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Head position signals used by parietal neurons to encode locations of visual stimuli

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THE mechanism for object location in the environment, and the perception of the external world as stable when eyes, head and body are moved, have long been thought to be centred on the posterior parietal cortex[1–8]. However, head position signals, and their integration with visual and eye position signals to form a representation of space referenced to the body, have never been examined in any area of the cortex. Here we show that the visual and saccadic activities of parietal neurons are strongly affected by head position. The eye and head position effects are equivalent for individual neurons, indicating that the modulation is a function of gaze direction, regardless of whether the eyes or head are used to direct gaze. These data are consistent with the idea that the posterior parietal cortex contains a distributed representation of space in body-centred coordinates.

We recorded from 128 cells in 2 monkeys trained in a task requiring saccades to visual targets from independent head and eye positions. Each monkey was trained to orient its head towards a large fixation spot (Fig. 1*a* and *d*) and its eyes to a small fixation spot (Fig. 1*b* and *e*). In each trial the monkey maintained fixation for a predefined period; a peripheral visual stimulus then appeared and the monkey made a saccadic eye movement to it (Fig. 1*c* and *f*). We analysed the neuron's activities during two time segments aligned to the beginning of the saccade. The first time segment was from 200 ms to 25 ms before the beginning of the saccade, and largely reflects activity related to the visual target, whereas the second time segment was from 25 ms before to 75 ms after saccade initiation, and largely reflects activity related to the eye movement[9].

In the first experiment we examined the effect of head position on the receptive fields of 51 of the 128 neurons by mapping them at two different head positions, 16° to the left and 16° to the right of straight ahead. The monkey held its head in each of the two positions with an initial eye position straight ahead in the orbits. Recording the activity of the cell during the presentation of the stimulus provided a tuning curve of the cell's activities to eight different radial directions in each of the two head positions.

Figure 2*a* shows the tuning curves at the two head positions for one of the cells. This cell had a receptive field centred down and to the left (at an eccentricity of 16°) when the animal was fixating to the right. Because this particular recording was made from the right hemisphere, the left visual field is contralateral with respect to the recorded hemisphere, and the right visual field is ipsilateral. If the receptive field was referenced with respect to the body, rather than with respect to the head or eyes, fixating to the left should rotate the centre of this receptive field anticlockwise (relative to the fixation point) by approximately 90° in the frontal plane to maintain the receptive field at the same location in space. Instead, the best direction was the same for the two head positions, but the magnitude of the activity at the peak was increased by 50% for contralateral (left) fixation.

We constructed a population tuning curve using all 51 cells, and investigated whether the curve shifted with changes in head position (Fig. 2*b*). The receptive field centres for the contralateral head position of all the cells were aligned at 0° on the abscissa, and the activity was averaged across the population of cells for both head positions. If the cells have receptive fields in body-centred coordinates, then the tuning curve for the ipsilateral head position should be shifted towards the contralateral side of the graph (to the right). However, the average tuning curve for the population peaks at 0° for both head positions. Instead, the magnitude of the population activity decreases for ipsilateral gaze. This decrease is due to the fact that the modulation by head position usually increases for the contralateral direction for area LIP neurons, which make up approximately two thirds of the sample. Therefore, a change in head position does not systematically change the peaks of the tuning curves of posterior parietal neurons. Similar effects were found for eye position in previous studies[10–12].

