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Modulation of Visual Responses by Behavioral State in Mouse Visual Cortex

Cristopher M. Niell[1] and Michael P. Stryker[1,*]
[1]W.M. Keck Foundation Center for Integrative Neuroscience, Department of Physiology, University of California, San Francisco, San Francisco, CA 94143-0444, USA
*Correspondence: stryker@phy.ucsf.edu
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SUMMARY

Studies of visual processing in rodents have conventionally been performed on anesthetized animals, precluding examination of the effects of behavior on visually evoked responses. We have now studied the response properties of neurons in primary visual cortex of awake mice that were allowed to run on a freely rotating spherical treadmill with their heads fixed. Most neurons showed more than a doubling of visually evoked firing rate as the animal transitioned from standing still to running, without changes in spontaneous firing or stimulus selectivity. Tuning properties in the awake animal were similar to those measured previously in anesthetized animals. Response magnitude in the lateral geniculate nucleus did not increase with locomotion, demonstrating that the striking change in responsiveness did not result from peripheral effects at the eye. Interestingly, some narrow-spiking cells were spontaneously active during running but suppressed by visual stimuli. These results demonstrate powerful cell-type-specific modulation of visual processing by behavioral state in awake mice.

INTRODUCTION

The perceptual response to sensory input clearly depends on behavioral state, as evidenced most directly by the dramatic decrease in responsiveness during sleep or some states of anesthesia. During wakefulness, attention can strongly affect the ability to perceive sensory stimuli (Posner and Petersen, 1990). The network mechanisms that underlie these state-dependent changes are only beginning to be understood, including the corresponding neural responses (Fontanini and Katz, 2008; Maunsell and Cook, 2002; Reynolds and Chelazzi, 2004), cell-type specificity (Chen et al., 2008; Mitchell et al., 2007), and the potential role of acetylcholine in modulating cortical responsiveness (Goard and Dan, 2009; Hasselmo and Giocomo, 2006; Herrero et al., 2008; Weinberger, 2007). Studies of sensory encoding are often performed in anesthetized animals, where the network dynamics are certainly perturbed by the anesthetic agents via mechanisms that are often unknown. The effects of anesthesia could include alteration of receptive field properties or disruption of correlation structure of activity (Friedberg et al., 1999; Greenberg et al., 2008), or it is possible that anesthesia might affect only the higher cortical areas, leaving primary sensory areas unperturbed. A particular concern about anesthesia is raised by recent studies in rodents, which have found much lower firing rates than are often observed in other mammals (Brecht et al., 2003; Kerr et al., 2007; Niell and Stryker, 2008). It is not clear whether the lower firing rates are a result of different experimental preparations or technology or whether they are simply a characteristic of rodent cortex (Hromádka et al., 2008). One recent study, using a two-photon microscope attached to the head to image calcium transients in freely moving rats, found similarly sparse patterns of activation to visual stimuli, although selectivity and tuning properties were not measured (Sawinski et al., 2009).

We therefore sought to characterize visual responses in the mouse primary visual cortex while the awake animal engaged in two simple behaviors: standing still or running. We studied the mouse because neurons in its visual cortex show response properties essentially identical to those known from decades of study in higher mammals (Hübener, 2003; Niell and Stryker, 2008), and powerful genetic tools for the dissection of the underlying circuit mechanisms are available in this species (Luo et al., 2008). In order to provide controlled visual stimuli while performing extracellular recording in an awake, moving animal, we adapted a recent technique to fix the head of the mouse while it stood or ran atop a freely floating foam ball (Dombeck et al., 2007; Harvey et al., 2009), which acts as a spherical treadmill.

We found that locomotor activity is associated with a dramatic increase in visual responsiveness in essentially all broad-spiking (presumed excitatory) cells without any concurrent changes in spontaneous firing rate or tuning properties. Interestingly, stimulus selectivity of visual neurons in the awake animal is nearly identical to that of the neurons we had studied previously in anesthetized mice (Niell and Stryker, 2008). The dependence on behavioral state was cell-type specific, in that a subset of the narrow-spiking cells showed a suppressive response to visual stimuli only during locomotion. The response magnitudes of neurons in the visual thalamus during periods of locomotion were similar to those while the mouse was standing still, indicating that the modulation of visual responses by behavioral state is not due to peripheral sensory effects.

