LETTER

Inhibition dominates sensory responses in the awake cortex

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The activity of the cerebral cortex is thought to depend on the precise relationship between synaptic excitation and inhibition⁴–⁷. In the visual cortex, in particular, intracellular measurements have related response selectivity to coordinated increases in excitation and inhibition⁸–¹⁰. These measurements, however, have all been made during anaesthesia, which strongly influences cortical state¹ⁱ and therefore sensory processing². The synaptic activity that is evoked by visual stimulation during wakefulness is unknown. Here we measured visually evoked responses—and the underlying synaptic conductances—in the visual cortex of anaesthetized and awake mice. Under anaesthesia, responses could be elicited from a large region of visual space¹² and were prolonged. During wakefulness, responses were more spatially selective and much briefer. Whole-cell patch-clamp recordings of synaptic conductances⁵,¹⁷ showed a difference in synaptic inhibition between the two conditions. Under anaesthesia, inhibition tracked excitation in amplitude and spatial selectivity. By contrast, during wakefulness, inhibition was much stronger than excitation and had extremely broad spatial selectivity. We conclude that during wakefulness, cortical responses to visual stimulation are dominated by synaptic inhibition, restricting the spatial spread and temporal persistence of neural activity. These results provide a direct glimpse of synaptic mechanisms that control sensory responses in the awake cortex.

To investigate how wakefulness affects the synaptic basis of visual selectivity, we made local field potential (LFP) recordings and whole-cell recordings of membrane potential (Vm) in layer 2/3 of the primary visual cortex (V1) in both anaesthetized and awake mice.

We first examined spontaneous activity and found that this activity was markedly affected by wakefulness (Fig. 1a, b). Under two widely used anaesthetic regimes, slow fluctuations in both Vm and LFP were common (Fig. 1a and Supplementary Fig. 4). During wakefulness, these slow fluctuations were abolished and were replaced by higher frequency activity of both Vm and LFP (Fig. 1b and Supplementary Fig. 1). In nearly all cases, Vm was distributed unimodally during waking⁹,¹⁰ but bimodally during anaesthesia (Supplementary Fig. 1a, b). Spontaneous firing rates were similarly low in the two conditions (anaesthetized, 0.3 ± 0.2 spikes s⁻¹, n = 14; awake, 0.1 ± 0.1 spikes s⁻¹, n = 14; P = 0.07). These results indicate that in awake mice, V1 rarely shows the spontaneous fluctuations that are common during anaesthesia or sleep and that have been reported in area S1 of quietly awake mice¹¹.

We next probed visual responses with flashed bars and found that wakefulness had a striking effect on response duration (Fig. 1c–f). Briefly flashed bars (100 ms duration, at 1.5 s intervals) elicited long-lasting LFP responses under anaesthesia (Fig. 1c; 553 ± 22 ms, n = 7 mice) and much briefer responses during wakefulness (Fig. 1d; 171 ± 11 ms, n = 7; P < 0.001). This striking difference in LFP response duration was observed across the depth of the cortex (Supplementary Fig. 2). Awake Vm responses were also rapidly truncated (Fig. 1h; 148 ± 31 ms, n = 14) compared with anaesthetized responses (Fig. 1g; 553 ± 73 ms, n = 14; and Supplementary Fig. 3). The prolonged responses in both Vm and LFP were remarkably similar across anaesthetic regimes and persisted regardless of the depth of anaesthesia (Supplementary Figs 4 and 5).

This marked difference in awake and anaesthetized responses was not confounded by spontaneous alternations of excitability that are present during anaesthesia (Fig. 2). We asked whether responses under anaesthesia differed when neurons were spontaneously hyperpolarized (down) or depolarized (up)². After correcting for the tendency of Vm to spontaneously alternate between these two states (Fig. 2c), we found that during anaesthesia, the Vm responses evoked from either state (hyperpolarized or depolarized) were remarkably similar in amplitude and duration (Fig. 2e) and were much longer than responses during wakefulness (Fig. 2f).

Responses in awake mice were more selective across visual space than responses under anaesthesia (Fig. 3a–e). Vm responses were twice as spatially selective during wakefulness as under anaesthesia. This difference in spatial localization was even more pronounced for spikes²¹ (Fig. 3e), even when we accounted for sustained responses during anaesthesia by restricting the spike counts to the earliest portion of the sensory response (0–200 ms; Supplementary Fig. 6). We observed fewer visually evoked spikes during waking than during anaesthesia (Fig. 3b). This difference was particularly evident during the stimulation of regions that surround the centre of the receptive field. Under anaesthesia, stimuli in these regions evoked significantly more firing (0.6 ± 0.2 spikes per trial) than did blank stimuli (0.3 ± 0.2 spikes per trial; P < 0.001). By contrast, in awake animals, stimuli in this region produced no net increase in spikes above spontaneous activity (0.08 ± 0.03 for surround stimuli versus 0.08 ± 0.04 for blank stimuli; P = 0.89).

