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Gaze direction controls response gain in primary visual-cortex neurons

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To localize objects in space, the brain needs to combine information about the position of the stimulus on the retinae with information about the location of the eyes in their orbits. Interaction between these two types of information occurs in several cortical areas[1–12], but the role of the primary visual cortex (area V1) in this process has remained unclear. Here we show that, for half the cells recorded in area V1 of behaving monkeys, the classically described visual responses are strongly modulated by gaze direction. Specifically, we find that selectivity for horizontal retinal disparity—the difference in the position of a stimulus on each retina which relates to relative object distance—and for stimulus orientation may be present at a given gaze direction, but be absent or poorly expressed at another direction. Shifts in preferred disparity also occurred in several neurons. These neural changes were most often present at the beginning of the visual response, suggesting a feedforward gain control by eye position signals. Cortical neural processes for encoding information about the three-dimensional position of a stimulus in space therefore start as early as area V1.

Area V1 is the first cortical area where orientation and horizontal retinal disparity are encoded[13–15]. Here, cells have oriented receptive fields that may occupy disparate locations on both retinae. Most of these cells have their activity (visual and/or spontaneous) modulated by the viewing distance in the straight-ahead sagittal direction[16,17]. But do such modulations also occur as a function of the direction of gaze? This would imply that V1 cells would be more dedicated to certain volumes of visual space, in which case changing the direction of gaze should affect some or all of the visual properties encoded in the primary visual cortex, such as horizontal retinal disparity and orientation selectivity.

We obtained data from 142 neurons in two monkeys that were trained to fixate a target at three different positions in the frontoparallel plane (Fig. 1a). For studies of both disparity and orientation, changes in gaze direction produced significant changes in neuronal activity in 54% ($n = 67$) of cells tested for disparity and 50% ($n = 104$) tested for orientation. The main effect was a significant change in the evoked firing rate (gain) in 72% of cells studied for disparity and in 85% studied for orientation. Shifts in preferred disparity angle were observed in 17% of cells; the remainder showed inconclusive changes in the tuning curves. Three examples of the gain effect on disparity coding are shown in Fig. 2. The cell shown in Fig. 2a is disparity selective with the preferred response in the plane of fixation (0°) when the monkey fixates in the centre of the screen or on the left, but shows a significant drop in the level of visual response, close to the spontaneous activity level, when the monkey fixates on the right. The cell shown in Fig. 2b exhibits significant progressive increase in the evoked firing rate in the plane of fixation (tuned 0°) from the left to the right direction of gaze. That shown in Fig. 2c displays a shift in preferred disparity angle: it has a preferred disparity angle in the plane of fixation (0°) for a gaze directed to the left, but shifts its peak just behind that plane (centred on 0.2°) for the right direction, with an intermediate step for the straight-ahead direction.

