP6f expression reached a somewhat steady state level ~21 days post-injection.

Our virtual reality and spherical treadmill system were similar to those previously described22,23 but with the following differences. A curved screen monitor (CRVD, Ostendo) was used for displaying the virtual reality environment. The screen was adjusted for low light emission (brightness, 15/100; contrast, 50/100; all RGB intensities, 1/100) and was placed ~14 inches in front of the mouse covering 133° and 48° of the mouse’s horizontal and vertical field of view, respectively. The Quake2 video game engine described previously23 was used here for the virtual simulation, with minor modifications: the virtual environment was rendered with 2,880 × 900 pixels, and the horizontal field of view in the virtual environment was 105°. Mouse locomotion speed and direction on the spherical treadmill were read using a G-400 optical computer mouse (Logitech) and forward and yaw movements of the treadmill were used to update forward position and view angle in the virtual environment, respectively, as described previously23. The forward movement gain was set such that the full length of the virtual track was traversed by ~2.8 rotations of the ball (180 cm of linear distance) and the yaw gain was set such that ~5.5 rotations of the ball resulted in one full field of view rotation (360°) in the virtual environment.

Two-photon imaging of place cell soma, axon and dendrites. We customized a Moveable Objective Microscope (Sutter Instruments) for our imaging experiments. The microscope consisted of water cooled 6215H galvos with 3-mm B1 coated mirrors (Cambridge technology), a back aperture and the focal plane was rapidly switched after each collected image of the ball regions. For population imaging, ROIs were identified offline by their morphology and signal change. They were smaller in diameter than dendritic branches and also had a lower resting fluorescence level. Furthermore, their calcium transients were longer in duration and larger in signal change compared to dendritic branches.

Region of interest selection and calcium transient analysis. For single-cell imaging (spase labelling), regions of interest (ROIs) were selected by hand on the soma or dendrite images (mean time projection of all frames in the motion-corrected time-series at each plane). ROIs were drawn to closely follow the outline of the structure of interest (soma, axon or dendrites).

For population imaging, ROIs were defined as previously described24 (µ = 0.5, 150 principal components, 100 independent components, s.d. threshold = 1.5, s.d. smoothing width = 1.5, 100 pixels < area of ROI < 400 pixels; see Mukamel et al.26 for parameter definitions). As seen previously24, ROIs nearly always defined single cell regions.

From single-cell and population time-series, ΔF/F versus time traces were generated for each ROI as previously described1. In brief, slow changes in the fluorescence traces were removed by examining the distribution of fluorescence in a ~5 s (for single-cell/spase labelling) or ~3.2 s (for population imaging) interval around each sample in the trace and normalized by the 8th percentile value. These baseline-corrected traces were then subjected to the analysis of the ratio of positive- to negative-deflecting transients of various amplitudes and durations described previously24. We used this analysis to identify significant transients with <0.1% false positive error rates; these identified significant transients were used in the subsequent analysis and are marked with an asterisk in.
the figures. Note that brain movements can cause small fluorescence transients in the positive- and negative-deflecting directions (equally) during movement. Because GCaMP6f indicates activity with positive-deflecting transients only, the negative-deflecting transients are assumed to be due to brain movements. The above cited analysis detects positive-deflecting transients of a duration and amplitude that almost never occurs in the negative-deflecting direction (<0.1% false positive rate). Thus, most of the small positive-deflecting transients not detected as significant by this analysis are probably induced by brain motion, since events of the same duration and amplitude often occur in the negative-deflecting direction; however some of these small positive-deflecting transients may be due to neural activity (though the number is likely small, see for example our ability to record single-spine events in Extended Data Fig. 2d, e).

The mean duration of somatic, axonal and dendritic calcium transients were calculated as the full duration of the significant transients: soma, 2.89 ± 0.59 s; axon, 2.0 ± 1.2 s; dendrites, 1.07 ± 0.65 s. These durations were calculated from sparsely labelled cells only, where all 3 structures could be identified (not from population labelling). Only transients occurring during consistent runs through the place field, in which a long running period covered >90% of the place field (see below), were included.

