

Eye Position Influences Auditory Responses in Primate Inferior Colliculus

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Summary

We examined the frame of reference of auditory responses in the inferior colliculus in monkeys fixating visual stimuli at different locations. Eye position modulated the level of auditory responses in 33% of the neurons we encountered, but it did not appear to shift their spatial tuning. The effect of eye position on auditory responses was substantial—comparable in magnitude to that of sound location. The eye position signal appeared to interact with the auditory responses in at least a partly multiplicative fashion. We conclude that the representation of sound location in primate IC is distributed and that the frame of reference is intermediate between head- and eye-centered coordinates. The information contained in these neurons appears to be sufficient for later neural stages to calculate the positions of sounds with respect to the eyes.

Introduction

The ability to localize sounds is critical to survival—predators and prey alike use sound to detect friend and foe. The location of a sound source can be deduced from differences in sound arrival time and pressure level across the two ears (for review, see Blauert, 1997). Brain areas involved in sound localization have been assumed to use a head- (or ears-) centered frame of reference derived from these cues. However, only a few studies have actually addressed the frame of reference of auditory signals in the brain, and those that did have found evidence that auditory signals are ultimately encoded in a frame of reference anchored to the positions of the eyes. The superior colliculi of primates and cats contain neurons whose auditory receptive fields move when the eyes move, even though the head and ears are stationary (Jay and Sparks, 1984, 1987; Hartline et al., 1995; Peck et al., 1995). In primate frontal eye fields, motor activity related to saccades to auditory stimuli depends on the position of the sound with respect to the eyes (Russo and Bruce, 1994). In lateral intraparietal cortex, memory activity for sounds is affected by the position of the eyes in the orbits (Stricanne et al., 1996).

Because this eye-centered frame of reference for sound location was discovered in oculomotor areas, it has been presumed to relate specifically to eye move-

ments. However, an eye-centered reference frame for sounds could be valuable for a variety of reasons. Perceptual comparison with visual information (e.g., visual capture and the ventriloquism effect) would be well served by an eye-centered reference frame, as would guidance of any behavior that can be governed by both visual and auditory stimuli (e.g., Cohen and Andersen, 2000). If an eye-centered reference frame for sound has broad utility, then sound locations may be encoded in an eye-centered reference frame beginning much earlier in the auditory pathway than has previously been imagined.

The goal of the current study was to investigate the frame of reference at an early point in the ascending auditory pathway, namely the inferior colliculus (IC). The IC is situated above the convergence of binaural signals in the superior olivary complex (for review, see Ehret, 1997), and nearly all input to all higher areas passes through it. Lesions of the IC can cause deficits in sound localization behavior (Wagner, 1993; Kelly and Kavanagh, 1994; Zrull and Coleman, 1997). Neurons sensitive to the locations of sounds in space have been reported by a variety of studies using free field acoustic stimuli in cats, owls, and guinea pigs (Bock and Webster, 1974; Knudsen and Konishi, 1978; Semple and Aitkin, 1979; Semple et al., 1983; Aitkin et al., 1984, 1985; Calford et al., 1986; Aitkin and Martin, 1987; Wagner et al., 1987; Volman and Konishi, 1989; Aitkin and Martin, 1990; Binns et al., 1992), but little is known about the spatial response properties in monkeys (Jay and Sparks, 1987). In addition to having a strategic location, the IC shows some intriguing multisensory properties, receiving visual input (to the pericentral nucleus: Itaya and Van Hoesen, 1982; cats: Mascetti and Strozzi, 1988) and somatosensory input (to the external nucleus: Schroeder and Jane, 1976; Aitkin et al., 1978, 1981; Paloff and Usunoff, 1992) in addition to auditory input. It has also been implicated in visually guided recalibration of auditory spatial processing in barn owls (Brainard and Knudsen, 1993a, 1993b; Feldman et al., 1996).

We report here that eye position modulates the responses of many IC neurons to sound and that cells in IC encode sound location in a distributed fashion that is intermediate between head- and eye-centered reference frames. A computational analysis of the signals present in IC suggests that the information they contain is sufficient for computing an eye-centered reference frame without requiring any additional information. These results suggest that the coordinate transformation of auditory signals from a head- to an eye-centered frame of reference is gradual and that it has begun by an earlier point in auditory processing than has previously been appreciated.

A preliminary version of this work has appeared elsewhere (K.R. Clark et al., 2000, Soc. Neurosci., abstract).

Results

Reference Frame

We found that eye position modulated the auditory responses of ~33% of neurons recorded in the IC (24 of

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Table 1. Summary of Cell Characteristics

| | N | Percent |
|--|----|---------|
| Main effect of eye position | 24 | 33% |
| and sound location | 17 | 23% |
| and interaction | 6 | 8% |
| and both | 5 | 7% |
| Main effect of sound location | 43 | 59% |
| and interaction (but no main effect for eye position) | 1 | 1% |
| Interaction | 7 | 10% |
| Total main effect of eye position and/or interaction | 25 | 34% |
| Total: | 73 | 100.0% |

Values in the table are derived from a two-way ANOVA with eye position and sound location as the two factors. The dependent measure was cell discharge rate following stimulus presentation minus the baseline discharge rate on each trial.

73 cells, two-way ANOVA with sound location and eye position as factors, $p < 0.05$; see Table 1). Figure 1 shows four examples. The responses to sound of each of these cells depended on where the eyes were pointing (left, straight ahead, or right). The top graph in each panel (Figures 1A–1D) shows the activity of a cell plotted as a function of sound location with respect to the head. Each trace within each graph shows the responses collected at a different eye fixation position (left, center, or right). The influence of eye position is made apparent by the fact that these three traces are not superimposed on one another.

