LETTER

Sensory stimulation shifts visual cortex from synchronous to asynchronous states

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In the mammalian cerebral cortex, neural responses are highly variable during spontaneous activity and sensory stimulation. To explain this variability, the cortex of alert animals has been proposed to be in an asynchronous high-conductance state in which irregular spiking arises from the convergence of large numbers of uncorrelated excitatory and inhibitory inputs onto individual neurons1–4. Signatures of this state are that a neuron’s membrane potential ($V_m$) hovers just below spike threshold, and its aggregate synaptic input is nearly Gaussian, arising from many uncorrelated inputs5–7. Alternatively, irregular spiking could arise from infrequent correlated input events that elicit large fluctuations in $V_m$ (refs 5, 6). To distinguish between these hypotheses, we developed a technique to perform whole-cell $V_m$ measurements from the cortex of behaving monkeys, focusing on primary visual cortex (V1) of monkeys performing a visual fixation task. Here we show that, contrary to the predictions of an asynchronous state, mean $V_m$ during fixation was far from threshold (14 mV) and spiking was triggered by occasional large spontaneous fluctuations. Distributions of $V_m$ values were skewed beyond that expected for a range of Gaussian input5–7, but were consistent with synaptic input arising from infrequent correlated events5,6. Furthermore, spontaneous fluctuations in $V_m$ were correlated with the surrounding network activity, as reflected in simultaneously recorded nearby field potential. Visual stimulation, however, led to responses more consistent with an asynchronous state: mean $V_m$ approached threshold, fluctuations became more Gaussian, and correlations between single neurons and the surrounding network were disrupted. These observations show that sensory drive can shift a common cortical circuitry from a synchronous to an asynchronous state.

Cortical neurons show variable activity even after efforts are taken to fix temporal variations in sensory stimuli and attentional state8. This ongoing activity affects stimulus encoding and synaptic plasticity9, but its neural basis is not well understood. One hypothesis is that the variable activity in alert animals arises from connections between numerous uncorrelated excitatory and inhibitory inputs10–12. Such a network is consistent with studies of neural architecture13, and shows spiking statistics similar to those measured in extracellular studies8. Predictions of this hypothesis12–14 are that numerous uncorrelated inputs (Fig. 1a, bottom) cause $V_m$ to hover near spike threshold (Fig. 1a, top left) and to show distributions that are near Gaussian or skewed with tails at depolarized potentials (Fig. 1b, top right). In contrast, neurons may receive correlated input15 (Fig. 1b, bottom) such that $V_m$ lies far below threshold and shows infrequent large excursions (Fig. 1b, top left), forming skewed distributions with tails at depolarized potentials (Fig. 1b, top right). Measurements of $V_m$ from awake, non-behaving cats suggest an asynchronous state16, but are also consistent with correlated input17. Data from behaving rodents in various attentional states have suggested different pictures18–20, but unequivocally, because of the potential contributions of uncontrolled sensory inputs and attentional states to $V_m$ dynamics. Extracellular recordings in drowsy humans have demonstrated correlated spontaneous cortical activity, leaving open the possibility that correlations are absent during alertness21. Accordingly, we performed the first whole-cell $V_m$ measurements from the cortex of monkeys actively engaged in a visual fixation task, allowing us to examine $V_m$ in single V1 neurons of alert primates while minimizing variability due to sensory stimuli, eye movements and attentional state.

We obtained intracellular22, whole-cell19,20, current-clamp measurements of $V_m$ from 31 V1 neurons in three macaque monkeys while they viewed gratings of different orientations (see Supplementary Information and Supplementary Video). Each trial began when a fixation spot was displayed at the centre of a monitor in front of the monkey. The monkey had to shift gaze to the fixation point and maintain tight fixation for at least 1,500 ms to receive a reward. A drifting sinusoidal grating was presented for 1,000 ms while the monkey was maintaining strict fixation. We analysed $V_m$ during the fixation period only from trials in which the monkey performed the task successfully. V1 neurons were orientation-selective, and were classified as simple or complex (Supplementary Information and Extended Data Fig. 1).