Previous studies have consistently found that somatic calcium transients are caused by action potential firing where the number of underlying action potentials correlates with the change in fluorescence. Thus, somatic ΔF/F fluorescence traces are often used as a surrogate measure of action potential firing activity. The following three related measurements of somatic and axonal calcium transients in the present study are consistent with conclusions of prior studies asserting that somatic calcium transients are caused by action potential firing:

1. An axonal calcium transient co-occurred with the soma 100% of the time (130 transients; n = 4 place cells); axonal transients are tightly coupled to somatic firing and thus provide an independent indicator that action potential firing causes our somatic calcium transients.

2. Averaging our smallest-amplitude somatic calcium transients produced a trace (Extended Data Fig. 1a) nearly identical in amplitude, shape and duration to what is expected from a single somatic action potential based on previous combined cell-attached and imaging measurements.

3. Place fields defined by somatic calcium transients are highly similar to those defined by somatic action potential firing in a comparable virtual track.

Taken together, these three points indicate that somatic action potential firing occurs throughout nearly the entire somatic calcium transient-defined place field. Further, somatic calcium transients varied in amplitude, consistent with a difference in the number of underlying action potentials, and varied in duration, consistent with the summation of multiple transients (Extended Data Fig. 1).

Dendritic calcium transients occur as a result of either non-regenerative or regenerative depolarizations that involve calcium influx through local NMDA and voltage-gated calcium channels. Excitatory input to a single spine leads to a non-regenerative post-synaptic depolarization typically detected as a spine-head-resistant (that is, restricted to the head of the spine) calcium transient with little or no shaft component. Dendritically generated spikes (such as Na⁺, NMDA and calcium spikes, collectively referred to here as dendrites) and bAPs also lead to dendritic calcium influx, but by contrast, these events are regenerative depolarizations often detected as both shaft- and spine-invasive calcium transients larger in both amplitude and spatial extent than transients associated with single-spine input.

In CA1 pyramidal neurons of navigating mice (not necessarily place cells), we observed calcium transients restricted to single spines, with no detectable shaft transient; however, we more frequently observed calcium transients invading all visible pixels of the recorded branch (both shaft and spines) that were larger in amplitude and spatial extent than single-spine transients (Extended Data Fig. 2d, e). These transients were considered non-regenerative or regenerative depolarizations, respectively. The regenerative dendritic events were defined here as ‘branch spikes’—events caused by either dendrites or bAPs or both.

Defining place fields. Place fields were identified and defined as described previously, with minor changes outlined below. Place fields were defined solely based on somatic (not dendritic) calcium transients. First, long running periods were defined in each direction in which mouse movement along the virtual track consisted of virtual velocity >7 cm s⁻¹ and run length >40 cm (straight run without changing direction or hitting the end of the track). These long run periods were first categorized based on the running direction (positive or negative direction) and then further subdivided into two categories based on the animal’s current task performance. Segments of time between two rewards in which long running periods of only one direction occurred were defined as high-reward-rate periods, all other long running periods were defined as low-reward-rate periods. Only high-reward-rate periods were analysed and all time-series data sets included here had at least 20 (mean of 50) long running segments during high-reward-rate periods in each of the positive and negative directions. For each running direction for each cell, the mean somatic ΔF/F was calculated as a function of virtual track position for 80 position bins and this mean fluorescence versus position plot was then averaged over 3 adjacent points.

Potential place fields were first identified as contiguous regions of this plot in which all of the points were greater than 25% of the difference between the peak somatic ΔF/F value (for all 80 bins) and the baseline value (mean of the lowest 20 out of 80 somatic ΔF/F values). These potential place field regions then had to satisfy the following criteria: 1. The field must be >13 cm in width; 2. The field must have one value of at least 10% mean ΔF/F; 3. The mean in field ΔF/F mean value must be >3 times the mean out of field ΔF/F value; and 4. Significant calcium transients must be present >20% of the time the mouse spent in the place field. Potential place field regions that met these criteria were then defined as place fields if their P value from bootstrapping was <0.05, as described previously and their mean widths were <125 cm.