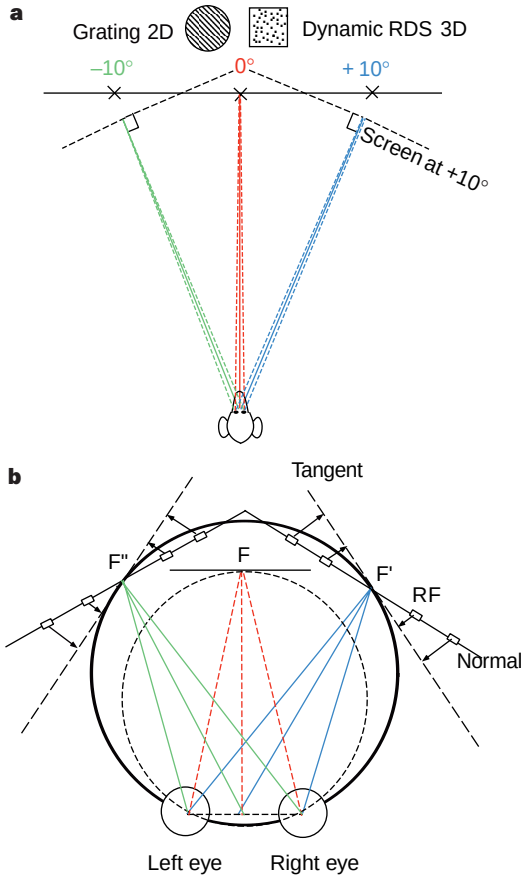

Figure 1 Experimental set-up. **a**, Dynamic random dot stereograms (RDS) and square-wave gratings were flashed on a video monitor screen subtending 42° or 32° of visual angle at three directions of gaze (straight ahead, 0°; left, –10°; and right, +10°) in the frontoparallel plane. For the left and right directions, the video monitor was rotated by 10° to maintain geometrical configurations with the viewing distance kept constant at 50 cm. Continuous lines of view represent the binocular axis. **b**, Vieth–Müller circles passing through both eyes and through fixation point for the three directions of gaze (F, F′ and F″) (adapted from ref. 19).

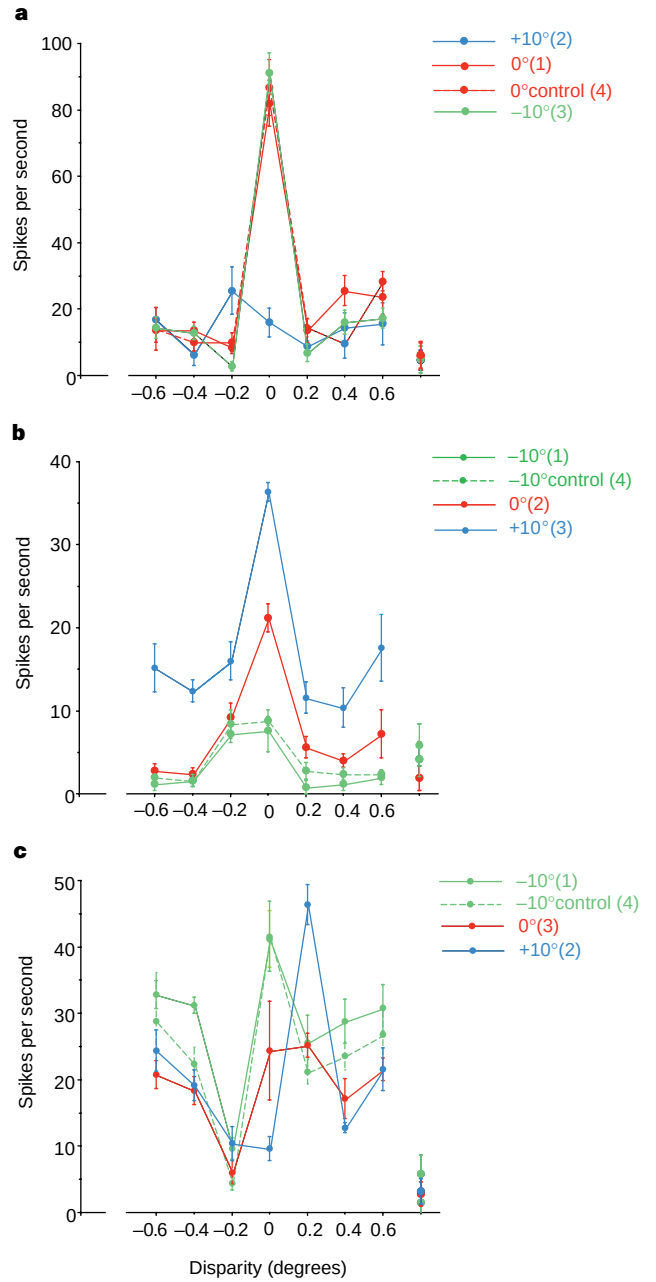

Figure 2 Retinal disparity tuning curves obtained in three individual neurons at three directions of gaze (–10°, green; 0°, red; +10°, blue). **a–c**, The three individiual neurons. Numbers in parentheses indicate the temporal sequence of recordings. For each cell, the first condition (curve 1) was repeated (control, dotted curve 4) at the end of the session of tests. The level of spontaneous activity is indicated on the right of the curves. Vertical bars show standard errors of the mean (five trials).