RESULTS

Our experimental configuration, based on Dombeck et al. (2007), is shown in Figure 1A. The mouse was free either to sit still or to

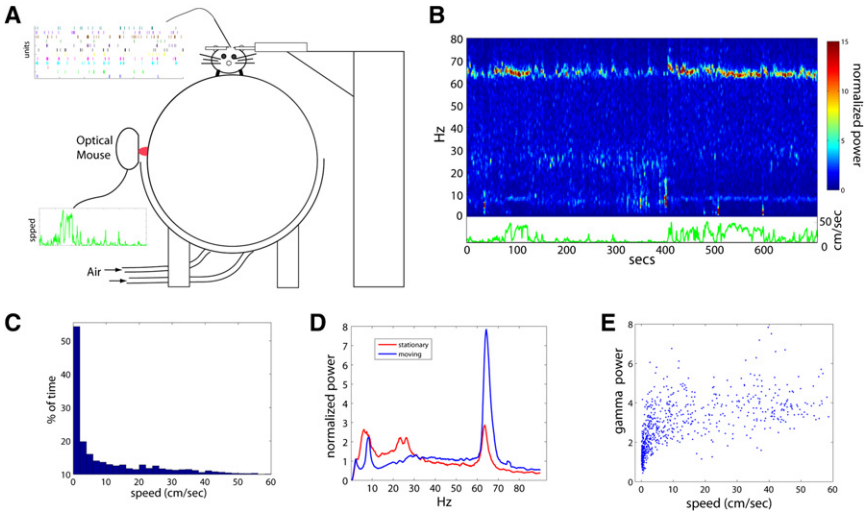

Figure 1. Experimental Setup and LFP Dependence on Behavioral State

(A) The mouse's head is fixed on top of a styrofoam ball suspended by air. Multisite silicon probes are used to measure spiking units, while data from pairs of optical mice are used to calculate the motion of the ball under the mouse. (B) Local field potential (LFP) power during the duration of a single recording, with corresponding speed trace shown below in green. (C) Distribution of mouse speed, showing a large fraction of time spent stationary and a wide distribution of running speeds. (D) Average power spectrum from recording shown in (B), during stationary versus moving periods. (E) Scatter plot of power around gamma peak (60–70 Hz) versus speed of movement, demonstrating a sharp transition between stationary and moving states. See also Figure S1 and Movie S1.

run on a foam ball floated on a stream of air, while its head was fixed to a crossbar via a small metal headplate implanted with dental acrylic. A small craniotomy allowed us to insert a silicon multisite electrode into either primary visual cortex or the thalamic lateral geniculate nucleus (LGN), which enabled recording of up to 12 single units simultaneously. We also used two optical mice to measure the displacement of the ball as the mouse ran (Dombeck et al., 2007), allowing us to calculate the physical speed of the ball at a point directly underneath the mouse. A histogram of typical speeds on the ball is shown in Figure 1C, demonstrating that the mouse spent a significant amount of time nearly stationary (which we defined as <1 cm/s), as well as running at up to ~50 cm/s, speeds consistent with measurement of open-field running (Friedman et al., 1992). The mouse also occasionally performed grooming behavior, which was manually marked and removed from subsequent analysis. Under these conditions, the mouse would readily feed and manipulate objects placed in its mouth or forepaws. The animal was allowed to behave freely; in a few cases, the animal spent all its time either running or stationary, preventing us from acquiring sufficient data to compare the two states. These cases were not included in our analysis. Movie S1 shows typical behavior of the mouse on the ball, including sitting still, running, and grooming.

Figure 1B shows the typical power spectrum of the local field potential (LFP) measured in cortex throughout a recording period as we presented drifting bars at a range of orientations. The speed of the ball's movement is shown in green at the bottom. During periods when the mouse was stationary, there was a broad band of power at low frequencies, including a peak between 10–30 Hz, and a narrow peak in the high gamma, which varied across animals from 50 to 70 Hz. Locomotion was correlated with a decrease in low-frequency power and a dramatic increase in the amplitude of the high-frequency gamma peak, as illustrated in Figure 1D, which shows the average power spectrum from stationary versus running periods. A scatter plot of high-frequency gamma power versus speed shows an abrupt increase once the animal is moving (Figure 1E). A similar, though smaller, increase in high-frequency power was also observed in the absence of visual stimuli on the gray mean-luminance background (Figure S1). During active periods, we could also observe a narrow peak at the theta frequency (8–9 Hz), which may be due to volume conduction from the hippocampus (Sirota et al., 2008) and is consistent with exploratory behavior (Buzsáki, 2002). These shifts in the LFP suggest a difference between the cortical states during these two behaviors.