For calculation of BSP, somatic firing intensity, spatial precision and centre of mass (see below) only consistent runs through the place field, in which a long running period covered >90% of the place field, were considered. Because place field spatial precision might be artificially increased in place fields occurring at the track ends due to edge effects, we only included place fields in which neither edge of the identified field was at a track end. Additionally, we determined that place field spatial precision (for the included fields) does not correlate with distance from track end (not shown).

Place field centre of mass and spatial precision index. To calculate the somatic transient centre of mass (COM) on each traversal (n) along the linear track when a somatic transient occurred in the defined place field, we first split location into 4.5 cm bins (i) and measured somatic ΔF/F in each bin. We then used the following equation to calculate the COM for each traversal (COMi):

\[ \text{COM}_i = \frac{\sum_k D_F k_i x_i}{\sum_k D_F k_i} \]

Where \( D_F \) is the somatic ΔF/F in bin i and \( x_i \) is the distance of bin i from the start of the track. We then calculated the peak ΔF/F weighted mean COM (COMw) from all traversals (n) (COMi for each traversal was weighted by the peak transient ΔF/F on that traversal \( A_i \)):

\[ \text{COM}_w = \frac{\sum_i A_i \text{COM}_i}{\sum_i A_i} \]

Spatial precision (SP) was then calculated as the inverse of the peak ΔF/F weighted COM, standard deviation as follows:

\[ \text{SP} = \sqrt{\frac{1}{\sum_i A_i (\text{COM}_i - \text{COM}_w)^2}} \]

Branch spiking analysis. The images shown (at left) in Figs 3a–c, 4b, e and Extended Data Fig. 8a were generated as follows: somatic and branch spiking events that occurred in the cell’s place field (if a cell had more than one place field, each field was treated separately) were converted to ones (a significant transient occurred) and zeros (no significant transient was detected). Branch-spike prevalence (BSP) was then calculated for each place field traversal with a somatic transient by dividing the sum of the number of branches with a detectable significant transient by the total number of recorded branches. The BSP distribution for each place field in each session could then be examined (Fig. 3a, b, c, Extended Data Figs 7 and 8 histograms) or used to calculate the average BSP for the field (the average of all BSP values for the session). Note that average BSP and resting fluorescence level for each place cell were not statistically significantly related (Extended Data Fig. 5g).

The branch spikes all co-occurred with somatic firing (except when stated otherwise; that is, in Fig. 2d and in Extended Data Figs 2 and 4b). All BSP numbers presented are from dendritic activity that occurred during somatic place field firing, except for specified values in Extended Data Fig. 8b (green dots).

To compare in-place field to out-of-place field BSP we examined 5 cells (Extended Data Fig. 8b green dots) that had place fields and also had at least 3 somatic calcium transients occurring randomly along the track (typically during running), but outside of the place field and the reward zones. Note that out-of-place field somatic and dendritic firing along the track (outside of reward zones) was extremely rare. For each recorded dendritic branch, the onset of each branch spike with respect to the co-occurring somatic transient was measured as the time difference between the onset of the somatic and dendritic significant transients (Fig. 2e and Extended Data Fig. 1d). If multiple branch spikes occurred during the somatic transient, the onset of each branch spike relative to the soma onset was measured.

To calculate how widespread each of the three main types of somato-dendritic observations were (Fig. 2a–c), we classified each event type using one dendritic
imaging plane and then included all of the branches from a more distal imaging plane (Extended Data Fig. 5a, b) and calculated the percentage of time our classification was correct before and after the distal plane was included.

**Somatic firing intensity**: The somatic firing intensity is the mean somatic calcium transient integral, calculated by summing the integrals of each somatic calcium transient that occurred in the place field and dividing the sum by the total number of place field somatic calcium transients.

**Branch-spike prevalence analysis for stable and transitory place cells.** Stable place cells were defined as cells with a mean place field centre of mass (COM,) on day 1 and day 2 that occurred within 15 cm of each other. In rare cases when place fields shifted between 15 and 50 cm, they were excluded from the analysis. Shifts of >50 cm were considered distinct place fields and so day 1 fields were classified as transitory. Place fields were excluded if they had fewer than 5 place field transients. Day 1 and day 2 were consecutive days. Average branch-spike prevalence and mean somatic firing intensity were measured on day 1 for both stable and transitory place fields.