Comparison of $V_m$ in blank trials in which no visual stimulus was presented (Fig. 2a–c, left) with suprathreshold responses evoked by preferred orientation gratings (Fig. 2a–c, right) shows that blank trial $V_m$ was generally far from spike threshold. There were occasional large depolarizations during blank trials, which were manifested in the positive skewness of $V_m$ amplitude histograms: these had longer tails at depolarized potentials, even though traces had had spikes removed (Fig. 2a–c, left, orange histograms; see also Supplementary Information and Extended Data Fig. 2). Across neurons, the median distance between blank trial

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Figure 1 | $V_m$ characteristics depend on network state. a, Diagram of an asynchronous high-conductance state. A neuron receives numerous uncorrelated inputs (bottom), $V_m$ hovers near spike threshold (top left), forming distributions with low or negative skewness $\zeta$ (top right). b, A neuron may instead receive correlated inputs (bottom) such that $V_m$ lies farther from spike threshold and shows occasional large fluctuations (top left), forming distributions with high skewness $\zeta$ (top right).
V_m and spike threshold was 13.9 mV (Fig. 2d). The median skewness of 0.72 (Fig. 2e, f) differs from the near zero or negative skewness expected for a range of Gaussian input (Fig. 1a; see also Supplementary Information and Extended Data Fig. 2c), but is consistent with synaptic input arising from infrequent correlated events (Fig. 1b). These data show that in the absence of visual stimulation, V1 of macaques performing a visual fixation task is not in an asynchronous high-conductance state1–4.

By comparison, visual stimulation depolarized neurons (Fig. 2a–c, right, and Fig. 3a–c) and decreased the skewness of V_m deviations from the mean (Fig. 3d; see also Supplementary Information and Extended Data Fig. 3), an effect that was significant across the population (Fig. 3d; Wilcoxon signed-rank test, P < 0.0001; see also Supplementary Information and Extended Data Fig. 4). Together with observed increases in membrane conductance during visual stimulation11,22 (Supplementary Information and Extended Data Fig. 5), these results suggest that visual stimulation shifts the cortical network towards an asynchronous high-conductance state1–4.

Visual stimulation also caused significant changes in the power of V_m fluctuations. Membrane potential showed greater power at low frequencies than at high frequencies during fixation, both before and during visual stimulation. Visual stimulation increased the power of V_m fluctuations from the trial average (that is, residuals) at high frequencies (30–50 Hz) but did not cause systematic changes at low frequencies (30–50 Hz, right). Distribution across neurons of mean V_m for blank trials is the average of each neuron’s normalized mean-subtracted distribution. Light and dark bars in d and f indicate simple and complex cells, respectively.

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Figure 2 | Occasional large spontaneous fluctuations in V_m during fixation. a–c, V_m (top), horizontal and vertical eye position (bottom) from three blank trials, and corresponding histograms from the period indicated by the orange line (left). Horizontal scales for the histograms are logarithmic. Right: traces from three preferred orientation trials; the arrow indicates stimulus onset. Lower and upper dashed lines indicate the period of required fixation and the spike threshold, respectively. Results in a, b and c are from different neurons. d, Distribution across neurons of distance between mean V_m during blank trials and spike threshold (n = 26). e, The population distribution of V_m for blank trials is the average of each neuron’s normalized mean-subtracted distribution. f, Distribution across neurons of blank trial V_m skewness. Light and dark bars in d and f indicate simple and complex cells, respectively.