Though influenced by eye position, these cells do not appear to encode sound location in an eye-centered frame of reference. If they did, then the difference between the responses measured at each eye position would disappear if the data were realigned as a function of each speaker’s location with respect to the direction of gaze, as shown in the bottom graphs in each panel. Instead, even in an eye-centered reference frame, the discrepancy between the data collected at different eye positions can still remain. Comparison of the top and bottom panels in Figures 1A–1D shows that the responses of these four cells often align as poorly in an eye-centered frame of reference as they do in a head-centered frame of reference.

An obvious aspect of the cells illustrated in Figure 1 is that their response patterns are quite complex. Neither eye position nor sound location per se affect neural responses in a manner reminiscent of analogous stimulus–response relationships in other areas of the brain. The receptive fields, if they can be called such, are not bounded: auditory responses occurred for all the tested speaker locations. Furthermore, the shape of the spatial response function was not necessarily maintained across different fixation positions (Figures 1A and 1D). Nevertheless, sensitivity to both eye position and sound location is certainly present. This complexity was a common feature of the cells in our sample and suggests that the representation of sound location contained in the IC is highly distributed. Accordingly, we employed a variety of means of characterizing the population of cells as a whole.

To summarize the trend in coordinate frame across

the whole population of cells, we computed a head-centered and an eye-centered mean response offset for each cell:

$$offset = \frac{\sum_{i=1}^n \sum_{e=left,right} abs(\bar{R}_{e,i} - \bar{R}_{c,i})}{2n \cdot abs(\bar{R})} * 100 \quad (1)$$

where $\bar{R}_{e,i}$ and $\bar{R}_{c,i}$ are the average responses of the cell to a sound at speaker location i , while the eyes fixated either eccentrically (e) or at the center (c). We only included speaker locations that existed for all three fixation positions in both head- and eye-centered frames of reference for this analysis; n corresponds to the number of speaker locations. \bar{R} is the average response across all stimulus conditions. In short, this metric represents the average difference between the responses for each eye position when plotted in head- and eye-centered reference frames, respectively, expressed as a percentage of the average auditory response overall. These metrics therefore summarize the agreement between the response curves for the three fixation positions in head- and eye-centered reference frames, respectively. A true head-centered frame of reference would have a head-centered mean response offset of 0, and a true eye-centered frame of reference would have an eye-centered mean response offset of 0.

Figure 2 summarizes the trend across the whole population of cells, plotting the head-centered mean response offset versus the eye-centered mean response offset for each cell. If the frame of reference in the IC were head-centered, the points should cluster at a value of 0 on the y axis and spread out along the x axis below the line of slope 1. The opposite pattern should appear for an eye-centered frame of reference. Instead, the head- and eye-centered mean response offsets tend to correspond with one another. The linear regression line has a slope of 1.00 and the correlation coefficient (r) is 0.99, indicating a strong correlation between the head and eye offset metrics. This suggests that the frame of reference in IC is intermediate between head- and eye-centered coordinates, and about equally similar (or dissimilar) to both.

Sensitivity to Spatial Location

One notable aspect of our results is the relative modesty of the dependence of the cells’ responses to the location of the speaker, regardless of eye position. The cells shown in Figure 1 all responded to sounds delivered from any of the 12–15 speakers occupying a wide range of space, though the level of the response clearly depended on the location of the sound. A larger portion of the cells show a main effect of sound location (43 of 73, 59%; Table 1) than for eye position. However, the ANOVA may be a somewhat unfair basis for comparison because we used a wider range of speaker locations than eye positions. Thus, the speaker location factor may be expected to have a greater impact in the ANOVA. To obtain a more fair comparison between the effects of eye position and the effects of sound location per se, we computed a sensitivity index using the three eye positions and the three speaker locations that matched those eye positions: -12° , 0° , and 12° . The sensitivity

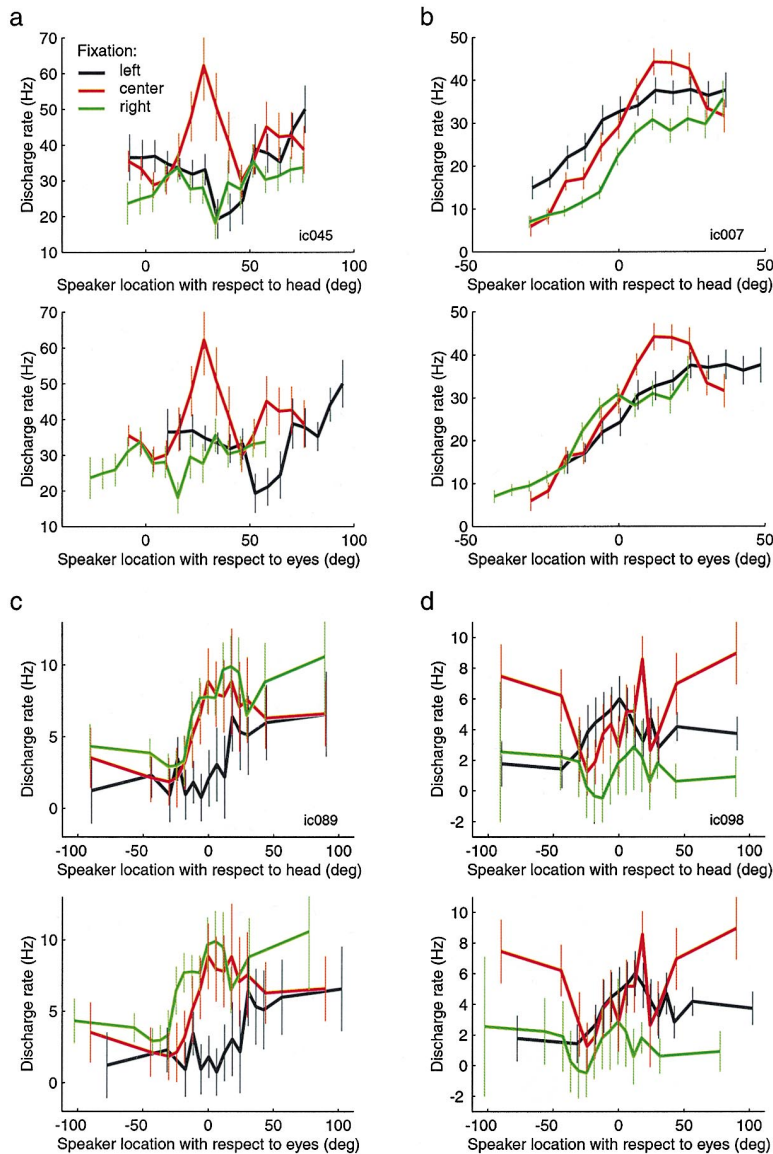


Figure 1. Responses of Four Inferior Colliculus Neurons to Sounds at Different Locations as a Function of Eye Position