**Population analysis for stable and transitory place cells (Extended Data Fig. 9).** Place cells were excluded if they had fewer than 5 place field transients, had a place field with one edge at a track end or if the field of view on day 2 did not include the cell. Day 1 and day 2 were consecutive days. Day 8 was seven days after day 1 and no imaging or training took place between day 2 and day 8.

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Extended Data Figure 1 | Somatic and dendritic place field $\text{Ca}^{2+}$-transient amplitudes and onset times. a–c, Histograms of somatic transient peak $\Delta F/F$ (a), branch-spike peak $\Delta F/F$ (b) and ratio of branch-spike peak $\Delta F/F$ to somatic transient peak $\Delta F/F$ (c). Inset in a shows the smallest significant amplitudes of somatic transients detected (grey) and their mean (blue; average triggered when grey transients were first $>2$ s.d. above the baseline). These small transients are nearly identical in amplitude, shape and duration to what is expected from single somatic action potentials based on previous in vivo combined cell-attached and imaging measurements in the visual cortex using GCaMP6f (ref. 21). d, Histogram showing the distribution of branch-spike onset time relative to somatic firing onset. Note that branch-spike onset leading somatic firing onset was not observed, and when branch spiking occurred in multiple branches, their onsets were nearly always simultaneous with respect to each other. Mean ± s.d. is shown for a–d.
unclassified dendritic events occurring without detectable somatic firing
classified single spine transients

Mean ΔF/F (%)
Area of fluorescence (μm²)