Figure 3 | Visually evoked V_m is closer to threshold and has more Gaussian fluctuations. a–c, Left: V_m (top) and eye position (bottom) over pre-stimulus, stimulus and post-stimulus periods during fixation (green, lavender and grey bars, respectively) and inter-trial periods. Right: pre-stimulus, stimulus period raw value and residual (green, lavender-filled and lavender-outlined respectively) histograms and power spectra; shaded areas indicate low and high frequency ranges. Results in a, b and c are from different neurons. d, Skewness of V_m residuals during the preferred orientation versus that during blank trials, for each neuron. e, Mean power in V_m residuals during blank versus visual stimulation at low frequencies (0.5–4 Hz, left) and high frequencies (30–50 Hz, right). f, Distribution across neurons of mean V_m during stimulus (lavender) and post-stimulus (grey) periods, relative to mean pre-stimulus V_m. Light and dark circles in d indicate simple and complex cells, respectively.
This was the case. During fixation with no visual stimulus, deflections indicating spontaneous increases in activity are evident in $V_m$ and LFP (Fig. 4a, left, depolarization for $V_m$ downward deflections for LFP). These deflections are coincident in both signals (asterisks in Fig. 4a); across our population, the zero-lag $V_m$–LFP cross-correlation was negative during blank trials, reflecting coincident activation of the network and individual neurons (Fig. 4d, green, median cross-correlation $-0.24$; Wilcoxon signed-rank test, $P < 0.01$). To determine whether visual stimulation alters this relationship we examined $V_m$–LFP correlations after trial averages had been subtracted (Fig. 4b, c, centre panels). Correlations declined when grating gratings were presented (Fig. 4b–d; Wilcoxon signed-rank test, $P < 0.01$), such that the median cross-correlation was nearer zero (Fig. 4d, lavender; Wilcoxon signed-rank test, $P = 0.91$), providing further evidence that visual stimulation drives V1 towards an asynchronous state. The visually-evoked decline in $V_m$–LFP correlation was apparent for low frequency (0.5–4 Hz), but not high frequency fluctuations (Fig. 4e; Wilcoxon signed-rank test, $P < 0.01$ (0.5–4 Hz), $P = 0.13$ (30–50 Hz)); $V_m$–LFP coherence decreased at low (0.5–4 Hz), but not high frequencies (30–50 Hz) (Fig. 4b, c, right, and Fig. 4f; Wilcoxon signed-rank test, $P < 0.05$ (0.5–4 Hz), $P = 0.34$ (30–50 Hz); see also Supplementary Information and Extended Data Fig. 7).

We have shown that in the absence of visual stimulation, V1 in alert behaving primates is not in an asynchronous high-conductance state1–4.

Rather, spontaneous $V_m$ fluctuations are non-Gaussian and characterized by occasional excursions from rest, consistent with synaptic input arising from infrequent correlated events5,6. In our recordings, sensory stimulation drove V1 towards an asynchronous state, as visually evoked $V_m$ was closer to spike threshold, showed more Gaussian fluctuations and became less correlated with low-frequency LFP. The visually evoked reduction in correlation between $V_m$ and LFP is consistent with previously reported decreases in spiking correlations23,24. In an analogous fashion, the correlated activity patterns observed in mouse sensory cortex during quiet wakefulness are disrupted by thalamic activation25. (See also Supplementary Information and Extended Data Fig. 8.) Our records focused on activity in superficial cortical layers; membrane potential characteristics may differ across layers, potentially reflecting laminar specificity in network state26.

How can cortical circuitry support synchronous and asynchronous states? One salient difference between the states was the amount of external input: without visual stimulation the thalamic drive to cortex is weak, whereas visual stimulation activates those afferents. We propose that this difference in afferent drive explains the shift in network state. Our proposal unifies observation and theory: a lower input spike rate reduces synaptic input so that $V_m$ lies further from threshold; postsynaptic potentials due to different sources are less likely to overlap in time and instead appear as distinct events. Crucially, theory indicates that a low thalamic

![Figure 4](image-url)
spike rate destabilizes the asynchronous state towards low-frequency correlations\textsuperscript{4,27,28}, but higher thalamic spike rates drive the network towards an asynchronous state in which correlations weaken\textsuperscript{4,27,28}, as observed in our data. It is clear that external drive alters the cortical state\textsuperscript{29}, but internal factors are also essential. In extrastriate cortex, certain increases in overall response that is also accompanied by a decline in the correlation between neurons\textsuperscript{29,30}. Explaining how these external and internal drives are synthesized will require understanding how V1 interacts with downstream areas.

**METHODS SUMMARY**

Macaque monkeys were trained to perform a visual fixation task (see also Supplemental Information and Extended Data Fig. 9), and implanted with recording chambers. Blind in vivo whole-cell–patch recordings were performed\textsuperscript{19,20}. Patch pipettes were filled with (in mM) 135 potassium gluconate, 4 NaCl, 0.5 EGTA, 2 MgATP\textsuperscript{2-}, 10 phosphocreatine disodium, 10 HEPES, pH adjusted to 7.3 with KOH (Sigma-Aldrich) (see also Supplementary Information and Extended Data Fig. 10).

**Online Content** Any additional Methods, 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.

Received 27 September 2013; accepted 17 February 2014.

Published online 30 March 2014.

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**Supplementary Information** is available in the online version of the paper.