The lower spike counts observed during wakefulness were also associated with a reduced variability in Vm responses (awake s.d., 3.5 ± 0.03 mV, n = 14; anaesthetized s.d., 4.4 ± 0.03 mV, n = 14; P < 0.001). This lower variability reduced the number of threshold crossings of Vm in awake animals, despite peak responses that were, on average, more depolarized than those during anaesthesia (Fig. 3d). The spike threshold did not differ between wakefulness (~40.0 ± 1.1 mV) and anaesthesia (~40.0 ± 1.2 mV; P = 0.6). However, spikes evoked during wakefulness were quickly followed by a significant and long-lasting hyperpolarization (Fig. 3f). We hypothesized that this hyperpolarization—and indeed the finer spatiotemporal resolution of the awake responses—was indicative of enhanced synaptic inhibition.

To test this hypothesis, we blocked the intrinsic conductances in single neurons and recorded synaptic currents in voltage-clamp mode near the reversal potentials for glutamate-mediated excitation and GABA (γ-aminobutyric acid)-mediated inhibition (Supplementary Fig. 7). We then estimated the relative change in total conductance (∆G; Supplementary Figs 7 and 8) visible at the soma in response to visual stimulation. Resting conductance and peak-evoked conductance were unaffected by wakefulness (Supplementary Fig. 7).

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Therefore, the differences between awake and anaesthetized $V_{m}$ must result from changes in the relative strength of the excitatory conductance ($\Delta G_{e}$) and inhibitory conductance ($\Delta G_{i}$).

Under anaesthesia, the estimated excitatory conductance and inhibitory conductance behaved as expected from previous studies.\(^{1,3,7,8,17,22,23,25,26}\) (Fig. 4a). On stimulation, increased excitation was quickly followed by inhibition. Then, excitation and inhibition co-varied at a sustained and elevated level for hundreds of milliseconds after the stimulus offset. In other words, excitation and inhibition were balanced in that they had a similar amplitude and time course.

During wakefulness, by contrast, inhibition dominated excitation during the entire time course of the visual response (Fig. 4b). During

Figure 1 | Spontaneous and evoked activity in the anaesthetized and awake visual cortex (V1). 

a, $V_{m}$ and simultaneous LFP measured in V1 under anaesthesia. The spikes are shown truncated at $+20 \text{ mV}$. b, $V_{m}$ and simultaneous LFP measured in V1 in awake animals. c, d, Visually evoked LFP responses across space during anaesthesia (c) and wakefulness (d). An average of 15 trials per location was used. Top, the dashed line indicates the best location. Bottom, single trial responses (grey) and the average (mean ± s.e.m.) response (black or green) with the stimulus (stim) at the best location. deg, degrees. 
e, $V_{m}$ responses to stimuli at the best location while under anaesthesia: single trials (grey) and mean (± s.e.m.; black). The spikes are shown truncated at $-30 \text{ mV}$. f, $V_{m}$ responses to stimuli at the best location during wakefulness. 
c–f, $n = 4$ different mice. g, h, Normalized probability distributions of $V_{m}$ response durations to stimuli at the best location, across the population ($n = 14$), measured under anaesthesia (g) and during wakefulness (h). The arrow indicates the mean duration.

Figure 2 | Anaesthetized responses are long lasting regardless of cortical state.