To explore the visual responses of neurons during these two states, we recorded single-unit activity in layer 2/3 of the visual cortex in eight animals. We measured visual responses during trials that consisted of 1.5 s presentations of drifting gratings of six different spatial frequencies moving in 12 directions at 2 Hz separated by 0.2 s intervals of blank screen. The screen was centered at 45° from the midline in front of the contralateral eye, with receptive fields near the center of the monitor; furthermore, the small amplitude of eye movements that we recorded (<5°, Figure S4) ensures that the mouse did not move its gaze away from the monitor. Figure 2A shows rasters for a typical response to three cycles of an optimally oriented grating, demonstrating the strong periodic response characteristic of linear (simple) cells. The color coding of individual trials (red, stationary; blue, moving) reveals that, while the unit was responsive on nearly all trials, it fired more spikes when the mouse was moving than when stationary. This is further demonstrated in Figures 2B and 2C, which show the peristimulus time histograms (PSTH) for stationary and moving periods, respectively. Figure 2D shows the orientation tuning curve at the optimal spatial frequency, which demonstrates that the unit has relatively narrow tuning for the two directions of motion of a single orientation, ~25° half-width at half-maximum, and almost no response to the orthogonal directions. The increased responsiveness during moving periods consists of a multiplicative increase in firing rate across the tuning curve. There is little change in the low spontaneous rate, shown by the dashed lines.

We classified units as broad- or narrow-spiking according to their average spike waveform (Figure S2), which has been shown to correspond roughly to excitatory versus inhibitory cell type (Barthó et al., 2004; McCormick et al., 1985) and has also been shown to correspond to different visual response properties in

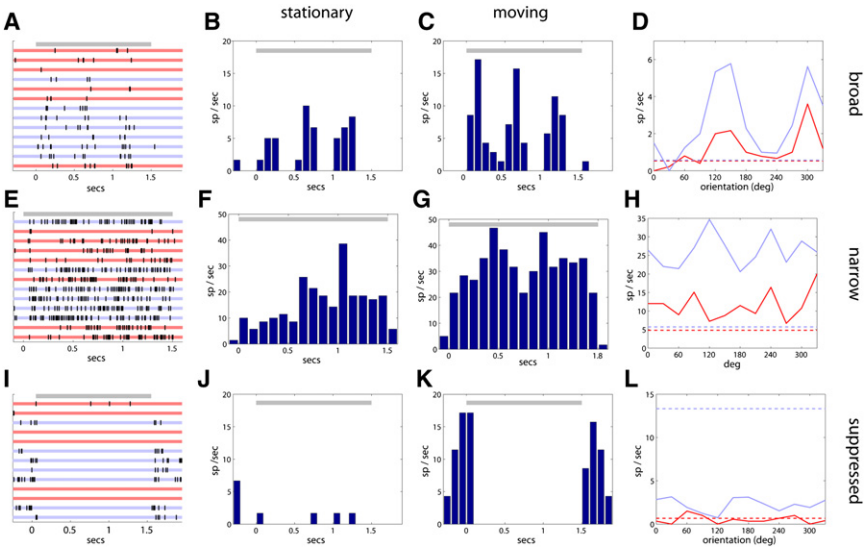

Figure 2. Visual Responses in Stationary versus Moving Periods in the Awake Mouse

Gray bar represents the period of stimulus presentation to an optimal full-field drifting grating. (A) Raster plot for a typical broad-spiking neuron, with individual trials coded as red (stationary) and blue (moving). (B and C) Histogram of responses during stationary (B) and moving (C) periods. (D) Orientation tuning curve. (E)–(H) show similar results for a typical narrow-spiking neuron. (I)–(L) show similar results representative of a subset of narrow-spiking neurons whose activity is suppressed in response to visual stimuli. See also Figure S2.