**Acknowledgements** We thank T. Calkic for assistance with this project, and J. Hanover, D. Ferster, K. D. Miller and A. C. Huk for discussions and comments. A.Y.Y.T., B.S. and N.J.P. were supported by grants from the National Institutes of Health (NIH) (EY-016454 and EY-16752). D. Ferster, K. D. Miller and A. C. Huk for discussions and comments. A.Y.Y.T., B.S. and N.J.P. were supported by grants from the National Institutes of Health (NIH) (EY-019288) and the Pew Charitable Trusts; Y.C. and E.S. were supported by grants from the NIH (EY-016454 and EY-16752).

**Author Contributions** A.Y.Y.T., E.S. and N.J.P. initiated and designed the study. All authors collected the data, analysed the results, discussed the findings and wrote the paper. A.Y.Y.T., Y.C. and B.S. contributed equally to this work. E.S. and N.P. contributed equally to this work.

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Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to A.Y.Y.T. (atyy@alum.mit.edu) or N.J.P. (nicolaujas@utexas.edu).
METHODS

All procedures were approved by the University of Texas Institutional Animal Care and Use Committee and conformed to National Institutes of Health standards. Our general experimental procedures in behaving macaque monkeys have previously been described in detail10,12,13.

**Behavioural task and visual stimulus.** Three adult male macaque monkeys (Macaca mulatta) were trained to perform a visual fixation task in which gratings of different orientations were presented. Each trial began when a fixation spot was displayed at the centre of a monitor in front of the monkey. The monkey had to shift gaze to the fixation point and maintain fixation within a small window (less than 2° full width) for at least 1,500 ms to receive a reward. A drifting sinusoidal grating was presented at a randomized orientation for 1,000 ms while the monkey was maintaining strict fixation, thus minimizing variability due to eye movements. (See Supplementary Information and Extended Data Fig. 9 for characteristics of post-fixation saccades.)

Visual stimuli were presented on a gamma-corrected high-end 21-inch colour display (Sony Trinitron GDM-F520) at a fixed mean luminance of 30 cd m\(^{-2}\). The display subtended 20.5° × 15.4° at a viewing distance of 108 cm and had a pixel resolution of 1,024 × 768, 30-bit colour depth and a refresh rate of 100 Hz. Visual stimuli were generated by using a high-end graphics card on a dedicated PC, using custom-designed software. Behavioural measurements and data acquisition were controlled by a PC running a software package for neurophysiological recordings from alert animals (Reflective Computing). Eye movements were measured with an infrared eye-tracking device (Dr Bouis).

**Whole cell recordings.** Recording chambers were located on the dorsal portion of V1, with the anterior portion of the chamber reaching close to the lunate sulcus and the border between V1 and V2. We verified the retinotopic organization by voltage-sensitive dye imaging35, and by recording multiunit activity or local field potential with tungsten microelectrodes (Alpha Omega Co; MicroProbes for Life Sciences). The cortex in our cranial windows represents stimuli that are approximately 2.5–5° away from the fovea in the lower quadrant of the contralateral hemifield.

Intracellular recordings of \(V_m\) (refs 18, 34, 35) were obtained with blind in vivo whole-cell recordings36–38. The recording chamber was filled with 2–4% agarose in artificial cerebrospinal fluid (CSF). Intracellular records were from neurons in the top 1,300 μm of V1. As a reference electrode, a silver–silver chloride wire was inserted into the agarose. The potential of the CSF was assumed to be uniform and equal to that of the reference electrode. Pipettes (6–12 MΩ) were pulled from borosilicate glass capillaries (KG-33, 1.2 mm outer diameter, 0.70 mm inner diameter; King Precision Glass) on a P-2000 micropipette puller (Sutter Instruments). Patch pipettes were filled with (in mM) 135 potassium glutamate, 4 NaCl, 0.5 EGTA, 2 MgATP\(^2−\), 10 phosphocreatine disodium, 10 HEPES, pH adjusted to 7.3 with KOH (Sigma–Aldrich). Whole-cell current-clamp recordings were performed with an Axoclamp 2B Microelectrode Amplifier (Molecular Devices). We subtracted 7 mV from all raw membrane potential values to compensate for the liquid junction potential39. (See Supplementary Information and Extended Data Fig. 10 for intrinsic properties of recorded neurons.)