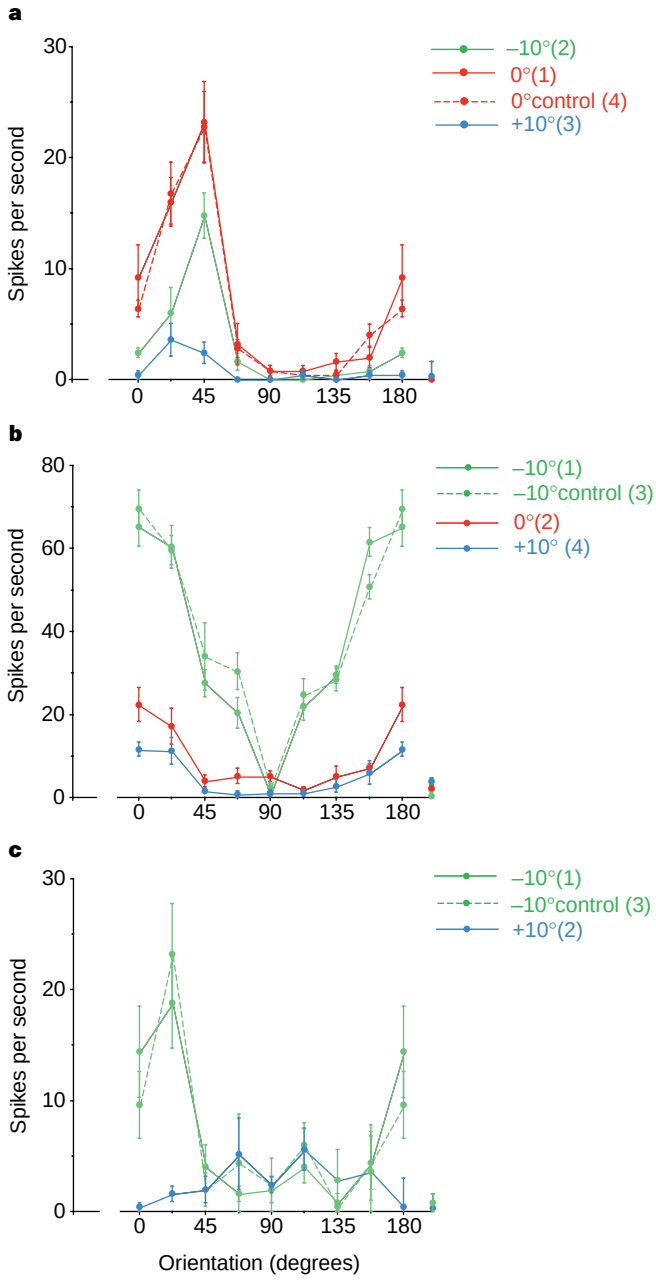

Figure 3 Effects of changing gaze direction on the responses of three individual neurons to oriented stimuli. Otherwise as Fig. 2; the three neurons are shown in **a–c**.

Three examples of the gain effect on orientation are shown in Fig. 3. The cell shown in Fig. 3a is visually responsive with a preferred orientation of 45° for the straight-ahead direction; a significant decrease in visual response occurs for the left direction and there is an almost total loss of visual response for the right direction. The cell shown in Fig. 3b is responsive when the monkey fixates on the left, but the level of visual response drops significantly for the other gaze directions. Finally, the cell in Fig. 3c shows a clear visual response (22.5°) for the left, but not for the right, direction of gaze.