To test the effect of head position and eye position on the magnitude of the visual and saccade activities of cells at several gaze directions, we performed a second experiment in which we recorded the magnitude of the activities from each of five different head positions and five corresponding eye positions. After the receptive field of a cell was mapped and the preferred direction of the cell determined, the monkey was required to make saccades in this preferred direction from each of five different fixation points on the horizontal axis. These saccades were made under two conditions. First, the effect of head position was examined by having the monkey orient its head towards each fixation point with its eyes centred in their orbits (Fig. 1*d–f*). Second, the animal positioned its head straight forward with its eyes deviated to each of the fixation points (Fig. 1*a–c*). This allowed us to determine separately the modulation of the cell's activities due to eye and head position. Figure 3*a* and *b* shows the effects of head position and eye position, respectively, on the activity of a cell which preferred saccades directed contralaterally with 16° amplitude. In Fig. 3*c* the magnitude of the activity is plotted as a function of initial gaze angle. Two plots are shown, one for different head positions and one for different eye positions. Linear relationships between the activity of the cell and the initial gaze angle were demonstrated in both situations (as determined by linear regression and the analysis of variance of the residuals), with their slopes representing the 'gain fields' for eye and head position in this cell. Because the gain fields were very similar, it can be concluded that the activity of this cell was modulated by gaze position (the sum of eye and head position).

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A significant modulation of activity by head position was found for 32 cells in the first time segment and 31 in the second, with 52 of 128 cells showing significant modulation in at least one of these two time segments ($P<0.05$). The relationship between the gain fields for head and eye position for the two time segments is shown in Fig. 4. The slope of the head gain field (vertical axis) is plotted against the slope of the eye gain field (horizontal axis) for each neuron. If a cell displays identical gain fields for head and eye position its point will lie on a 45° positive diagonal in the graph. Most of the points for both time segments were clustered about this diagonal. Therefore, for most cells that demonstrated statistically significant gain fields for head position, the gain fields were best described as a function of gaze position (eye and head position).

These results show that the visual receptive fields of posterior parietal neurons are in retinal (eye-centred) coordinates, but are strongly modulated by gaze direction. Thus individual cells carry information about retinal position, eye position and head position. However, each individual cell is ambiguous about the location of a target in body-centred coordinates because its activity may vary with any one of these three parameters. Thus a particular rate of firing of a single cell can correspond to many locations in space. Interestingly, when we trained neural networks to convert retinal receptive fields to body-centred locations, the units that perform this coordinate transformation develop gain fields for eye and head position which are also a function of gaze direction, similar to those found in the experimental data[13]. Thus the current results are consistent with a model of the posterior parietal cortex in which space is represented in body-centred coordinates, not at the level of single cells, but at the level of populations of cells. This distributed representation could be the final stage for coding locations in space, or it could be used as