**Data analysis.** We analysed \(V_m\) during the fixation period in trials during which the monkey performed the task successfully, provided that the mean \(V_m\) in the absence of a visual stimulus was less than −50 mV. \(V_m\) was detrended by high-pass filtering at 0.1 Hz. Data were analysed with MATLAB (Mathworks). Shot noise contributions to \(V_m\) were assessed by the skewness37–39 of \(V_m\) distributions. Coherence estimates were performed with Chronux40, a MATLAB library (freely available from http://chronux.org/).

**Data analysis for Supplementary Information.** The relationship between spike rate \(R\) and \(V_m\) was described with a threshold followed by a power law41–43: \(R = A|V_m - V_{t0}|^p\), where \(A\) is a fitted constant, \(V_{t0}\) is the resting membrane potential, \(p\) indicates rectification, and \(p\) is the fitted exponent. Orientation selectivity was assessed with an orientation selectivity index44,45 (vector average = 1 – circular variance). Temporal modulation was assessed with the Fourier component of the response with the same temporal frequency as the moving sinusoidal grating visual stimulus divided by the time-averaged response\(^4\) (\(F/R_s\)). Simulations of Hodgkin–Huxley neurons used parameters adapted from refs 47 and 48, and were performed with Brian49,50. We estimated membrane conductance from voltage responses to hyperpolarizing current pulses of constant amplitude, and a fit of a sum of two exponentials to the voltage response51:

\[
V'(t) = I_m/[R_{M}(1 - \exp(-t/\tau_{M})) + (R_{E}(1 - \exp(-t/\tau_{E})))
\]

where \(V\) is the voltage response, \(t\) is time, \(I_m\) is injected current, \(R_{M}\) is membrane resistance, \(\tau_{M}\) is membrane time constant, \(R_{E}\) is electrode resistance and \(\tau_{E}\) is electrode time constant. Membrane conductance is \(1/R_{M}\).

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Extended Data Figure 1 | Orientation tuning of $V_m$ and spike rate. a, $V_m$ responses (top traces), eye position traces (bottom pairs of traces) from three blank trials (left), three trials at the preferred orientation (centre), and three trials at the orthogonal orientation (right). b, Trial averaged $V_m$ (top) and spike rate (bottom) for all orientations, from the neuron in a. c, Spike rate versus membrane potential, and best-fit thresholded power law, from the neuron in a. d, Orientation tuning curves for $V_m$ and spike rate, and predicted spike rate orientation tuning curve using the $V_m$ orientation tuning curve and the best-fit thresholded power law in c, from the neuron in a. e, Orientation selectivity index (OSI) for spike rate versus OSI for $V_m$. Lines represent expected relationships between spike rate OSI and $V_m$ OSI for thresholded power laws with exponents 2, 3 and 5 (blue, red and black, respectively). f, Fourier component of the response with the same temporal frequency as the moving sinusoidal grating visual stimulus divided by the time-averaged response for spike rate ($R_1/R_0$) versus that for $V_m$ ($V_1/V_0$). Lines represent expected relationships between $R_1/R_0$ and $V_1/V_0$ for thresholded power laws with exponents 2, 3 and 5 (blue, red and black, respectively).
Extended Data Figure 2 | Estimation and implication of \( V_m \) skewness during blank trials. a, Gaussian excitatory (black) and inhibitory (red) conductances, \( V_m \) with spiking disabled (green), \( V_m \) with spiking enabled (light blue), and \( V_m \) with spikes removed (dark blue), and corresponding \( V_m \) amplitude histograms and skewness values \( \zeta \), for a simulated neuron with Hodgkin–Huxley conductances. b, \( V_m \) with spiking (light blue) and with spikes removed (dark blue) and corresponding \( V_m \) amplitude histograms and skewness values \( \zeta \), for a recorded neuron. c, Apparent skewness from \( V_m \) with spikes removed versus skewness from \( V_m \) with spiking disabled from a simulated neuron with Hodgkin–Huxley conductances, for a range of Gaussian inputs.
Extended Data Figure 3 | Estimation of $V_m$ skewness during visual stimulation trials. a, Raw traces from several trials. b, Traces after bandpass filtering and spike removal. c, $V_m$ responses from each cycle (top grey traces), cycle-averaged response (top black trace) and histogram of $V_m$ responses (top histogram); residual traces from each cycle after subtraction of cycle-averaged response (bottom grey traces), cycle-averaged residuals (bottom black trace) and histogram of $V_m$ residuals (bottom histogram). Note the change in vertical scale from top to bottom panels.
Extended Data Figure 4 | Joint distribution of $V_m$–threshold distance and skewness. 