The top graph in each panel shows the responses to sounds at various locations with respect to the head. The three traces represent responses measured at each of the three eye fixation positions (left, center, and right). The bottom graph in each panel realigns the data to show the responses as a function of sound location with respect to the eyes. Responses shown are the mean discharge rate (after subtraction of the baseline discharge rate) of all stimulus presentations from each speaker and the two adjacent ones; the bars represent standard error of the mean. This pooling across adjacent speaker locations was done for display purposes only—different speaker locations were treated independently in all other quantitative analyses. All cells shown here were recorded from the left IC. Negative values on the abscissa indicate leftward (ipsilateral) speaker locations. The data in each panel (A–D) represent the results of 572, 309, 396, and 364 stimulus presentations, roughly evenly distributed among the three eye positions and 12 (B) or 15 (A, C, and D) speaker positions. The fixation positions for the cells shown in (B)–(D) were -12° , 0° , and 12° ; the fixation positions for the cell shown in (A) were -18° , 0° , and 18° .

index for speaker location compared the responses to the left and right speakers when the eyes were directed straight ahead. Similarly, the sensitivity index for eye position compared the responses when the eyes were directed to the left and right when the sound was delivered through the speaker at the center.

$$\text{Index} = \frac{\text{abs}(\text{response}_{\text{left}} - \text{response}_{\text{right}})}{(\text{response}_{\text{left}} + \text{response}_{\text{right}})} \quad (2)$$

A value of 0 would indicate that the factor in question had very little influence over the cell's responsiveness, while a value of 1 would indicate a very strong influence. Figure 3 shows the results of this analysis. Eye position and sound location influenced cell responses to about the same degree (Figure 3A). There was no correlation between a cell's sensitivity index for eye position and its sensitivity index for sound location (Figure 3B). This analysis demonstrates that the impact of eye position is comparable in magnitude to the impact of sound loca-

tion across the population, but that the two effects are unrelated in individual neurons.

Controls

We conducted two controls to ensure that the response modulation we attribute to eye position could not be accounted for by other factors. Our first concern was that the monkeys might be moving their ears systematically when they moved their eyes, as cats do (Populin and Yin, 1998). Such changes in ear position would alter the level and spectral properties of the sound cues reaching the cochlea in a way that varied systematically with eye position and, thus, could provide a strictly acoustic explanation for the apparent influence of eye position. To test this possibility, we monitored ear position for many experimental sessions. We taped a precalibrated coil of wire to the back of the contralateral pinna and measured the horizontal component of ear position using the magnetic field coil technique (Populin and Yin,

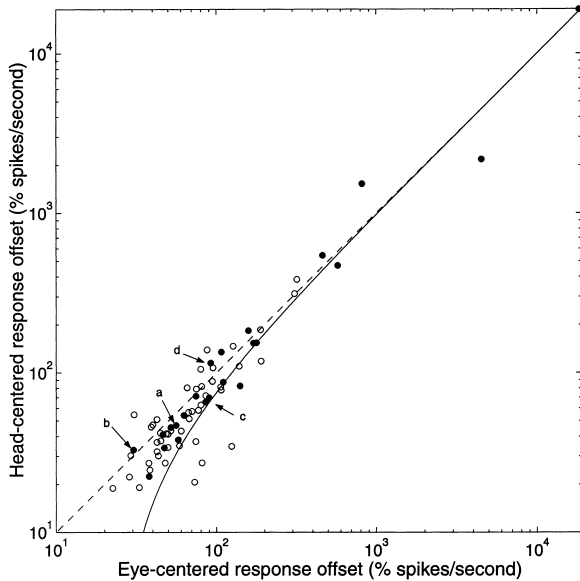


Figure 2. Average Response Offset Due to Fixation Position in Head-Centered versus Eye-Centered Reference Frames, Expressed as Percentage of the Average Response of Each Cell across All Stimulus Conditions

Points lying on the line of slope 1 (dashed trace) indicate responses that align equally well (or poorly) in head- and eye-centered reference frames. Points falling below the dashed line indicate responses that were better aligned in a head-centered reference frame; those above the line were better aligned in an eye-centered reference frame. Filled circles indicate cells that showed a significant main effect of eye position in the two-way ANOVA (Table 1). The linear regression line (solid) had a slope of 1.00, $R^2 = 0.98$, ($R = 0.99$) $p < 0.001$. The line appears curved on this log-log plot due to its intercept at a value of -25 . The labeled points correspond to the cells shown in Figures 1A–1D.

1998). We found that the mean change in ear position as a function of eye position of both monkeys were very small, averaging 0.48° . In no cases did either monkey generate guided ear movements of the sort observed in cats (Populin and Yin, 1998). Figure 4A shows the average ear position at the time of sound onset as a function of fixation position for the cell shown in Figure 1D. The histogram in Figure 4B shows the average change in ear positions across all the cells for which we collected ear position data. Note that in all cases the range of ear movements was less than 3° , and, for the vast majority of cells, the ear movements were so small as to be barely detectable using the magnetic field coil method (which has a resolution of 0.25°). We also conducted a one-way ANOVA with fixation position as the factor of interest and ear position as the dependent measure to determine if these small changes in horizontal ear position were correlated with the direction of gaze. Although the results were statistically significant in 7 of 41 experiments ($p < 0.05$, 17%), this significance was unrelated to the effect of eye position on neural responses (Table 2; $\chi^2 = 0.578$, $p > 0.05$).