V1 (Cardin et al., 2007; Chen et al., 2008; Niell and Stryker, 2008; Nowak et al., 2003). For most narrow-spiking units, we found a similar increase in responsiveness during locomotion, with a typical response demonstrated in Figures 2E–2H. Consistent with our previous findings in anesthetized mice, narrow-spiking units generally did not show a periodic response to grating stimuli and did not have strong orientation selectivity either in the stationary or moving condition (Figure 2H).

The increased amplitude of response without a change in tuning was typical of most neurons recorded (Figure 3) and was consistent across all animals studied. However, a small subset of units, which all had narrow-spike waveforms, showed dramatically different properties, as exemplified by the unit in Figures 2I–2L. This unit showed very little activity during stationary periods (Figure 2I, red trials, and Figure 2J). However, when the animal was moving on the ball, the spontaneous rate increased dramatically, as shown before and after the stimulus presentation in Figures 2I and 2K. When a visual stimulus was presented during locomotion, the firing rate was then dramatically suppressed. Figure 2L shows that this suppression below the spontaneous rate was consistent across all orientations.

Summary data across the population of recorded single units (n = 93 units, 8 animals) are shown in Figure 3. Broad-spiking neurons showed quite low spontaneous rates (Figure 3A), which did not change significantly going from the stationary to moving state (Figure 3D). Most narrow-spiking units also did not change their spontaneous rates, although they generally had higher spontaneous activity than the broad-spiking units. However, five narrow-spiking units (Figure 3A, blue triangles) showed the dramatic increase in spontaneous rate as exemplified in Figures 2I–2L.

The increase in evoked activity in response to an optimal drifting grating was consistent for most broad-spiking units (Figure 3B), resulting in a greater than 2-fold increase in the median evoked firing rate (Figure 3D, 2.9 ± 0.4 sp/s stationary, 8.2 ± 0.9 sp/s moving, $p < 0.001$). As seen for the example in Figure 2, most narrow-spiking units showed similar increases in response amplitude (Figure 3C, blue circles), except for the five neurons that had the largest increases in spontaneous rate; these units showed strong suppression of firing in response to visual stimuli (Figure 3C, blue triangles).

Overall, the firing rates we observed in awake recordings from upper-layer cortical neurons were not dramatically different from recordings of neurons in the same layers under chlorprothixene plus urethane anesthesia (Figure 3D, gray bars) reported previously (Niell and Stryker, 2008). The spontaneous rates were quite low in both cases, but ~2-fold greater during awake states (0.17 ± 0.07 versus 0.08 ± 0.05, $p < 0.05$), consistent with previous findings in rat visual cortex (Greenberg et al., 2008). The firing rates evoked by identical stimuli in anesthetized animals were intermediate between those in the awake stationary and running states observed here.

To determine whether the modulation of response by locomotion affects the selectivity of neurons, we calculated the orientation selectivity (based on the difference in response between the optimal orientation and the orthogonal orientation) and the orientation tuning width (based on the half-width of tuning at half the maximum above the untuned baseline). Figures 3E and 3F show that for broad-spiking units that were responsive in both states, there was no overall change in either the orientation selectivity or tuning width. This relationship held true across the distribution of units (Figures S3A and S3B). Furthermore, the orientation selectivity and tuning width measured in the awake animal is quite similar to that measured previously for layer 2/3 broad-spiking units under anesthesia (compare awake data to gray bars in Figures 3E and 3F).

Within the moving state, the increased amplitude was not strongly correlated with the speed of motion. Figure 3G shows normalized response amplitude on individual stimulus trials versus speed of locomotion for all units, demonstrating that beyond a sharp transition around 1 cm/s, there was little further increase in response with speed. The increase in response magnitude also did not depend on the direction of visual motion that a cell responded to (Figure S3C), as one might expect if the cells were registering a mismatch between perceived self-motion and optic flow.

The dramatic increase in visual responsiveness might in principle result from either peripheral or central effects of eye movements. In four animals, we recorded eye position during visual