a, Joint distribution of $V_m$–threshold distance and skewness $\zeta$ during blank trials. 
b, Joint distribution of $V_m$–threshold distance and skewness $\zeta$ during preferred orientation trials.
Extended Data Figure 5 | Membrane conductance during blank and visual stimulation trials. a, Distribution of membrane resistance (left) and corresponding membrane conductance (right) during blank trials. b, Change in membrane conductance during visual stimulation in two example neurons during blank (left), preferred (centre) and 45° from preferred (right) trials. Each row shows data from a different neuron.
Extended Data Figure 6 | Power spectra of $V_m$ and LFP fluctuations from the trial average. a, Power spectrum of $V_m$ (top panels) and LFP (bottom panels) fluctuations from the trial average (residuals) during blank trials (left panels), residuals during preferred orientation stimulation (middle panels), and raw $V_m$ traces during preferred orientation stimulation (right panel). Each trace corresponds to an individual neuron. b, Population-averaged ratio of power spectrum at the preferred orientation to power spectrum for blank trials for $V_m$ fluctuations from the trial average (‘$V_m$ residuals’, left panel), LFP fluctuations from the trial average (‘LFP residuals’, middle panel), and raw $V_m$ (right panel). Error bars are jack-knifed standard errors.
Extended Data Figure 7 | V_m–LFP coherence magnitude for blank trials and visual stimulation. Population-averaged V_m–LFP coherence magnitudes for blank trials (green) and at the preferred orientation (lavender). Error bars are jack-knifed standard errors.
Extended Data Figure 8 | Decreased magnitude of $V_m$–LFP correlation during a flashed stimulus in a visual saccade task. a, Each trial began when a fixation spot was displayed at the centre of a monitor in front of the monkey. The monkey had to shift gaze to the fixation point and maintain tight fixation for at least 1,500 ms. A flashed Gabor target stimulus appeared at a random time between 1,000 and 1,500 ms after the monkey had established tight fixation. The monkey had to saccade to the target stimulus within 600 ms to receive a reward. We analysed $V_m$ and LFP only from trials in which the monkey performed the task successfully. b, Simultaneously recorded $V_m$ and LFP, as well as eye movement traces, in two trials from an example neuron. Asterisks indicate near-simultaneous deflections in $V_m$ and LFP during the pre-stimulus fixation period. Grey shading indicates the analysis period for correlations during the flashed Gabor stimulus; we included 30 ms after saccade onset in this period, because the visual latency for spike responses in the lateral geniculate nucleus is greater than 30 ms. c, Zero-lag cross-correlation between $V_m$ and LFP fluctuations from the trial average during the flashed Gabor stimulus versus during the pre-stimulus period.
Extended Data Figure 9 | Summary of first saccade latency and peak velocity in monkeys T and W, which together contributed the majority of the recorded data. 

**a**, Top: histogram of latency of first saccade after fixation point termination in three neurons (158 trials) in monkey W. Arrow indicates median latency (217 ms). In 1.9% of the trials no saccade was detected in the 600 ms after fixation point termination. Bottom: histogram of peak eye velocity for first saccades during the 600 ms after fixation point offset. Arrow indicates median peak velocity (292° s⁻¹). **b**, Results from eight neurons (464 trials) in monkey T. The format is the same as in **a**. Median latency is 314 ms and median peak velocity is 229° s⁻¹. Monkey W tended to make larger saccades away from fixation, whereas monkey T tended to make smaller saccades and in a small subset of the trials remained close to the fixation point location until the next trial was initiated. This may reflect the fact that the minimal inter-trial interval was shorter in monkey T than in monkey W. The short latency of the saccades after fixation point termination in the vast majority of the trials indicates that both monkeys were alert and attentive and were actively engaged in maintaining tight fixation.
Extended Data Figure 10 | Regular-spiking neurons. a. $V_m$ response to injections of current steps of different magnitudes in an example neuron. b. Interspike interval during the current step versus interval ordinal. The interspike interval increased with interval ordinal, indicating that this neuron was regular-spiking.