a, b, Normalized probability distributions of spontaneous $V_{m}$ during anaesthesia ($n = 14$ neurons) (a) and wakefulness ($n = 14$ neurons) (b). c, Mean (± s.e.m.) anaesthetized $V_{m}$ responses (solid lines), sorted by pre-stimulus $V_{m}$ level. Depolarized (grey) and hyperpolarized (black) groups are shown (with the mean $V_{m}$ of the two groups indicated by arrows of the corresponding colour in a). The pre-stimulus baseline $V_{m}$ was subtracted before averaging. The dashed lines indicate the average spontaneous $V_{m}$ (in response to blank stimuli), sorted similarly into two groups ($n = 14$ neurons). d, As for c, during wakefulness ($n = 14$). e, Average anaesthetized $V_{m}$ response for hyperpolarized (black) and depolarized (grey) trials, after subtraction of spontaneous $V_{m}$ traces. f, Average awake $V_{m}$ response for all trials, after subtraction of spontaneous $V_{m}$ traces. The grey line shows the average of all of the anaesthetized responses (for comparison).
Figure 3 | Responses are spatiotemporally restricted during waking. a, The number of spikes evoked per trial (normalized to each neuron’s response at the best location). Symmetrical locations on either side of 0° were combined. The centre is defined as 0° ± 9°, and the surround is defined as ±18° to ±45°. The response window is defined by the average duration of the population’s Vm response (Fig. 1g, h) (n = 14 for each group). b, Under anaesthesia (anaesth, black), centre and surround stimuli evoked more spikes (P < 0.001 for both) than during spontaneous activity (dashed line). During wakefulness (green), there were fewer spikes than under anaesthesia (P < 0.001 for both stimulus locations); the centre stimuli evoked more spikes than did the surround stimuli (P < 0.0009), and the surround stimuli did not evoke a significantly different response from spontaneous activity. Nine of 14 neurons were active during anaesthesia, and 5 of 14 were active during waking. c, As for a, for peak Vm responses (normalized to each neuron’s response at the best location). d, As for b, for peak Vm responses. The responses to centre stimuli were greater than to surround stimuli in both anaesthetized and awake animals (P < 0.04 for both conditions), and all responses were greater than spontaneous activity (dashed lines, P < 0.001 for all). The awake responses were larger than the anaesthetized responses (P < 0.001 for both stimuli locations). e, The Vm and the spike responses were more spatially selective during waking (Vm, anaesthetized, 0.3 ± 0.1; awake, 0.6 ± 0.1; P < 0.001; and spikes, anaesthetized, 0.1 ± 0.1; awake, 0.6 ± 0.2; P < 0.001). f, The spike-triggered average of Vm under anaesthesia and during wakefulness. The spike threshold (the peak of the second derivative of Vm) was aligned at 0 mV. a–f, mean ± s.e.m.

the initial 100 ms of the response, the ratio of inhibition (ΔGi) to excitation (ΔGe) was 1.4–2.9 (interval defined by the geometric s.e.m. around the geometric mean, see Methods), which is significantly larger than the ratio measured under anaesthesia (0.7–1.0) (P < 0.05, one-tailed two-sample t-test; Supplementary Fig. 9). Inhibition remained above baseline significantly longer than did excitation (by 29 ± 13 ms; P < 0.001), but both excitation and inhibition disengaged within 200 ms of the stimulus, mirroring the rapid termination of awake Vm and LFP responses observed earlier (compare with Figs 1 and 2). Wakefulness also reduced the amplitude of ΔGi, presumably because the intracortical sources of excitation were themselves subject to the same enhanced inhibition as the recorded neuron.

Strikingly, in awake animals, visually evoked inhibition was strongly activated even by stimuli that were placed far from the receptive field centre (Fig. 4d and Supplementary Fig. 9). During anaesthesia, by contrast, placing stimuli in these surrounding regions evoked little inhibition (Fig. 4c). Across all recordings in anaesthetized mice (n = 6), ΔGi over the first 100 ms of the response was 1.8–2.4-fold larger for stimuli in the centre than in the surround (ΔGi centre/surround ratio significantly >1; P < 0.005, one-tailed t-test). In awake mice, ΔGi was remarkably unselective for position: it was not significantly different in amplitude regardless of whether it was elicited from the centre or from the surrounding regions (P = 0.07). In fact, in every neuron recorded during wakefulness (n = 16; Supplementary Fig. 9), the ΔGi to ΔGe ratio for surround stimulation was greater than 1; for all recorded neurons, the ΔGi/ΔGe ratio evoked by surround stimulus was 0.8–1.1 under anaesthesia and a much larger 2.7–3.5 during wakefulness (P < 0.01).