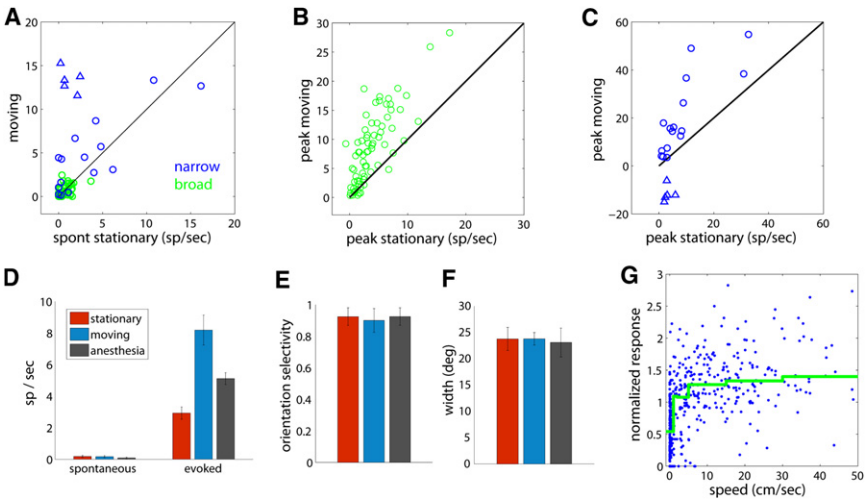

Figure 3. Effects of Locomotion on Cortical Responses

(A) Spontaneous firing rate during moving versus stationary periods, for narrow- and broad-spiking units. The five units that show negative amplitude in (C) are denoted by triangles (n = 93 units in 8 animals). (B) Peak firing rate in response to drifting gratings during moving versus stationary periods for broad-spiking cells. (C) Peak response amplitude for narrow-spiking cells. (D) Population medians for spontaneous and evoked firing rates, for broad-spiking units, compared with urethane anesthesia data from Niell and Stryker (2008). (E) Mean orientation selectivity index (OSI) for all broad-spiking cells that responded in both states (n = 28 units). (F) Mean orientation tuning width for units shown in (E). (G) Response amplitude versus speed from 0 to 50 cm/s for all individual trials of the optimal grating stimulus. Amplitude is normalized by average evoked firing rate to the stimulus for each unit. Green line shows median curve. See also Figure S3. Error bars represent standard error of the median (D and F) and mean (E).

stimulus presentation (Figure S4A) and found that, although eye movements were more common during active periods (Figure S4B), the amplitudes of eye movements were generally quite small compared to receptive field sizes in the mouse. The RMS deviation of eye position was only several degrees across the duration of recording (Figure S4C), whereas typical mouse receptive fields are 10° or greater in diameter (Hübener, 2003; Niell and Stryker, 2008). Furthermore, even during active periods, the frequency of eye movements was too low to account for the consistent changes in visual responses, as eye movements occurred on average every 7.6 s during motion, while individual stimulus trials only lasted 1.5 s. To examine directly whether the subset of trials with eye movements might account for the large response modulation, we recorded eye movements simultaneously with single-unit recordings in two animals. Figure S4D shows that eliminating trials during which eye movements of greater than 1° occurred, which accounted for <20% of trials, had a negligible effect on response amplitudes in all units studied. The average peak visual response amplitudes in both stationary and moving states were similarly unaffected by eliminating the trials with eye movements (Figure S4E). These findings demonstrate that the presence or absence of eye movements does not account for the effect of locomotion on the amplitude of V1 visual responses.

To determine whether peripheral effects other than eye movements were responsible for the increase in cortical response during locomotion, we recorded from neurons in the thalamic lateral geniculate nucleus (LGN), which conveys visual information from the retina to cortex. We presented drifting grating stimuli identical to those used during cortical recordings except at only four directions of motion, since LGN neurons generally lack orientation selectivity. The response of an LGN unit to a full-field drifting grating is shown in Figures 4A–4C. This unit showed a periodic response with a temporal frequency equal to that of the grating (2 Hz). In Figure 4A, the individual trials are color coded to denote stationary versus moving trials, demonstrating the similarity between responses in the two states. This is further illustrated in Figures 4B and 4C, which show PSTHs corresponding to the trials in Figure 4A.

The LGN neuron illustrated in Figures 4A–4C was typical. Spontaneous firing rates in the LGN were an order of magnitude higher than in cortex but did not show any change with behavioral state (Figures 4D and 4F). Most geniculate neurons showed strong periodic modulation of firing at the temporal frequency of the gratings (F1) as demonstrated in Figures 4A–4C, consistent with previous findings on the linearity of most mouse LGN cells (Grubb and Thompson, 2003), as well as increases in the average firing rate (F0) upon visual stimulation. Changes in behavioral state from stationary to running did not cause a consistent change in either the evoked F1 response or F0 firing rate (Figures 4E and 4F). Thus, using identical stimuli, running produced more than a 2-fold change in cortical response but no similar change in the response rate of the geniculate neurons that convey visual information to the cortex. This observation demonstrates that the modulation of response amplitude with behavioral state arises in the cortex, rather than in thalamus or the periphery.