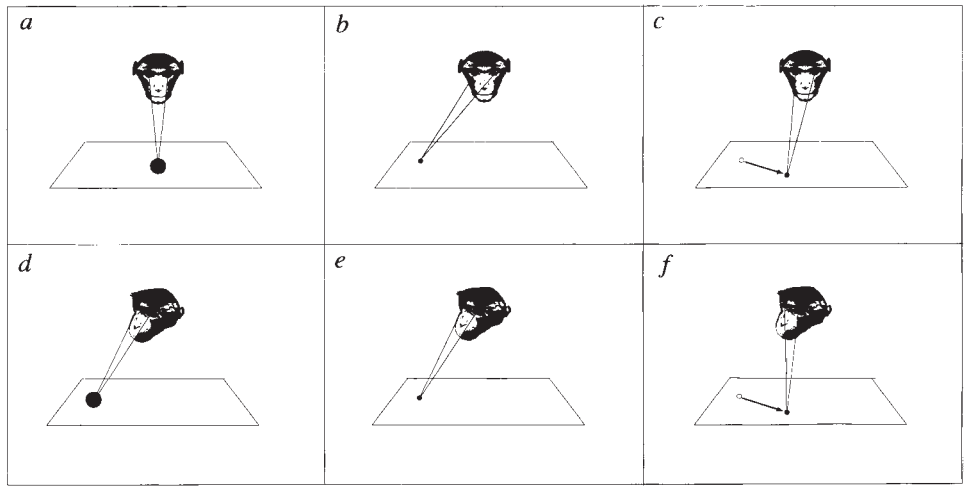

FIG. 1 The monkey uses its eyes (*a–c*) or head (*d–f*) to change the initial gaze direction before a saccade. *a*, *d*, Each trial begins with a 0.4° diameter fixation point appearing on the tangent screen at eye level. The animal orients its eyes and head toward the stimulus. *b*, *e*, The 0.4° stimulus disappears and a smaller, 0.2° diameter stimulus appears at either a different or the same location. The monkey maintains its previous head position and, if necessary, deviates its eyes to fixate the smaller stimulus. *c*, *f*, After 1,500 ms the fixation light is turned off and another 0.2° stimulus appears at a peripheral location. The monkey saccades to the new location while keeping its head still, and the sensory and saccade activities are recorded. For cells with both visual and saccade activity, the visual receptive fields and saccadic motor fields overlay one another in oculocentric coordinates[28] and eye position has the same modulation effects on both[10]. Control experiments, using a delayed-saccade task which separates temporally the visual and saccade activities, determined that head position has a similar modulation effect on both visual and saccade activities for individual neurons.

METHODS. Experiments were performed in the dark. Gaze direction was recorded using the scleral search coil technique, and head position was recorded using a high-precision potentiometer connected to the head post which allowed the animal to move its head horizontally. Receptive fields were mapped systematically in 8 directions at eccentricities of 8° and/or 16°. If the cell's receptive field eccentricity was reasonably close to one of these two distances, further tests were made to assess the effects of head and eye position.

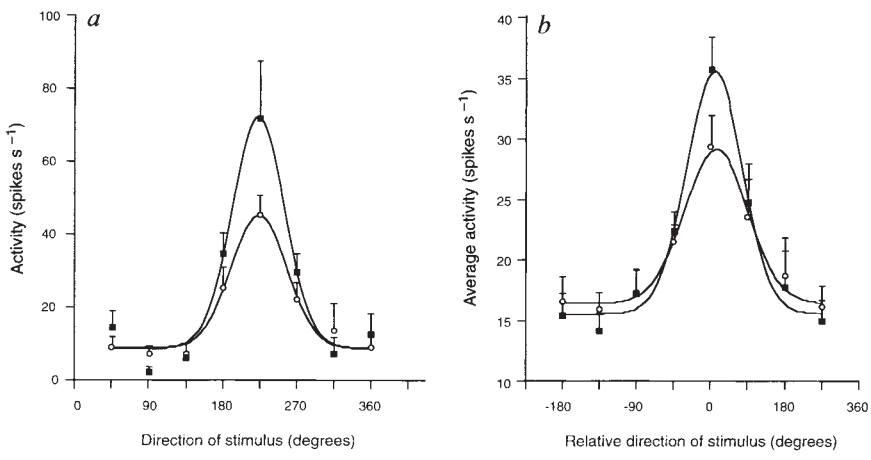

FIG. 2 *a*, Tuning curves of one cell at two head positions, calculated from the first time segment (200 ms to 25 ms before saccade initiation). The horizontal axis indicates the direction of the stimulus, where 0° was directly to the right (ipsilateral), and 180° was to the left (contralateral), and 90° was directed up. Filled squares indicate contralateral head position, and open circles ipsilateral head position in both panels. Bars indicate one standard error. *b*, Plot showing the average tuning curve of the population of 51 cells, calculated from the first time segment. The maximal activity of each cell at the contralateral head position was aligned to 0° on the horizontal axis. The region to the left of 0° is for ipsilateral direction with respect to the receptive field centre of each cell, and to the right of 0° indicates contralateral directions. The vertical axis is mean activity of the population, with bars indicating one standard error.

an intermediate step in the construction of body-centred receptive fields elsewhere in the brain[14,15].