single spine transients
putative dendritically generated spikes

Low res
High res

Spine
Shaft

Non-regenerative
Regenerative

Spine
Shaft

Large area branch spiking
Putative dendritically generated spike

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Extended Data Figure 2 | Identifying putative dspikes and discriminating between regenerative and non-regenerative dendritic events. a, Mean ΔF/F of significant calcium transients localized to a single branch (using the same imaging parameters to measure co-occurring somatic firing and branch spikes in Figs 1–4), plotted against the area of significant ΔF/F increase (>3 s.d.). The mean ΔF/F and the area of significant fluorescence change was calculated for each transient as follows. ΔF/F movies were generated where each pixel value in each frame of the movie represents the change in fluorescence with respect to the baseline mean for that pixel. The frames during the transient of interest were averaged together and the number of pixels with ΔF/F > 3 were counted, converted to μm² and used as the area of significant fluorescence change. The mean ΔF/F value for the transient was then calculated as the mean value of the pixels with ΔF/F > 3. Black circles represent known single-spine calcium transients acquired using low resolution time-series acquisition (the same resolution used to identify branch spiking), but confirmed as spines using higher-resolution time-series acquisitions where calcium transients were restricted to the spine head (see d and e). Green circles represent calcium transients restricted to a single dendritic branch and occurring in the absence of somatic firing. Because no high-resolution time-series were acquired from these structures, it was unknown whether they represent transients restricted to single spines or branch spiking. The panels and analysis presented in b and c indicate that a majority of these events are due to branch spiking and not single-spine transients. b, As a combined metric of mean ΔF/F and area of fluorescence change, we normalized mean ΔF/F and area of fluorescence to their maximums and measured the distance from the origin (the normalized Euclidean distance of each point in a); we refer to this metric as the activity area index (AAI). Histogram showing that known spine transients all fall into the lowest AAI bins (black bars; AAI < 40), and most unclassified events (putative dspikes) in a have higher AAI (green bars). The events in the larger AAI bins (with greater mean ΔF/F covering a larger area; AAI > 40; separated from the lower AAI bins by the dashed line) fit known characteristics of dspikes. c, Using the AAI threshold defined in b, most of the unclassified transients fall into a separate group (red) from the known single-spine calcium transients (8 of the 13 unclassified transients had distinctly larger AAI compared to spine transients, blue) and were therefore considered branch spikes (putative dspikes). d, Example calcium transients restricted to a single spine head (bottom left) and invading both spine head and shaft (bottom right) in a place cell. Mean somatic place field is indicated by the grey dashed line. e, Example of a stretch of dendrite imaged at low (left) and high (right) resolution in a navigating mouse. The red box and ROIs indicate the same structures that were imaged at both low and high resolution. The same spine head is indicated by arrows at different resolutions in all images. Calcium transients restricted to the same single spine head are shown at both low and high resolution by the colour-coded per cent ΔF/F map and by the per cent ΔF/F traces labelled non-regenerative; note that the shaft ROI includes other non-active spines. Calcium transients invading the branch and all spines are shown at both low and high resolution by the colour-coded per cent ΔF/F map and by the per cent ΔF/F traces at the bottom, labelled regenerative. f, Image of a dendritic branch split into four ROIs. Calcium transients are seen in all parts of the branch during large area branch spiking (see both colour-coded map and traces of per cent ΔF/F). A putative dspike, during navigation, in the same branch causes a significant increase in fluorescence in only part of the branch (ROI 2), which includes the shaft.
Extended Data Figure 3 | Expanded views of traces showing the variability in detectable events in the soma, dendrites and axon. Traces from Fig. 1b showing variable branch-spike prevalence in the same cell. Three events are shown amplified (for the amplified traces, the bottom y-axis scale bar refers to the green, blue and cyan dendritic traces, and the top scale bar refers to the red and brown soma and axon traces).
Extended Data Figure 4 | Expanded views of traces showing variability of dendritic branch spiking during somatic place field firing. **a**, Traces from Fig. 2 are shown here amplified (each trace has a y-axis scale bar representing 100% ΔF/F). **b**, Two examples of branch spikes detected in single branches in the absence of detectable somatic firing and branch spiking in other dendrites. In each case the soma y-axis is amplified relative to the dendrite traces to show the absence of detectable somatic transients.
Extended Data Figure 5 | Branch spiking in a single dendritic plane is representative of activity throughout a large portion of the dendritic arbour and average branch-spike prevalence is independent of the number of sampled branches in the field, their distance from the soma and the resting fluorescence level of the soma. a, An example of spiking throughout all imaged branches during 3-plane imaging. Co-acquired somatic and dendritic time-series were recorded using three planes; dendritic plane 1 is approximately mid distance between the soma and dendrite tips, dendritic plane 2 is near the branch tips. Numbered arrows indicate branches connected to the imaged soma with the same numbers in dendritic plane 1 and 2 indicating the same branch. An example run through the cell’s somatic place field (grey) and corresponding ΔF/F traces from the soma and numbered branches from the two dendritic planes is shown. Distance along dendrite between branch and soma, and per cent distance from soma to dendritic tip, are on the right of each trace. b, Same as a, except a different cell where branch spiking is absent throughout all imaged branches in both