Although the response magnitude in the LGN was not changed between behavioral states, changes in spike timing, such as increases in bursting or synchronized firing, could change the effectiveness of signal propagation to cortex. Thalamic relay neurons are known to fire in two modes, tonic and burst (Sherman, 2001), with tonic firing more common in attentive awake states, and burst firing, which results from de-inactivation of T-type calcium channels, predominating in sleep or inattentive states, and much less frequent during attentive wakefulness (Bezdudnaya et al., 2006; Ramcharan et al., 2005; Weyand et al., 2001). Using a standard definition of thalamic bursting that has been used previously in the mouse LGN (spikes with interspike interval of <4 ms following >100 ms of inactivity) (Lu et al., 1992; Grubb and Thompson, 2005), we found burst responses in both stationary and moving states (Figure 4A, green circles). The frequency of LGN bursting was higher during stationary periods (Figure S5), with a median of 25.3% ± 2.6% of action potentials occurring during bursts when the animal

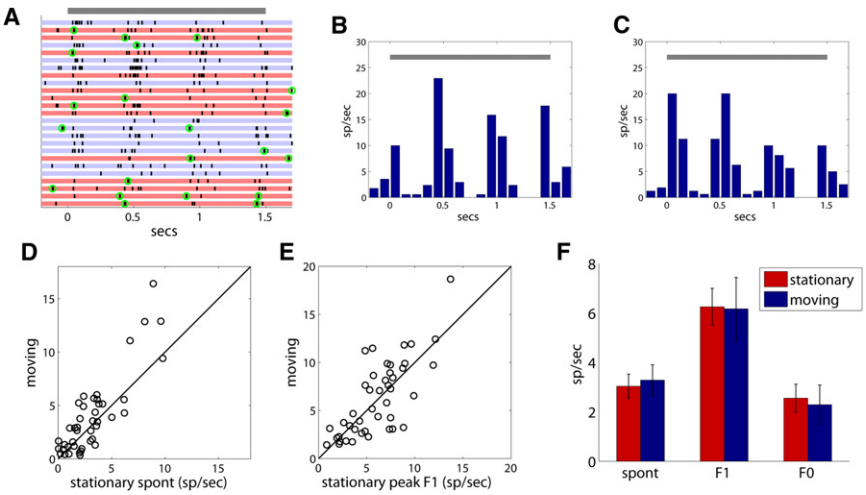

Figure 4. LGN Response Amplitude Does Not Depend on Behavioral State

(A) Raster plot for a transient LGN cell, in response to drifting gratings at 2 Hz, with individual trials coded as red (stationary) and blue (moving). Burst events are circled in green. Gray bar shows stimulus duration. (B and C) Histograms of response during stationary (B) and moving (C) trials. (D) Spontaneous rate during stationary versus moving periods. (E) Peak F1 response to periodic gratings in both behavioral states. (F) Median value across all units for spontaneous rate, and peak F1 and F0 response (n = 46 units, 4 animals). See also Figures S4 and S5. Error bars represent standard error of the median.

was stationary, versus 4.9% ± 1.2% during locomotion ($p < 0.001$). There was no indication of short-timescale synchrony of neuronal firing across pairs of simultaneously recorded units, as measured by the cross-correlation within a ±10 ms time window normalized by that in a ±50 ms time window (1.00 ± 0.02 while stationary versus 0.99 ± 0.02 during locomotion, n = 107 pairs).