We tested 29 cells with both types of stimuli. Among the 38% of cells that showed an effect of the two properties, only one showed a modulation for orientation but not for disparity; in all other cases, the effects were congruent for a common gaze direction.

We quantified differences in response magnitude between the gaze directions for the two properties. The distributions of the modulation index (Fig. 4) are similar for disparity and orientation studies: modulation index, mean 0.48 ± 0.05 for disparity and 0.53 ± 0.04 for orientation (analysis of variance, $P < 0.0005$ between distributions gain effect/no effect for both properties). From the distributions of the modulation index, it follows that about 50% of cells showing an effect have a ratio of more than two for the visual activity evoked for the 'best' over the 'worst' direction of gaze, a proportion similar to that described in the parietal cortex[1].

For both disparity and orientation properties, modulations of the amplitude of the neural discharge occurred for the three directions of gaze, with no preference for either the contralateral or the ipsilateral field of view, and occurred equally for cells recorded in supra- and infragranular layers. Effects were independent of the preferred orientations or disparity angles encoded by cells. The gaze

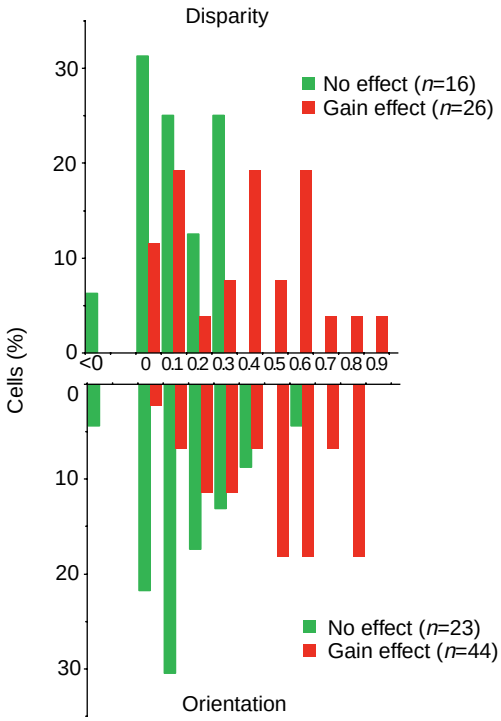

Figure 4 Distributions of the modulation index. Data are for horizontal disparity (top) and stimulus orientation (bottom) for cells showing a gaze direction effect (red) and cells that do not (green); *n*, number of cells.