dendritic planes. c, Scatter plot showing the average branch-spike prevalence for individual branches during somatic firing as a function of branch distance from the soma (each point represents one branch). The average branch-spike prevalence for individual branches is not significantly related to the distance from the soma (Spearman’s rank correlation coefficient: $P = 0.16$, $\rho = -0.128$). d, Branch-spike peaks normalized to co-occurring somatic peaks during place field traversals from all place cells and branches plotted against branch distance from soma. Spearman’s rank correlation coefficient shows a significant correlation ($P = 5.4 \times 10^{-12}$, $\rho = 0.135$) and a linear fit shows a significant positive slope within 95% confidence bounds. e, Histogram showing the branch-spike prevalence for individual dendritic branches taken from all cells. f, Average branch-spike prevalence (for each place field) plotted against the number of branches sampled in the imaging field shows no significant correlation (Spearman’s rank correlation coefficient: $P = 0.75$, $\rho = -0.057$). g, Average branch-spike prevalence (for each place field) plotted against normalized resting fluorescence intensity of the soma. Relative resting fluorescence between cells was calculated by dividing the mean measured fluorescence of each soma (not during transients; excluding nucleus) by the squared laser power arriving at the soma (which was estimated based on the soma depth below the surface). Spearman’s rank correlation coefficient shows no significant correlation ($P = 0.9$, $\rho = -0.034$).
Extended Data Figure 6 | Place field branch spikes in basal and proximal apical dendrites often co-occur. Co-acquired somatic, basal dendritic and apical dendritic (depicted in cartoon in the centre) time-series from two example place cells showing somatic spiking with co-occurring branch spikes (top) and somatic spiking in the absence of detectable branch spikes (bottom) in the basal and main apical dendrites (89.6 ± 19.5% correlation between spiking in the basals and main apical; mean distance of apical site to soma, 109 ± 38 μm; n = 6 place fields; mean ± s.d.) during place field traversals (grey). Note that our findings from the basal and proximal apical dendrites may not extend to the oblique dendrites or apical tuft.
Extended Data Figure 7 | The distribution of branch-spike prevalence differs from a model in which each branch fires independently with a specific probability during place field traversals. Seven histograms from seven example place fields showing the distribution of branch-spike prevalence in each field for real data (grey bars) and modelled data (red bars). The modelled data was generated for each place field example as follows. The probability ($P_i$) that each dendritic branch ($i$) in the imaging field would spike in the place field was defined as the branch-spike prevalence for the individual branch (total number of traversals in which branch $i$ spiked divided by the total number of traversals; from real data). For modelled/mocked place field traversals, each branch fired with its random probability $P_i$ and the branch-spike prevalence (fraction of the total number of branches with spikes during the traversal) was calculated. The distribution of branch-spike prevalence was generated for 1,000 modelled/mocked place field traversals (red bars). A two-sample Kolmogorov–Smirnov test was used to compare real and modelled distributions ($P$ values shown in each plot).
**Extended Data Figure 8** | Average branch-spike prevalence can differ between different place fields of the same cell and also between in-place field and out-of-place field somatic firing. **a**, Coloured plots (left) show occurrence of detectable spiking in each branch (blue or black) during somatic place field firing (red) in different co-occurring place fields (A and B, in different running directions) of the same place cell. Right, histograms of branch-spike prevalence on each traversal for the two place fields. Cartoons (far right) do not represent real data. Note that the running behaviour differed in the two running directions causing differences in the number of traversals reaching behaviour criteria. **b**, Plot comparing average branch-spike prevalence of two distinct place fields in the same place cells (black) or of in-place field versus out-of-place field somatic firing in the same cells (green).
Extended Data Figure 9 | Place field spatial precision is correlated to place field stability. **a**, Schematic showing single-plane imaging of the same population of cell somata over multiple days (1, 2 and 8). **b**, Population images with place cells colour coded by their place field location. Top and bottom rows show place cells in the negative and positive track running directions, respectively. Examples of place cell field fate shown at right: transitory fields occurring on day 1 only (indicated with a minus symbol on the right; black arrows on the left), fields persisting for at least one day (indicated by asterisks on right, white open arrowheads on left) or seven days (indicated by double asterisks on right; white arrows on left); no symbol indicates that the field did not meet the criteria for inclusion (Methods). **c**, Mean fields of the same cell measured over different days with COM locations from day 1 (bottom; black circles) indicating a precise place field. **d**, Spatial precision is significantly higher in stable versus transitory place fields (0.127 ± 0.016 cm⁻¹ versus 0.065 ± 0.007 cm⁻¹, respectively; t-test; \( P = 0.0003 \)). In **d**, individual data points are depicted by circles to the right of bars and error bars represent s.e.m.
**Extended Data Figure 10 | Examples of dissociation between somatic firing and branch spiking in a place cell.** a, ΔF/ΔF traces from the (co-acquired) soma and numbered dendritic branches of a place cell during the same imaging session demonstrate that somatic firing and branch spiking are often dissociated. b, Plot of somatic firing intensity versus branch-spike prevalence for all individual place field traversals from all cells (open circles) and binned (solid circles; error bars represent s.e.m.). Branch spiking did not strongly correlate with mean (binned) somatic firing intensity (Spearman’s rank correlation coefficient: $P = 0.04; \rho = 0.57$).