A second source of concern was that the eye position modulation might in fact reflect visual influences. Although the pericentral nucleus of the IC does receive a retinal projection (Itaya and Van Hoesen, 1982), it seems unlikely that this could cause the eye position effect

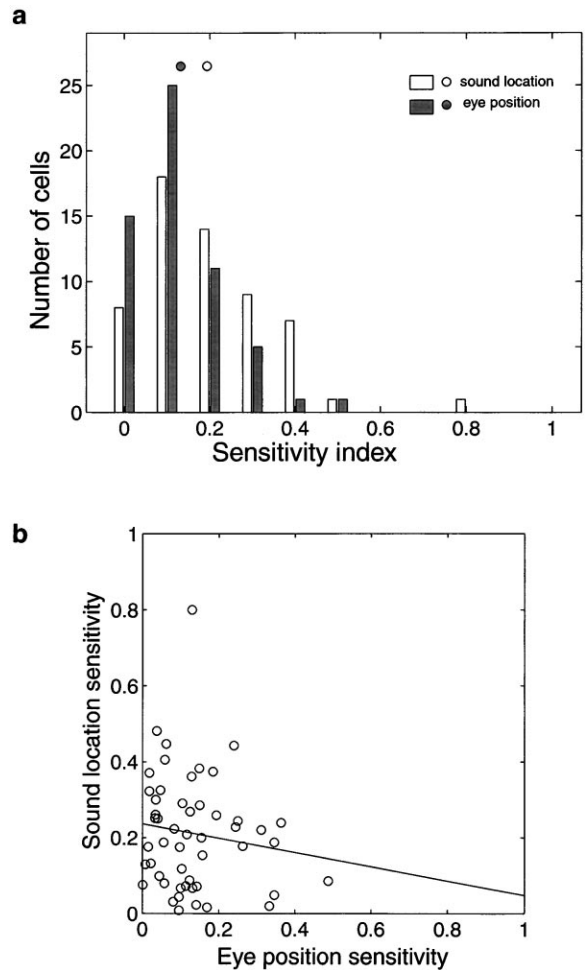


Figure 3. Sensitivity Index to Sound Location (with Respect to the Head) and Eye Position

(A) The frequency of occurrence of different levels of these indices across the population of cells. The mean sensitivity index for eye position was 0.13 (gray circle), while the mean sensitivity index for sound location was 0.19 (open circle).

(B) Correlation between the sound location sensitivity and eye position sensitivity. The regression line is not significant ($p = 0.35$). Raw responses (without baseline subtraction) were used for computing the sensitivity index, as negative activity levels could cause the index to depart from the range of 0 to 1. Fifty-eight cells for which we collected data with sounds at -12° , 0° , and 12° and eyes at -12° , 0° , and 12° were included in this analysis, and 15 cells were omitted due to lack of data at one or more of these fixation or sound locations.

seen here for a number of reasons. First, the visual responses are rare ($<10\%$ of cells in cat ICP) and have never been reported in cells that respond to auditory stimuli (Mascetti and Strozzi, 1988). Second, our experiments were conducted in the dark, and the only source of visual information was the LED that served as a fixation target—and this visual stimulus lay at a fixed location on the retina after the animal made its saccade to fixate it—thus, the visual image was not affected by eye position. Third, no effects of eye position were present during the fixation period prior to onset of the auditory stimulus (this aspect of our results is discussed in greater detail in the following section). Finally, we inves-

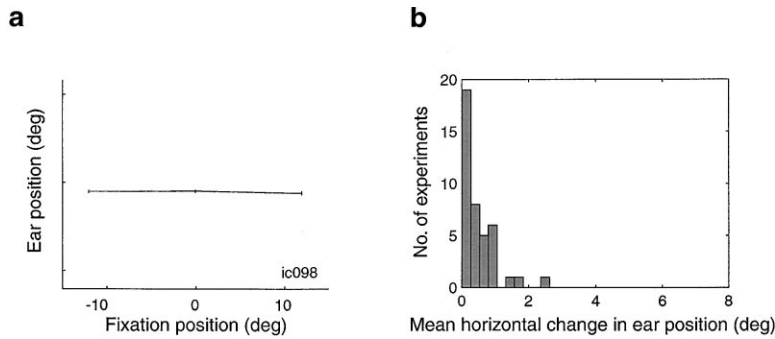


Figure 4. Relationship between Ear Movements and Eye Movements

(A) The mean ear position at stimulus onset as a function of fixation position for the cell shown in Figure 1D. The tick marks on the ordinate represent 10° increments in ear position; the absolute direction of orientation of the ears is of course unknown.

(B) A histogram of the mean horizontal change in ear position for all the sessions in which ear movements were measured. The mean change in ear position was taken as the largest difference in the average positions of the ears for any two of the three fixation positions. The mean change in ear position for the whole dataset averaged 0.48°.

tingated the possibility that the slight illumination of the visual scene provided by the LED could affect the results. We collected data from an additional 20 cells while illuminating the testing room with a nightlight. The proportion of cells showing a significant effect of eye position was 5 out of 20, or 25%, which was smaller than the proportion of eye position-dependent cells in the data set collected in the dark ($\chi^2 = 0.4539$, $p = 0.50$). One in 20 showed significant modulation in baseline firing rate ($p < 0.05$), which again was no different from chance. Thus, it seems extremely unlikely that strictly visual influences could account for the variation in auditory responses as a function of eye position.

Multiplicative Gain Fields?