The saccade signals, like the visual signals, are modulated by eye and head position, suggesting that they are both coded in the same distributed, body-centred coordinate frame. That some cells show only sensory or only movement activity, whereas others show both, is consistent with a distributed coding strategy in which each cell is not required to carry all of the signals involved in a neural computation. The role of the saccade signal in the posterior parietal cortex is at present not clear. It could represent an efference copy signal or proprioceptive signal which updates the spatial representation with each eye movement[16]. The saccade activity of nearly all area 7a neurons and nearly one-third of the LIP cells begins after the beginning of the eye movement, strongly suggesting a feedback role[9]. However, the many LIP cells that are activated well in advance of a saccade could code the decision or intention to make an eye movement. Activities related to intentions to make eye movements have been shown in area LIP by using delayed saccade tasks which separate in time the planning and triggering of saccades[17].

Possible sources for the head position signal are proprioceptive inputs from the neck muscles[19–22], an integration of the vestibular signal[23–26] or an integration of corollary discharge associated with head movement. The last of these seems unlikely to be the sole source because the signal has been observed when the head is rotated by the experimenter rather than by the animal

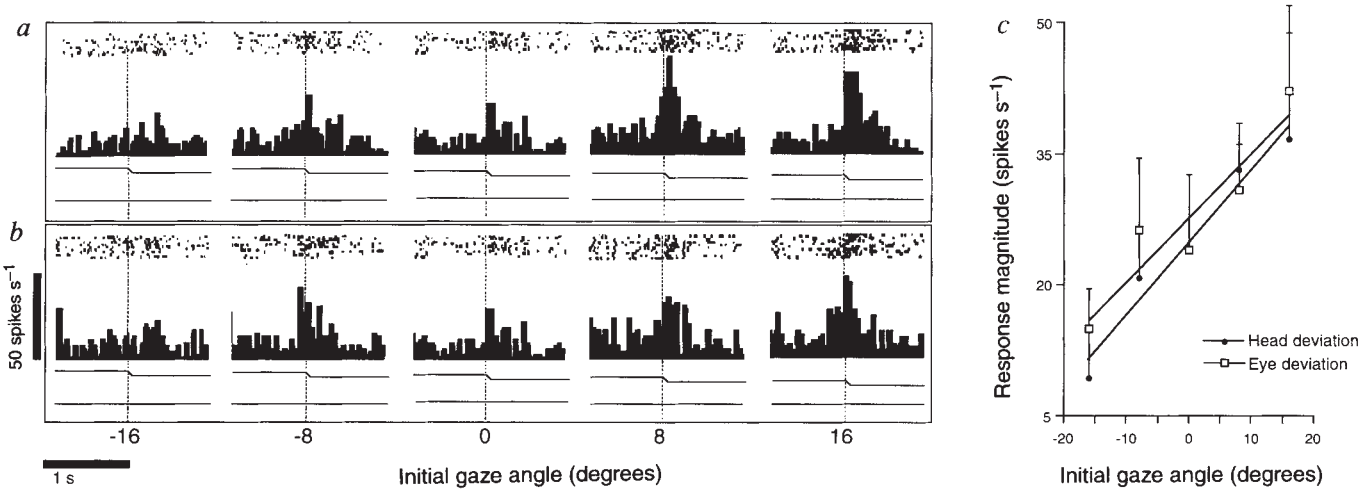

FIG. 3 Activity of a cell while the monkey is making identical saccades to the left from a fixation point placed at five different gaze positions on the horizontal plane. Gaze directions of ±16°, ±8° and 0° directions were used in approximately two-thirds of the cells showing significant head effects, and ±24°, ±12° and 0° were used for the remainder. All trials are aligned with the onset of the saccade, indicated by the vertical broken lines. *a*, The animal has its head oriented towards each of the fixation points, with the eyes centred in their orbits before each saccade. *b*, The head of the animal is directed towards the centre of the screen (0°) with the eyes deviated towards each of the fixation points before each saccade. *c*, Magnitude of the cell's activity around the time of the saccade (25 ms before to 75 ms after onset of the saccade) as it varies with initial gaze position. Bars indicate one standard error. A linear relationship of activity with gaze direction was confirmed by a significant linear regression ($P=0.009$ for head, $P=0.023$ for eye) and by a non-significant analysis of variance (ANOVA) of the regression residuals ($P=0.992$ for head, $P=0.944$ for eye).