DISCUSSION

The pioneering studies of Wurtz (1969) first addressed the effects of anesthesia on specific response properties in primary sensory cortex by comparing the selective properties of neurons in the striate cortex of alert monkeys with those described by Hubel and Wiesel (Hubel and Wiesel, 1962, 1968) in anesthetized cats and monkeys. His major finding, that the selective properties of neurons in primary visual cortex were similar in alert and anesthetized primates, is here shown also to be true in the mouse. The present study provides a characterization of single-unit receptive fields in the awake mouse, confirming previous findings in the anesthetized mouse of a high degree of selectivity in cortical receptive fields (Niell and Stryker, 2008). Indeed, the orientation tuning observed in the layer 2/3 broad-spiking cells of the awake animal (24° HWHM) is nearly identical to that measured previously in layer 2/3 under anesthesia (23°). Furthermore, the relatively low spontaneous firing rate and evoked responses previously observed are also consistent with the present findings in the alert animal, although spontaneous firing rates in layer 2/3 were roughly 2-fold lower under anesthesia, and visually evoked responses under anesthesia were intermediate between those in the stationary and running states in awake animals. Such a verification by the alert-animal "gold standard" allows the appropriately anesthetized preparation to be used to pursue many anatomical and circuit-level questions for which it is more amenable to experimentation.

A second issue raised in primates by the early studies of Wurtz and others concerns the modulation of cortical responses by behavioral state. Surprisingly, such modulation appears to be small in the monkey's primary visual cortex (Wurtz and Mohler, 1976). Indeed, Wurtz (2009) writes that "… modulations I thought I would find in striate cortex are indeed found in cortex, but they become prominent after visual information reaches higher levels." In contrast in the mouse, the difference in responses between the states of running and quiet wakefulness is nearly 3-fold. Perhaps this much larger effect in mouse primary cortex is an extreme example of encephalization, with changes that occur over multiple cortical areas in higher primates telescoped into the primary sensory area in rodents. Indeed, signals representing reward timing, which is generally thought to be a higher brain function, have been measured in rat primary visual cortex (Shuler and Bear, 2006).

We also provide new evidence linking visual responsiveness with locomotion. This effect is much greater than is typically observed for modulation of neural response by selective attention in primates that sit in chairs (Maunsell and Cook, 2002; Reynolds and Chelazzi, 2004); one wonders whether they too might show modulation of similar amplitude if allowed to locomote through their environment. The modulation found here in mouse V1 is reminiscent of the dependence of place cells on active locomotion through the environment (Foster et al., 1989). Because the mice were not actively engaged in a perceptual task, and the increase in response was seen across the visual field, it seems likely that it reflects a general activation associated with locomotion, rather than a mechanism of selective attention.

Interestingly, other studies linking sensory input with motor behavior have shown suppression of responsiveness during movement. Responses to forepaw stimulation during running showed decreased responsiveness in primary somatosensory cortex during specific phases of the leg movement (Shin et al., 1994). In addition, responses to whisker stimulation are reduced during active whisking (Fanselow and Nicolelis, 1999; Ferezou et al., 2007), although the signal-to-noise ratio appears to be increased (Jadhav et al., 2009; Poulet and Petersen, 2008). Motor activity may therefore have diverse effects on different sensory areas, gating sensory information as needed for a given behavior. However, it is not necessarily the case that visual

responses are linked exclusively to locomotion; it is possible that other tasks that engage the visual system would lead to similar changes in cortical responsiveness. Interestingly, a recent study has shown effects in the opposite direction; auditory responses in cortex are actually reduced when an animal is engaged in a discrimination task as compared to passive listening (Otazu et al., 2009).

The modulation in response amplitude during locomotion appears to arise in the cortex, as there was no overall shift in visual evoked responses in the LGN that could account for these changes. This rules out the possibility that changes in the eye, such as accommodation, pupil dilation, or frequency of eye movements, are leading to poor visual responses during stationary periods. The lack of modulation in the LGN differs from findings in immobile rabbits, which showed an increase in visual response amplitude as the animals shifted from inattentive to attentive state, based on the presence of theta oscillations in the hippocampal EEG (Cano et al., 2006). Although this may be a species difference, it may also be due to the fact that Cano et al. were observing a transition within the immobile state, which could be distinct from our stationary to moving transition. However, we did observe an increase in burst firing during the stationary state, consistent with other studies of inattentive states (Bezdudnaya et al., 2006). Burst firing and short interspike intervals are generally found to be more rather than less effective in driving cortical responses (Usrey, 2002); indeed, bursts have been postulated to serve as a "wakeup call" for cortex (Sherman, 2001). In the mouse, we find that LGN bursting occurs more frequently during the inactive state, when cortex is in fact less responsive to visual stimuli. It should be noted, however, that only ~15% of the spike events in our alert, stationary mice were in bursts, a state very different from those of sleep.