Although retinotopy is the primary determinant of sensory responses in the visual cortex, synaptic conductances are also known to depend on stimulus orientation.52,22,23. We asked whether changing the stimulus orientation would have an effect on the observations. The results were similar to those described above: regardless of the stimulus orientation during wakefulness, Vm responses were brief, and inhibition dominated across visual space (Supplementary Figs 10 and 11).
Taken together, these data identify a novel characteristic of awake cortical processing—elevated and spatially extended inhibition—that is associated with sensory responses that are more spatiotemporally selective (Fig. 4e). Previous measurements of sensory responses in anesthetized animals have led to debate about the role of inhibition—1,2,3,7,17,22,23,25,26—and our findings show that inhibition is a decisive factor in the awake cortex: it dominates excitation in amplitude and over time (Fig. 4b, d) and is evoked from regions of visual space that extend far beyond the central regions of the receptive field (Fig. 4e). This finding of increased inhibition during wakefulness is consistent with earlier suggestions—1,12,27,28—and indicates a regime of sensory processing that cannot be observed during anesthesia or sleep, in which more-balanced excitation and inhibition are evoked from large regions of space and persist long after the stimulus has disappeared. The increased inhibition in the awake cortex is ideally poised to extinguish any spatial or temporal spread of feedforward activity that is elicited by a sensory input. Accordingly, during wakefulness, we observed a brisk and highly selective impulse response to spatially localized visual stimuli.

At present, it is unclear which factors regulate the strength of inhibition in the awake cortex. Neurmodulators can desynchronize LFP and Vm—2,9 depolarize interneurons—36, and alter response reliability and sensory perception—9,13,19. It will be important to examine such factors in this context, including the contributions of laminar connectivity and interneuron subtypes—1,4 to the increased inhibitory conductances that we observed during wakefulness. Having identified inhibition as a major determinant of spatially selective and temporally succinct visual responses in the awake cortex, we suggest that behavioural factors such as attention and reward may also exert their influence by modulating inhibition.

METHODS SUMMARY

All recordings were performed in layer 2/3 of monocular V1 (0.5 mm anterior and 2.0 mm lateral from lambda) in female C57BL/6j mice (∼6 weeks of age). Anaesthesia was induced with 10−3 mg chlorprothixene per kg body weight (Figs 1–4) or with 10−5 mg chlorprothixene per kg body weight and 0.25–1% isoflurane in O2. Awake mice were habituated to head fixation over 4–5 days. The LFP was recorded with pipettes filled with HEPES-buffered artificial cerebrospinal fluid (which consisted of 135 mM NaCl, 5.4 mM KCl, 5 mM HEPES, 1 mM MgCl2 and 1.8 mM CaCl2; pH 7.3). Patch pipettes (−47 MΩ) were filled with standard internal solution (135 mM potassium gluconate, 6 mM KCl, 10 mM HEPES, 4 mM MgATP, 0.1 mM Na2GTP, 1 mM EGTA and 8 mM phosphocreatine; pH adjusted to 7.3; 290–295 mOsM) for current-clamp recordings. For voltage-clamp recordings, a 140 mM caesium-methanesulphonate-based solution also included 0.5 mM QX-314 and 5 mM teトラethylammonium (TEA)—32,33. Vm was not corrected for the junction potential. The series resistance was compensated online and was monitored throughout voltage-clamp recordings (anaesthetized mice, 15 ± 2 MΩ; and awake mice, 16 ± 2 MΩ). Conductance was calculated using the instantaneous current–voltage relationship at two holding potentials (near −80 and +20 mV), relative to baseline, as previously described—20,21. Vertically oriented black and white bars (9° wide, 100% contrast, 100 ms duration and 1.5 s interstimulus interval) were presented monocularly, one at a time in randomly chosen positions (245). Spatial selectivity was defined as (Rcentre − Rsurround)/(Rcentre + Rsurround), where R is the peak Vm (or number of spikes per trial) averaged across the centre or surround locations. Mean ± s.e.m. is reported throughout, unless noted. For ratios, we used the geometric mean and geometric s.e.m., defined as exp(mean[log(ratios)]) and exp[mean[s.e.m.[log(ratios)]]]. Statistical testing (α = 0.05) was carried out using Wilcoxon signed-rank tests (paired data), rank-sum tests (unpaired data) and sign tests (difference from unity), unless noted.

Full Methods and any associated references are available in the online version of the paper.

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

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Author Contributions B.H. performed the experiments. B.H. and M.C. performed the analyses. B.H., M.H. and M.C. designed the study and wrote the paper.

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 B.H. (b.haider@ucl.ac.uk).
As in previous studies, to better nullify excitatory currents, we used a holding potential of about +20 mV rather than 0 mV, as this mitigates the voltage decay across the dendrites. Current-clamp recordings had 0 current injection during stimulation protocols. Input resistance and series resistance were monitored between protocols with current pulse trains or voltage steps. Firing rate adaptation to supra-threshold pulses and broad spike widths confirmed that our recordings were from regular-spiking pyramidal neurons. Across all anaesthetized (n = 22; 305 ± 27 μm) and awake (n = 30; 279 ± 27 μm) whole-cell recordings, there was no significant difference in laminar depth (P = 0.94), as estimated from the micromanipulator reading after it was zeroed upon contact with the cortical surface.