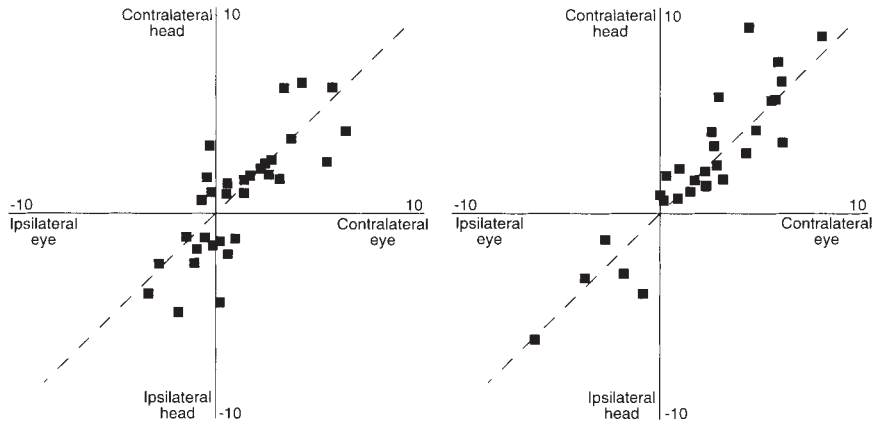

FIG. 4 Plot of the slopes of the regression lines for head and eye position for each cell with a significant modulation by head position ($P<0.05$). The vertical axis indicates the slope of the regression line for head position. The horizontal axis shows the slope of the regression line for eye position. Left, Plot for time segment 1 ($n=32$). A linear regression for these data points resulted in a line of slope 1.0 ± 0.1 s.e.m. and intercept of -0.3 ± 0.4 s.e.m. Right, Plot for time segment 2 ($n=31$) resulted in slope 1.0 ± 0.1 s.e.m. and intercept 0.1 ± 0.3 s.e.m. When computing the slopes of the gain fields, only 13% (4 of 32) of the time segment 1 cells and only 23% (7 of 31) of the time segment 2 cells had a significant departure from linearity ($P<0.05$, one-way ANOVA on residuals). Of the cells with no significant linear slope for head position ($P>0.05$), only 4% (3 of 76) had a significant nonlinearity in time segment 1, and 7% (5 of 76) in time segment 2 ($P<0.05$). A total of 32 cells were modulated by eye position in at least one of the time segments, but not head position in either time segment. Thus a large percentage (66%) of the cells were modulated by eye or eye-and-head position. This percentage is substantial, especially considering the fact that we did not test for vertical eye or head position effects.

in a willed movement. Experiments currently in progress suggest that both neck proprioceptive signals and integrated vestibular signals contribute to the head position signal[27]. □

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Neuronal deficits, not involving motor neurons, in mice lacking BDNF and/or NT4

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NERVE growth factor and other neurotrophins signal to neurons through the Trk family of receptor tyrosine kinases[1–6]. TrkB is relatively promiscuous *in vitro*, acting as a receptor for brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT4) and, to a lesser extent, NT3 (refs 3–5). Mice lacking TrkB[7] show a more severe phenotype than mice lacking BDNF[8,9], suggesting that TrkB may act as a receptor for additional ligands *in vivo*. To explore this possibility, we generated mice lacking NT4 or BDNF as well as mice lacking both neurotrophins. Unlike mice lacking other Trks[7,10,11] or neurotrophins[8,9,12–14], NT4-deficient mice are long-lived and show no obvious neurological defects. Analysis of mutant phenotypes revealed distinct neuronal populations with different neurotrophin requirements. Thus vestibular and trigeminal sensory neurons require BDNF but not NT4, whereas nodose–petrosal sensory neurons require both BDNF and NT4. Motor neurons, whose numbers are drastically reduced in mice lacking TrkB, are not affected even in mice lacking both BDNF and NT4. These results suggest that another ligand, perhaps NT3, does indeed act on TrkB *in vivo*.