Figures 1 and 2 show that eye position affects the level of response without necessarily shifting the speaker locations that produce the largest responses. This pattern of results is highly reminiscent of the eye position gain fields that have now been reported in a number of areas in the visual and oculomotor pathway (Andersen and Mountcastle, 1983; Andersen et al., 1985, 1990; Van Opstal et al., 1995; Bremmer et al., 1997a, 1997b; Duhamel et al., 1997; Guo and Li, 1997; Bremmer et al., 1999; Trotter and Celebrini, 1999). The term gain implies a multiplicative interaction between an eye position signal and the sensory signal. (Whether this implication is an accurate one has yet to be fully explored in these other areas.) We investigated whether the eye position effect in IC neurons is strictly additive or contains a

multiplicative component. If the interaction is additive, then changing eye position should produce a constant change in discharge rate that does not interact with any other factors which influence the response. An additive eye position effect might well be apparent in the baseline firing rate, in the absence of any auditory input. Accordingly, we did a one-way ANOVA on the activity level when the animal was fixating different fixation targets but before any auditory stimulus had been presented. We found only 4 of 73 (5.4%) of cells in IC had a significant modulation in baseline firing rates at $p < 0.05$. These numbers are no greater than would be predicted by chance variations, so we conclude that eye position does not modulate firing rate in the absence of an auditory stimulus.

This finding suggests the presence of a multiplicative interaction, but it is not conclusive: the eye position signal might simply be too small to exceed threshold unless an auditory stimulus is also present. So, we examined the interaction between eye position and the response to the auditory stimulus. For each cell, we computed a regression of the difference in response to a given speaker location that was due to a change in eye position (response with eyes center minus response with eyes eccentric, ΔR_{c-e}) as a function of the response to that speaker location when the eyes were pointing straight ahead (R_c):

$$\Delta R_{c-e} = mR_c + b \quad (3)$$

If the effect of eye position were solely additive, the slope (m) of the regression should be 0, and only the constant b would differ from 0. (While including a constant [b] in the regression equation is needed to permit a good fit in the event that the slope term is zero, the potential importance of a non-zero constant term in combination with a non-zero slope [m] is difficult to evaluate with our data since the “x” components of the data points—generally sizeable positive values—do not constrain the regression line in the vicinity of the y intercept. Near-threshold auditory stimuli would be needed to obtain an accurate estimate of the constant term under these circumstances.)

Figures 5A–5D show the results for the same cells as in Figures 1A–1D. In each cell, the change in response when the eyes moved eccentrically varied significantly with the level of response when the eyes were directed straight ahead, which is consistent with the presence

Table 2. Relationship between Eye Position, Ear Position, and Neural Activity

| | Ear Movement | | |
|-----------------|--------------|-----------------|-------|
| | Significant | Not Significant | Total |
| Eyes | | | |
| Significant | 2 | 15 | 17 |
| Not Significant | 5 | 19 | 24 |
| Total | 7 | 34 | 41 |

Each item of the table lists the number of cells showing a given combination of statistical significance in two domains. Columns indicate the statistical significance of the relationship between ear movements and eye position, while rows indicate the statistical significance of the relationship between eye position and neural responses (ANOVA, $p < 0.05$). The two factors were uncorrelated with one another ($\chi^2 = 0.578$, $p > 0.05$).

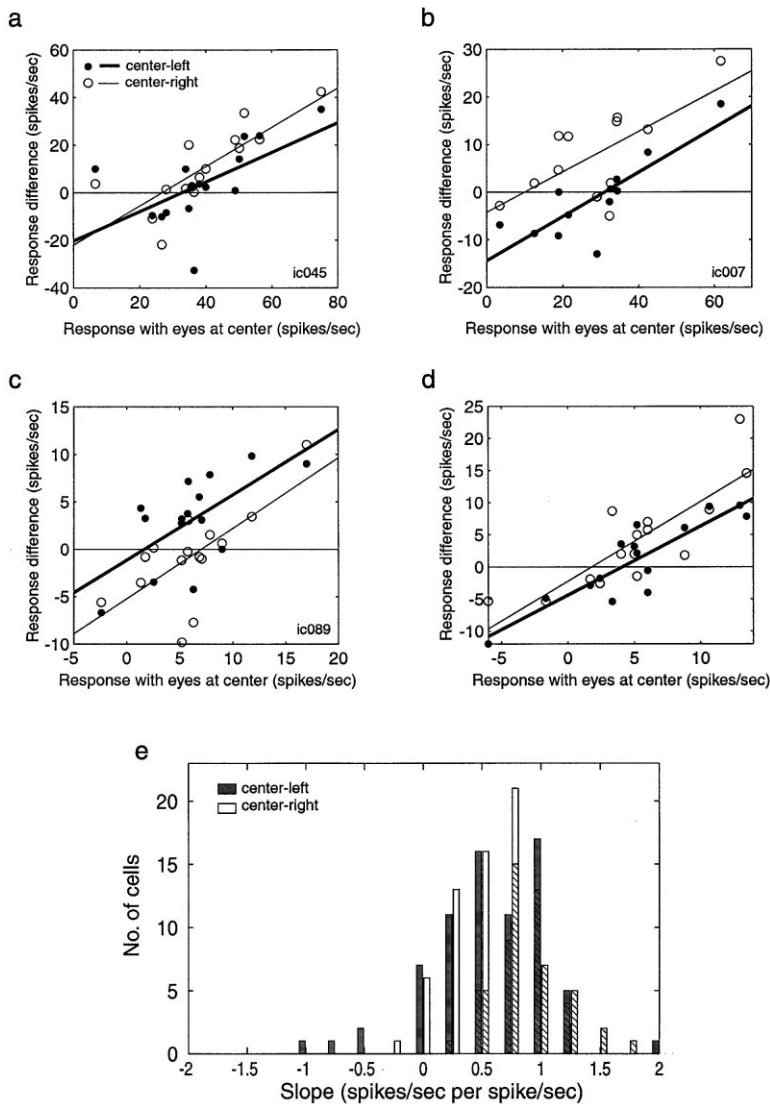


Figure 5. Response Difference Due to Change in Eye Position as a Function of the Response to Each Speaker when the Eyes were Gazing Straight Ahead

Responses consisted of the mean discharge rate (after subtraction of the baseline discharge rate) for all stimulus presentations involving a given speaker location and a given eye position.