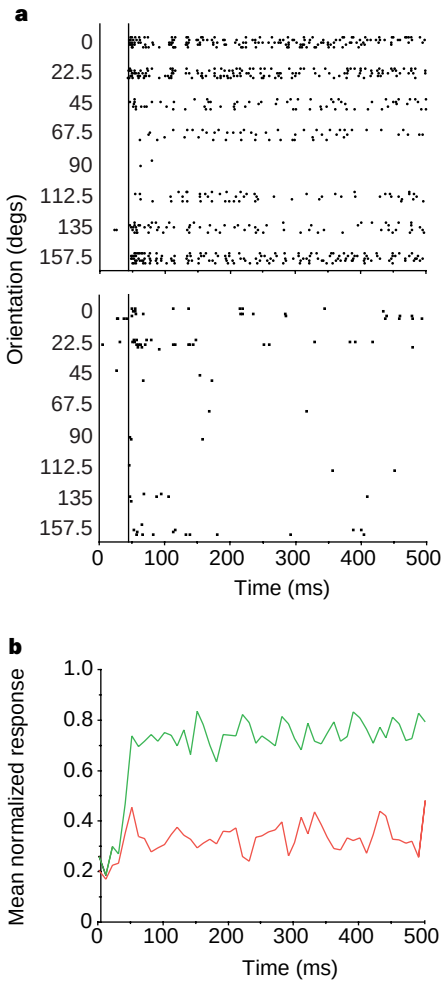

Figure 5 Time course of visual responses. **a**, Raster displays for an orientation-selective cell whose visual response was tested at –10° (top) and +10° (bottom). Vertical bars indicate the beginning of the visual responses. **b**, Mean time course of visual responses of the population of cells with a modulation index of more than 0.3 (17 cells for disparity and 35 cells for orientation were pooled together as there was no difference in their mean time course). The responses of cells to the preferred stimulus for the gaze direction giving the higher activity (green) and that giving the lower activity (red) are normalized and averaged for the 52 cells by 10-ms time bins over the 500 ms of the visual response.

direction also affected visually responsive cells that were non-stimulus selective, constituting 21% of disparity- and 9% of orientation-tested cells, in a similar way. Spontaneous activity was found to be modulated in only 11% of cases, with no correlation with the modulation on visual response.

Variations in the neural response are not due to effects such as fatigue or adaptation because controls of activity stability were performed for 90% of cells by repeating the first block of recordings after the last one to ensure that the tunings and levels of visual response remained similar. Turning the screen for the left and right directions of gaze, in order to maintain constant binocular distances of fixation, limits size deformation of the images on the retinae and so limits vertical retinal disparity[18].

For a gaze directed in the centre of the screen (F in Fig. 1b; symmetrical convergence), the normal to the binocular axis and the tangent to the Vieth–Müller circle, which is used as a reference for stereoscopic judgments[19], are superimposed. For a gaze directed on the left (F″) or on the right (F′) (asymmetrical convergence), the normal to the direction of gaze is rotated away from the tangent, which should induce a change in binocular correspondence. Therefore, for the normal surface to yield correct stereoscopic spatial perception, a compensation process must take place[19,20]. The subset of neurons that changes their preferred disparity angle may be the neural substrate that allows compensation for this shift in depth. For the example in Fig. 2c, the cell was recorded in the right hemisphere with the receptive field located in the left hemifield of view at 3° of retinal eccentricity. Any visual stimulus presented in its receptive field will appear 0.1° nearer than it should be for the fixation on the right, or 0.1° farther for a fixation on the left. So the shift of preferred disparity observed is a direct way of compensating for this misleading depth perception of the stimulus (as seen in five out of six cells).

The question arises if the effects of changing gaze direction are due to vertical disparity and/or oculomotor signals. Vertical disparity in our study is smaller than 1 min of arc, too small to account for the strong effects shown here. Moreover, six cells were tested monocularly for orientation selectivity, excluding vertical disparity, three of which showed clear modulations of neural activity as a function of gaze direction. This supports the idea than an eye-position signal is involved in the neural modulation process, at least for cells responding to oriented gratings. Other factors, such as contextual environment, attention or binocular fixation instability, are unlikely to be responsible for the modulations, as the monkeys were placed in total darkness, and the potential degree of attention required to fuse the target binocularly was similar for the three directions of gaze under the binocular control of eye movements. In addition, the variability of the visual response was similar for the three fixation locations.

This gain process, first described in parietal areas[1,2] and interpreted as forming a distributed representation of space in head-centred coordinates[2,21], now appears as a common functional rule of the dorsal visual pathway. So perhaps our observations from area V1 are the consequence of feedback influences from higher integrated cortical areas? If this were the case, these influences on the visual response in area V1 would be reflected by a delay after the onset response in the pattern of the visual discharge, as has been shown for

contextual modulations outside the receptive field in area V1 of the behaving monkey[22].

Two examples of raster displays of an orientation-selective cell in two conditions of fixation, left/right, are shown in Fig. 5a, where it can be seen clearly that the response is decreased (bottom raster) at the very beginning of the visual response. Indeed, the curves in Fig. 5b show that, on average, the difference in activity is present at the beginning of the visual response and remains constant throughout. This suggests that feedforward interactions may be involved in the modulation of visual activity by the gaze angle in area V1, a neural gating that could be mediated from the lateral geniculate nucleus, where eye-position signals have been shown to influence the visual activity[23–25].