Homologous recombination targeting vectors in which the BDNF (Fig. 1*a*) and NT4 coding regions (Fig. 1*b*) were disrupted and partially deleted were used to generate mice with these mutations at their endogenous BDNF and NT4 loci, respectively (Fig. 1*c*, *d*). In agreement with previous studies[8,9], mice homozygous for the BDNF mutation ($bdnf^{-/-}$) failed to thrive beyond postnatal day 8 (Fig. 2*a*), showed an impaired ability to right themselves (Fig. 2*c*), lacked proper coordination of movement and balance, alternated through periods of hyperactivity and immobility, and generally died by 3 weeks of age. In contrast, mice homozygous for the NT4 mutation ($nt4^{-/-}$) (Fig. 1*d*), which clearly lacked NT4 expression (Fig. 1*e*), appeared normal. Growth and righting responses of these mice were similar to those of controls (Fig. 2*b*, *c*), and the mice were able to mate and produce viable offspring; these mice have now survived for 10 months without obvious neurological or phenotypic abnormalities. Mice mutant for both BDNF and NT4 ($bdnf^{-/-}nt4^{-/-}$) did not appear to be more seriously affected than mice lacking only BDNF; they died within 3 weeks and displayed similar behavioural and growth disturbances. Thus the discrepancy between the phenotypes of mice lacking TrkB ($trkb^{-/-}$), which are severely affected and die within 24 to 48 hours[7], and mice lacking only BDNF[8,9] cannot simply be explained by the actions of NT4 on TrkB *in vivo*.

As in $trkb^{-/-}$ mice, gross examination of the brains of $bdnf^{-/-}$ or $nt4^{-/-}$ mice revealed no major cytoarchitectural abnormalities (Fig. 3*a*), although the brains of $bdnf^{-/-}$ mice were smaller than controls and had less neuropile. More detailed analysis may reveal subtle changes in the brains of $nt4^{-/-}$ mice similar to the maturational delays and the changes in neuropeptides and calcium-binding proteins observed in $bdnf^{-/-}$ mice[9], as well as behavioural and functional differences.

Examination of various sensory ganglia and motor neuron populations revealed distinct and overlapping requirements for BDNF and NT4. Consistent with the balance and movement abnormalities displayed by $bdnf^{-/-}$ mice, but not by $nt4^{-/-}$ mice (Fig. 2*c*), vestibular ganglia were reduced by more than 90% in volume in $bdnf^{-/-}$ mice, as previously noted[8,9], but appeared normal in $nt4^{-/-}$ mice (Fig. 3*b* and Table 1). The cochlear ganglia, however, were not reduced in size in mice lacking either BDNF or NT4. As with the vestibular ganglia, significant volume reductions (~40%) were seen in the trigeminal ganglia of $bdnf^{-/-}$ mice, but not of $nt4^{-/-}$ mice; reductions of ganglion size in mice lacking both BDNF and NT4 were not greater than those seen in mice lacking only BDNF (Table 1). However, the situation was quite different for the nodose–petrosal complex, which relays visceral sensory information critical for the regulation of respiration, heart rate, blood pressure and other autonomic functions. The nodose–petrosal complex as a whole was greatly reduced in both $bdnf^{-/-}$ and $nt4^{-/-}$ mice (~68% and ~61% reductions, respectively, in the volumes of the complex, with similar reductions in the number of neurons in the complex; Table 1 and Fig. 3*c*). Moreover, an even greater reduction (~83% reduction in volume, and a 79% reduction in neuronal number) was seen in mice lacking both BDNF and NT4 (Table 1 and Fig. 3*c*).

Previous findings that $trkb^{-/-}$ mice had marked reductions in motor neurons of the facial nucleus (70% reduction) and lumbar spinal cord (35% reduction)[7], but $bdnf^{-/-}$ mice did not[8,9], led