The weak responses to visual stimuli during stationary periods, even relative to the anesthetized state, suggest that the animal is perceptually disengaged from the visual environment. However, under these circumstances it is clear that the mice do not enter a state like sleep, as evidenced by the absence of characteristic sleep spindles and delta rhythm in the EEG and the lack of decreased responsiveness in the LGN, which typically gates information to cortex during sleep/wake. Furthermore, the animals do not close their eyes, a typical behavioral correlate of sleep, and they continue to make small postural adjustments to maintain their balance on top of the floating ball (Movie S1). They also readily take food if it is offered to them.

The present recordings in the awake animal also revealed an interesting subtype of narrow-spiking neuron, which had little activity when the animal was stationary but began firing at high spontaneous rates during movement and then decreased its firing in response to visual stimulation (Figures 2E–2H). This response is similar to the "suppressed-by-contrast" cells that have been observed in the cat retina (Rodieck, 1967) and monkey LGN (Tailby et al., 2007) but has not previously been described in rodents or in cortex. If these narrow-spiking units do turn out to be inhibitory, it is interesting to consider their potential role in the cortical response to locomotor activation. Their dramatically increased firing rate would increase overall inhibition, which could counteract an activating effect of arousal, serving to keep spontaneous rates relatively constant. Then in the presence of a visual stimulus, the reduction in their firing would relieve this inhibition, allowing the high-amplitude responses observed during locomotion.

There is unlikely to be a perfect correspondence of broad-spiking to excitatory and narrow-spiking to inhibitory neuron populations (Nowak et al., 2003). However, our previous work showed that in mouse V1 the waveforms are perfectly distinct (linearly separable with no overlap) and do indeed correspond to different visual response properties, consistent with their originating in distinct cell types with different synaptic and electrophysiological properties (Contreras, 2004). Two recent studies have also shown a difference in attentional modulation of visual response between narrow- and fast-spiking cells (Chen et al., 2008; Mitchell et al., 2007); our results demonstrate a further qualitative shift in cell-type-specific visual responses, by the recruitment of this subset of narrow-spiking cells.

The neuromodulator acetylcholine has been demonstrated to play a role in cortical activation and attentional modulation in many systems (Hasselmo and Giocomo, 2006; Weinberger, 2007). Our observations are consistent with the hypothesis that increased responsiveness in cortex may be due to cholinergic input, particularly from the nucleus basalis. We see a shift from low to high frequency in the LFP spectrum in cortex, which is a characteristic of the actions of acetylcholine and nucleus basalis stimulation (Buzsaki et al., 1988; Metherate et al., 1992; Rodriguez et al., 2004). Furthermore, cholinergic agonists have been shown to enhance visual responses in cortex, without significant change in selectivity or spontaneous rate (Sato et al., 1987; Sillito and Kemp, 1983), as we observed here. Nucleus basalis stimulation in the anesthetized rat has been shown to increase the reliability of visual responses to movies of natural scenes, in part through cholinergic mechanisms (Goard and Dan, 2009), an effect that may be related to the increase in response reported here.

Regardless of the mechanism of activation, it is apparent that the state of the cortical network has a profound impact on the response to sensory inputs (Fontanini and Katz, 2008; Haider and McCormick, 2009; Otazu et al., 2009; Poulet and Petersen, 2008). In this case, it appears that activation associated with locomotion acts as a gain modulator, increasing responsiveness without changing selectivity (Cardin et al., 2008). It is worth noting that the increased responsiveness was accompanied by an increase in gamma-frequency oscillations; two recent studies have demonstrated that gamma oscillations mediated by parvalbumin-expressing interneurons can facilitate transmission of information in cortical circuits (Cardin et al., 2009; Sohal et al., 2009).

Finally, it is interesting to consider these results in relation to experience-dependent plasticity. Environmental enrichment and antidepressant therapy have been shown to increase the capacity for ocular dominance plasticity in visual cortex in adult animals (Maya Vetencourt et al., 2008; Sale et al., 2007). Our finding that visual responses, even in primary visual cortex, are strongly modulated by behavioral state suggests that these treatments, which clearly affect behavioral state (although not necessarily locomotion per se), might thereby increase the amplitude of visual responses and thus provide a stronger drive for plasticity.

EXPERIMENTAL PROCEDURES

Full methods are available in Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, five figures, and one movie and can be found with this article online at doi:10.1016/j.neuron.2010.01.033.

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