Finally, area V1 appears to be an integrated cortical area in which attentional and contextual influences[26–28] may take place in addition to vergence angle-related signals[16,17] and, as we have shown, gaze direction signals. We propose that stimulus selectivity in area V1 is optimally expressed within restricted volumes of space. □

Methods

General. All experimental protocols, including care, surgery and training of animals, were performed according to the Public Health Service policy on the use of laboratory animals. Two monkeys (*Macaca mulatta*) were placed in complete darkness, with their head fixed, and trained to fixate on a small bright target (12 min of arc) on a video screen. Eye position was monitored using scleral search coils implanted in both eyes, and the monkeys maintained binocular fixation for random periods of 1–2 s, and were rewarded by a drop of fruit juice or water. All trials with binocular fixations shifted outside an angular window of ±1° were rejected. Receptive fields were located using a computer-controlled track-ball. Extracellular recordings were performed using insulated tungsten microelectrodes in area V1 within 4° of the foveal projection. Visual stimuli were flashed binocularly for 500 ms, and in six cases monocularly, centred on the receptive field and presented five times randomly interleaved for all disparity and orientation angles tested. Spike activity was collected 300 ms before the appearance of the fixation target (spontaneous activity) and 500 ms after the visual stimulus onset (evoked activity). Records were taken for three gaze directions in 75% of cells and two gaze directions in 25% of cells.

Visual stimulation. Three-dimensional stereoscopic stimulation was performed using dynamic random dot stereograms generated through ferroelectric stereo glasses (60 frames per s per eye), figure size 6° × 6°, dot density 20%, dot size 3.5 min of arc. Horizontal disparity (–0.6° to +0.6° by 0.2° steps) was introduced between each dot so the entire figure appeared in front (negative values), behind (positive values) or in the plane (0°) of the fixation target. Orientation selectivity (two-dimensional) was tested with square-wave gratings, flashed for 500 ms in a circular window (6°) with a spatial frequency of 2 cycles deg^{-1} in 8 steps of 22.5° angles for 180°.

Data analysis and controls. Disparity and orientation tuning curves were assessed for each direction of gaze using the same stimuli in identical retinotopic positions. Two-way analysis of variance was used to test for significant effects ($P < 0.05$) of the stimulus and of the direction of gaze on mean firing rates. For 90% of cells, the first tested direction was repeated at the end and, if the activity was significantly different ($P < 0.05$), together with visual inspection, the data were discarded. The modulation of visual activity (gain effect) was quantified for each cell by: 1-(min-SA)/(max-SA), where min is the mean activity taken at the peak of the tuning for the gaze direction that evokes the lower activity, max is the mean maximum response for the gaze direction giving the larger response, and SA is the spontaneous activity. An index of 0.5 indicates a ratio of two between max and min. The approximate laminar location of cells (supra- or infragranular) was determined by combining physiological criteria of layer-4 location (noticeable by its high neuronal activity) and depth of recordings.

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brinker is a target of Dpp in *Drosophila* that negatively regulates Dpp-dependent genes

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Growth and patterning of the *Drosophila* wing is controlled in part by the long-range organizing activities of the Decapentaplegic protein (Dpp)[1–4]. Dpp is synthesized by cells that line the anterior side of the anterior/posterior compartment border of the wing imaginal disc. From this source, Dpp is thought to generate a concentration gradient that patterns both anterior and posterior compartments. Among the gene targets that it regulates are *optomotor blind* (*omb*)[5], *spalt* (*sal*)[6], and *daughters against dpp* (*dad*)[7]. We report here the molecular cloning of *brinker* (*brk*), and show that *brk* expression is repressed by *dpp*. *brk* encodes, a protein that negatively regulates Dpp-dependent genes. Expression