(A–D) Data for the individual cells shown in Figures 1A–1D. Open circles and thin lines show the data and regression for the response with the eyes at the center minus the response when the eyes looked to the right. Closed circles and thick regression lines show the same for the response with eyes at the center minus the response when the eyes looked left. These eight regression lines were all statistically significant ($p < 0.05$); the slopes range from 0.42 to 1.24.

(E) Histogram of the slopes of the regression lines across the whole population. The hatched portions of the bars indicate the proportion of the slopes that were statistically different from 0 at $p < 0.05$.

of a multiplicative component to the interaction between the eye position and auditory signals. This was true of the population as a whole as well (Figure 5E). Cells with regression slopes significant at the $p < 0.05$ level are indicated by the hatched regions on the histograms. Nineteen of 72 cells (26%; one cell was excluded from this analyses because only two eye positions were tested) had slopes that differed from 0 for both the center-left and center-right comparisons at $p < 0.05$. Using a stricter criterion for significance ($p < 0.025$), but including cells if either the center-right comparison or the center-left comparison yielded a significant relationship, we found that 40 of 72 cells or 56% had at least one significant regression slope. Overall, the mean slope was 0.60, or, for every spike per second in the response to a sound, a change in eye position of 12° resulted on average in a change in the response of 60%.

Do IC Neurons Provide Sufficient Information for Computing Spatial Location in Eye-Centered Coordinates?

We have shown that eye position modulates IC responses to sounds, that the reference frame is neither

head- nor eye-centered, that the impact of eye position is comparable to that of sound location, and that eye position signals interact with the acoustic inputs in a multiplicative fashion. However, Figure 1 also illustrates that the effects of both sound location and eye position can be highly variable and unsystematic in individual cells. We therefore wondered whether these cells are capable of providing the information needed by subsequent stages of processing to properly compute the locations of sounds with respect to the eyes. To test this, we treated the cells in our sample as the input cells in a two-layer linear network. The output consisted of a single unit whose desired response level was the location of the stimulus with respect to the eyes. This output unit's response was a weighted sum of the responses of all the input units. Because this network design was strictly linear, determining the weights is equivalent to solving a system of linear equations. Accordingly, we fit the weights by minimizing the sum of squares of the error.

Figure 6A shows the actual response of the output unit versus the desired response (or the location of the stimulus with respect to the eyes). A line of slope one

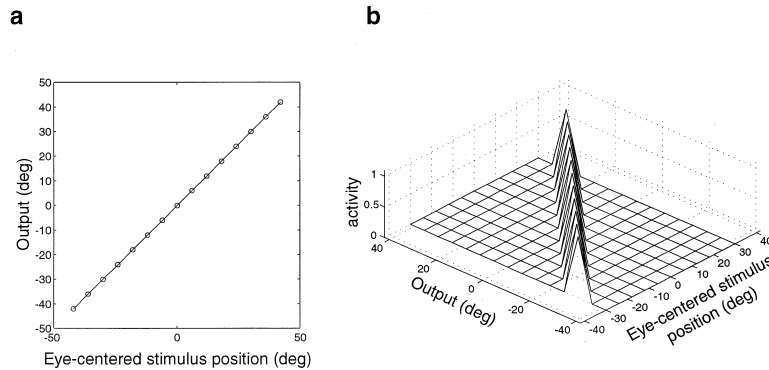


Figure 6. Results of a Simulation of Computation of Eye-Centered Representation of Sound Location from IC Neurons

Thirty-six cells in which the fixation positions were -12° , 0° , and 12° and speaker locations spanned at least -30° to 30° in 6° increments were included. The mean responses on trials with eye-centered target locations of -42° to 42° were used as the activity of the input layer. Output consisted of either a single neuron whose responses was a linear function of the eye-centered location of the stimulus (A) or a population of neurons with eye-centered receptive fields (B).

represents perfect performance. The output unit for this simulation performs very close to perfectly, showing that it is quite possible for the brain to compute the position of the stimulus with respect to the eyes in one linear step from the representation of the sound that is present in IC. No additional eye position or sound location information is required.

However, this version of the simulation doesn't produce the kind of eye-centered representation that has been found in superior colliculus, where cells have circumscribed receptive fields. So, we repeated the simulation using a place code for the output, or neurons that have receptive fields in an eye-centered frame of reference (Figure 6B). The output array contained one unit for every eye-centered speaker location, each of which was expected to have a response of 1 if the sound were in its eye-centered receptive field and 0 otherwise. Rather than achieving this response pattern using a binary "activation function" on the part of the output units, we attempted to do it using the same linear activation functions and linear combination of the inputs as in the previous simulation. This allowed us to continue to use linear methods, and we fit the weights by minimizing the sum of squares of the error. The results are shown in Figure 6B and demonstrate that it is also possible to generate a representation of sound location like that found in the superior colliculus by direct linear combination from the kind of representation found among the neurons of the inferior colliculus.

Location of Cells

Cells that were influenced by eye position were found throughout our recording locations within the IC. Localization of individual recording sites with respect to the three subdivisions of the IC (the central, external, and pericentral nuclei) is not possible based on our MRI images (see Figure 7), so whether eye position exerts a greater or lesser influence on cells in the different subnuclei remains an open question.

Physiological criteria for identifying the locations of cells in primate IC are not well established. Only two studies have compared the physiological response properties of the central and external nuclei in primate IC (Ryan and Miller, 1977, 1978). Neurons in both areas have similar spontaneous rates and response shapes, which consist of various combinations of phasic and tonic excitation and inhibition. Sensitivity to sound location (which is especially pronounced in the external nucleus in barn owls; Knudsen and Konishi, 1978) has not

previously been examined in primate IC. In any case, we found no relationship between the sensitivity to sound location and sensitivity to eye position (Figure 3B).