**Acquisition, visual stimulation and analysis.** All analyses and acquisitions were performed in MATLAB. V_m was low-pass filtered at 20 kHz. During voltage-clamp experiments, membrane current (I_m) was low-pass filtered at 2 kHz. LFP was filtered from 0.1–100 Hz. Data were acquired using a National Instruments board and were synchronized to stimulus onset with a photodiode signal. The liquid crystal display monitor was positioned 24 cm from the mouse and at 0° elevation and 30–45° azimuth. The azimuthal position was adjusted so that the centre of the LFP receptive field was roughly centred on the screen. Stimuli were presented on a grey background and randomly interleaved across space, with 8–20 repetitions per stimulus location. A blank screen (the grey background) was randomly presented every 11 stimulus presentations for the same duration as the stimulus trials. Stimuli were delivered monocularly. The unstimulated eye was gently sutured (anaesthetized mice) or shielded by black aluminium foil (awake mice). Throughout the entire recording session, the monitor was continuously illuminated with the same grey screen. This was to ensure that the spontaneous cortical state was not affected by transitions to and from complete darkness of the monitor.

In the awake recordings, on establishing a stable whole-cell configuration, 1–3 minutes of spontaneous activity was recorded before the presentation of any flashed bars. These data were used for all of the calculations of spontaneous activity (Figs 1a, b and 2a, b and Supplementary Figs 1 and 4); there were no systematic differences between the interleaved blank data and spontaneous data recorded before any visual stimulation. In some awake protocols, we shortened the inter-stimulus interval to 300 ms because the evoked responses returned to baseline well before this interval. There was no difference between the longer (1.5 s) and shorter interstimulus interval (n = 3) in terms of the magnitude or duration of evoked conductances. For measurements of V_m (Figs 2 and 3 and Supplementary Fig. 3), any stimulus-evoked filtering of the LFP was not applied and the resultant trace was smoothed.

In a subset of experiments, we optimized the orientation of the flashed bars for each individual neuron (Supplementary Fig. 10) by first presenting full-screen drifting gratings (50% contrast, spatial frequency of 0.03 cycles per degree, temporal frequency of 2 Hz and 2 s duration) that varied randomly in orientation (30 degree steps). The preferred orientation was designated as the orientation that evoked the largest number of spikes (or the largest depolarization of V_m) whereas the orthogonal orientation was 90° away from the preferred orientation. Bars that were identical to those in all other experiments (9° width, 100 ms duration, and 1.5 or 0.3 s interstimulus interval) were then presented randomly across space along the two axes defined by the preferred and orthogonal orientations.

To obtain robust estimates of reversal potential (V_m) and ΔG during the responses, we considered the response onset as the time when AG was 5–10% above baseline for 10 ms consecutively. Across the population of neurons, this time point occurred 30–40 ms after stimulus onset, so V_m, ΔG, ΔAG, and AG were averaged starting 40 ms after stimulus onset, across the population (Fig. 4; n = 5 urethane anaesthesia; n = 8 awake; both groups were tested identically with vertically oriented bars). Additional recordings of conductances under isoflurane anaesthesia (n = 1) and in awake mice that were presented with bars varying in orientation (n = 4) were not included in these plots to maintain equivalent group comparisons (but see Supplementary Fig. 9).

The state dependence of visual responses during anaesthesia (Fig. 2) was analysed by sorting trials (within neurons) by the pre-stimulus V_m level. The upper- and lower-most quartiles (that is, the 25% most depolarized and 25% most hyperpolarized non-overlapping trials) were then averaged across the population, and these largely correspond to trials in which the stimuli were delivered in the up state and the down state, respectively. Blank stimuli were also sorted in this manner to estimate the spontaneous state transitions from down to up, and vice versa, in the absence of sensory stimulation.

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Corrigendum: Inhibition dominates sensory responses in awake cortex
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In this Letter, there were two typographical errors in both the Methods Summary and the full Methods. The concentration of urethane should be 1.5 g per kg of body weight, not 1.5 mg. In addition, the intracellular solutions contained 0.3 mM Na3GTP, not Na2ATP. These errors have been corrected in the HTML and PDF versions of the manuscript. There were also errors in Supplementary Fig. 8, in which we inadvertently combined data from the wrong trial types to assess current–voltage (I–V) linearity. This has been corrected in the Supplementary Information of the original manuscript, and does not affect the results or conclusions.