The only known physiological difference between the subnuclei in primate IC is response latency: Ryan and Miller (1978) reported that the average response latency of neurons in the central nucleus was 15.13 ms, and the response latency of units in the external nucleus was 25.14 ms. The mean response latency of our cells was 13.4 ms, which is more consistent with their sample of central IC units. In our data, there was no relationship between the response latency of an individual neuron and the presence of an effect of eye position. In short, although we lack anatomical/histological evidence to identify the locations of our cells with respect to the different subnuclei, there is at present no evidence to suspect that a sensitivity to eye position is confined exclusively to the regions outside the central nucleus, for example.

Discussion

Localizing a sound is inherently different from localizing a visual or tactile stimulus. For the visual and somatosensory systems, the receptor surfaces provide a topographic place code representing stimulus location. The auditory system, in contrast, must *compute* the locations of sounds. Clearly, to do so the auditory system must compare the acoustic cues arriving at the two ears and/or analyze the spectral content of the sound to deduce the angle of incidence of that sound. The result of such a computation indicates the location of the sound with respect to the head and ears.

All this is true. But as our results show, it does not follow that the brain must *represent* sound location in a head-centered frame of reference throughout the auditory pathway. Instead, the representation of sound location may be more complex than has previously been appreciated. We have found that eye position begins to modulate responses as early as the IC. (How this eye position signal arrives at the IC is unknown.) The modulation by eye position suggests that the IC contains a representation of sound location that may be in the midst of a transition from head- to eye-centered coordinates. Our results indicate that the frame of reference in IC is equidistant from either point. Our simulation shows that the information needed to complete this transformation is present in the responses of these cells, and that no additional signals are necessary.

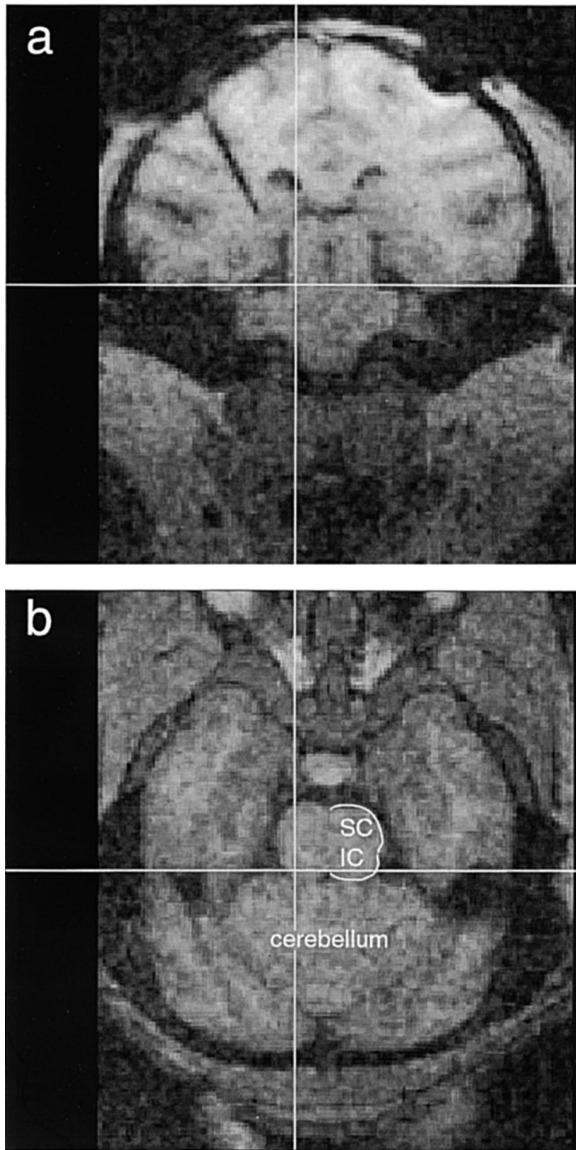


Figure 7. MRI Image of Electrode on a Penetration that Led to the Right Inferior Colliculus in One Monkey

(A) Coronal view, showing an electrode entering on angled penetration (see Experimental Procedures). Per radiologic conventions, the left side of the image corresponds to the right side of the brain. This penetration was located in roughly the center of our recording locations for this animal. The electrode was lowered only part of the way to the IC to minimize tissue damage during positioning of the animal in the scanner. The cross hairs indicate the point along the trajectory where the electrode would enter the brainstem if the penetration were to continue.

(B) A tilted horizontal view showing the position of the cross hairs in a plane of section where brainstem landmarks are easily visible. The IC, SC, and cerebellum are labeled on the right side of the image (left side of brain).

The representation for sound location in primate IC appears to be a highly distributed population code, with a large proportion of IC cells responding to sounds at any given location. This population response changes when the eyes move. Studies in other species have extensively explored the spatial sensitivity of IC neurons

and have identified a variety of classes of cells with different degrees of spatial tuning (Bock and Webster, 1974; Knudsen and Konishi, 1978; Semple and Aitkin, 1979; Semple et al., 1983; Aitkin et al., 1984, 1985; Calford et al., 1986; Aitkin and Martin, 1987, 1990; Wagner et al., 1987; Volman and Konishi, 1989; Binns et al., 1992). A detailed comparison between our results and those of prior studies is beyond the scope of this paper, but it is clear that many factors may influence the observed spatial tuning. Species differences, eye position, state of anesthesia, free field versus dichotic or virtual space stimulation, and sound intensity all may affect the type of spatial sensitivity observed and complicate efforts to compare across studies.

Mixed reference frames for spatial signals have been discovered in a variety of contexts: visual neurons from V1 to parietal cortex show a dependence on eye position (Andersen and Mountcastle, 1983; Andersen et al., 1985, 1990; Bremmer et al., 1997a, 1997b, 1999; Duhamel et al., 1997; Guo and Li, 1997; Trotter and Celebrini, 1999), and even the auditory receptive fields in the superior colliculus frequently only move 50% of the distance the eyes move (Jay and Sparks, 1987). Indeed, were it not for the modest spatial tuning of the IC neurons (independent of their frame of reference), the frame of reference present in IC would appear quite similar to the frame of reference of visual information in parietal cortex and auditory information in SC.

Our results suggest that eye position signals interact in at least a partly multiplicative fashion with auditory responses in IC. Eye position modulation in visual and oculomotor areas is widely assumed to behave in a multiplicative fashion, but hard evidence for this is scarce. The example cells presented in some studies do appear to show a multiplicative interaction between an eye position signal and the sensory response (e.g., Andersen et al., 1990; Trotter and Celebrini, 1999), but eye position modulations in the spontaneous activity of neurons in several areas have also been reported (e.g., Bremmer et al., 1997a; Duhamel et al., 1997), and very little in the way of quantitative analysis has actually been done. Indeed, the claim that eye position gain fields necessarily act in a multiplicative fashion on sensory responses may have arisen within the theoretical community (e.g., Salinas and Thier, 2000) based in part on the use of the term “gain” by the experimentalists. This confusing situation can certainly be resolved with appropriate experiments and analyses.

What is the purpose of representations in an intermediate reference frame? Modeling work has shown that such representations are not necessary for coordinate transformations, which can be computed in one (linear) step, depending on the representational format of the information (Zipser and Andersen, 1988; Groh and Sparks, 1992; but see Xing and Andersen, 2000). Assuming these representations are indeed participating in coordinate transformations, several possible conclusions can be drawn: either (a) the brain is not using the most efficient or optimal algorithm for performing the computation, or (b) the brain is optimizing for some feature of the computation whose importance we have yet to appreciate. The first possibility may well be correct, but it is a conclusion that should be settled on after thoroughly exploring the second.

Why should auditory information be converted into an eye-centered reference frame? The answer is likely to be that it is critical to be able to compare visual and auditory information. Localizing sounds is more difficult than localizing visual stimuli, and evidence that the brain relies on visual signals to help interpret auditory signals comes from a variety of sources. During development, the growing size of the head requires a constant reinterpretation of the relationship between interaural timing and level differences and the angle of incidence of sounds. Shifting the correspondence between the visual and auditory scenes using prisms causes substantial changes in the auditory pathway of maturing barn owls (Knudsen and Knudsen, 1985; Knudsen and Brainard, 1991; Brainard and Knudsen, 1993a, 1995). Interpretation of spectral cues must be learned and requires the observer to know something about the original spectral content of the sound before it has been filtered by the pinnae—vision can help provide the necessary feedback for this learning to take place. Comprehension of speech sounds is influenced by viewing the lips of the speaker (the McGurk effect: McGurk and MacDonald, 1976). All these factors make it critical for us to compare what we hear with what we see.

Experimental Procedures

Two adult female rhesus monkeys served as subjects for this experiment. All procedures were approved by the Institutional Animal Care and Use Committee at Dartmouth. Animals underwent a surgery to implant a head post for restraining the head and a scleral eye coil for monitoring eye position at 500 Hz (Robinson, 1963; Judge et al., 1980). They were then trained to maintain fixation of visual stimuli while 1–4 sounds were presented from any of 15 different speakers positioned between -90° and $+90^\circ$ along the horizontal meridian (negative numbers indicate leftward locations). Typical speaker positions were: -90 , -44 , -30 , -24 , -18 , -12 , -6 , 0 , 6 , 12 , 18 , 24 , 30 , 44 , and 90 . These speaker positions were chosen because they spanned the entire front hemisphere yet allowed for fine sampling of the spatial tuning functions of the neurons over a 60° range. Typical fixation positions were -12° , 0° , and 12° ; fixation positions of -18° , 0° , and 18° were used for a few sessions. The auditory stimulus was a band-limited white noise (500 Hz to 18 kHz, 53 ± 2 dB SPL, 500–1000 ms duration). The latter 48 experiments were conducted in a single-walled sound attenuation chamber (IAC), while the early experiments were conducted in an isolated room with concrete walls. Both the sound chamber and the isolated room were lined with sound absorbent foam (Sonex) to reduce echoes. Experiments were conducted in complete darkness except where otherwise noted. On many sessions, ear position was also monitored using a calibrated coil taped to the back of the pinna on the ear contralateral to the recording site.

Once the animals were trained, a cylinder was implanted using stereotaxic techniques to aim at the right IC in one monkey and the left IC in the other. Electrodes approached the IC at an angle of 33° lateral from vertical in the coronal plane. Standard recording techniques were employed: electrical potentials were amplified and action potentials were detected using a window discriminator (Bak Electronics). The time of occurrence of action potentials was stored for off-line analysis. The number of action potentials occurring within a specified time window following stimulus onset were counted. Because individual cells showed various different combinations of phasic and sustained responses (Ryan and Miller, 1977), this time window was chosen individually for each cell based on the peristimulus time histograms for that cell, and ranged from the first 50 ms after stimulus onset for very phasic cells to the first 500 ms for tonic or inhibitory cells. Unless otherwise noted, the baseline firing rate for a corresponding period before stimulus onset was subtracted.

The locations of our recordings were confirmed by visualizing an electrode approaching the IC of each monkey via MRI at the Dartmouth Brain Imaging Center (GE 1.5T scanner, 3D T1 weighted gradient echo pulse sequence, 5" receive-only surface coil). An example is shown in Figure 7. The head post and cylinder were plastic, and the skull screws were titanium. Although the skull screws did cause distortions, as can be seen in Figure 7A, these distortions were confined to the area immediately beneath the screws and did not affect imaging of the deeper regions of the brain. Using these techniques, we were able to visualize both the electrode and the morphological features of the brain. The position of the electrode with respect to the IC was readily apparent, though finer distinctions such as the locations of the subnuclei of the IC were not distinguishable using this method.

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