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Representation of Eye Position in Primate Inferior Colliculus

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Porter, Kristin Kelly, Ryan R. Metzger, and Jennifer M. Groh. Representation of eye position in primate inferior colliculus. *J Neurophysiol* 95: 1826–1842, 2006; doi:10.1152/jn.00857.2005. We studied the representation of eye-position information in the primate inferior colliculus (IC). Monkeys fixated visual stimuli at one of eight or nine locations along the horizontal meridian between -24 and 24° while sounds were presented from loudspeakers at locations within that same range. Approximately 40% of our sample of 153 neurons showed statistically significant sensitivity to eye position during either the presentation of an auditory stimulus or in the absence of sound (Bonferroni corrected $P < 0.05$). The representation for eye position was predominantly monotonic and favored contralateral eye positions. Eye-position sensitivity was more prevalent among neurons without sound-location sensitivity: about half of neurons that were insensitive to sound location were sensitive to eye position, whereas only about one-quarter of sound-location-sensitive neurons were also sensitive to eye position. Our findings suggest that sound location and eye position are encoded using independent but overlapping rate codes at the level of the IC. The use of a common format has computational advantages for integrating these two signals. The differential distribution of eye-position sensitivity and sound-location sensitivity suggests that this process has begun by the level of the IC but is not yet complete at this stage. We discuss how these signals might fit into Groh and Sparks' vector subtraction model for coordinate transformations.

INTRODUCTION

By definition, multisensory integration involves combining signals from different sources. For visual and auditory integration, three signals must necessarily be involved: the visual and auditory signals themselves and a signal specifying the orbital location of the eyes. This eye-position signal is necessary because visual and auditory spatial information arise in different reference frames, with visual information being eye-centered and auditory spatial cues being head-centered. The relationship between these two reference frames is determined by the angle of gaze with respect to the head. Mounting evidence suggests that eye-position information is present in numerous areas of the visual, auditory, and motor pathways (e.g., Andersen and Mountcastle 1983; Andersen et al. 1987, 1990; Boussaoud and Bremmer 1999; Boussaoud et al. 1998; Bremmer 2000; Bremmer et al. 1997a; Bremmer et al. 1999; Bremmer et al. 1997b, 1998; Fu et al. 2004; Guido et al. 1988; Jay and Sparks 1984, 1987; Lal and Friedlander 1990a; Stricanne et al. 1996; Trotter and Celebrini 1999; Werner-Reiss et al. 2003; Weyand and Malpeli 1993). The earliest reported incidence of eye position in the auditory pathway is within the inferior colliculus (IC) (Groh et al. 2001; Zwiens et al. 2004). Here, we investigate the nature of the representation for eye position in the IC.

We were interested in three specific issues. First, what is the format of this representation? A representational format may be defined as the particular fashion in which information is encoded in the activity patterns of a neural population. The two widely recognized categories of representational format are place codes (also called labeled line codes), in which information is encoded by the identity of the active neurons, and rate codes, in which information is encoded in the level of activity in the active population. Neurons that comprise a rate code should respond monotonically as a function of the parameter of interest, whereas neurons that comprise a place code should respond nonmonotonically with a peak response at some preferred value of the parameter. A distribution in preferred values across the population will result in different subsets of neurons responding to different stimuli. A classic example of a place code is the representation of visual stimulus location in populations of neurons with circumscribed receptive fields in the visual pathway. An example of a rate code is the monotonic responses to increasing stimulus contrast in these same cells.

These different coding schemes have different advantages and disadvantages. In particular, place codes require large populations of neurons to represent information, because the discharge pattern of any individual neuron is ambiguous: except at the peak of the response function, the same level of activity can correspond to more than one possible value of the parameter being encoded. The ambiguity can be resolved by evaluating the pattern of activity across the population. The chief benefit of this representational format seems to be that multiple stimuli can be encoded at the same time (e.g., multiple visual stimuli can be simultaneously represented in a retinotopic place code). The main advantage of a rate code is that the discharge of individual neurons is unambiguous: the firing rate is isomorphically related to the parameter value being encoded, due to the monotonic nature of the response function. The disadvantage of this representational format is that it is not possible to encode multiple values of the parameter at the same time.

We predicted that eye-position information should be encoded in a monotonic rate code among IC neurons. In this specific context, a rate code would be sensible for two reasons. First, eye position is not a parameter that can have more than one value at a time—the eyes do not look in two places at once. Thus the single-value limitation of a rate code is not a liability for encoding eye-position information. Second, encoding eye-position information in the same format as sound-location information might provide advantages for coordinate transformations. We have previously shown that information about azimuthal sound location in the primate IC is generally rate

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coded: neurons respond monotonically as a function of sound location with increasing responses for progressively contralateral positions (Groh et al. 2003). A similar pattern appears to occur in several other mammalian species (McAlpine et al. 2001; for discussion, see Groh et al. 2003). Our vector subtraction model of coordinate transformations, which predated our experimental investigations in the IC, assumed that some of the component signals were place-coded and others were rate-coded (Groh and Sparks 1992). Place-rate and rate-place transformations were built into the model to solve this problem. These steps could be omitted if the component signals are in the same format.

The format of the eye-position information in the IC is currently unknown. Monotonic sensitivity to eye position has been reported in many brain regions including the parietal cortex (Andersen et al. 1990), frontal eye fields (Bizzi 1968), the cerebellar flocculus (Noda and Suzuki 1979), and the premotor circuitry of the oculomotor pathway (Keller 1974; Luschei and Fuchs 1972; McCrea and Baker 1980; Sylvestre and Cullen 1999), although the eye-position signals we observed in the auditory cortex are not exclusively monotonic (Werner-Reiss et al. 2003).

A second issue relevant to coordinate transformations concerns the relationship between sound-location and eye-position sensitivity in individual neurons. Do the same neurons encode both sound location and eye position? When a neuron is sensitive to both sound location and eye position, how does the pattern of sensitivity to eye position vary with sound location? The answer to this question could shed light on the neural computations being performed with these signals and how they might contribute to translating auditory signals from one reference frame to another.

Finally, we were curious to know whether the prevalence or nature of eye-position sensitivity is correlated with other, nonspatial attributes of IC neurons, such as frequency sensitivity or the temporal response profile. The answer to this question will reveal whether eye-position information is broadly incorporated into the sound-processing pathway or whether it is limited to subgroups of neurons that might prove to have a more specialized repertoire.

Here, we report that eye-position sensitivity is largely monotonic and favors contralateral eye positions; eye-position and sound-location signals are partially segregated from one another; and eye-position sensitivity is slightly more prevalent among neurons with high versus low best frequencies, but it occurs in approximately equal proportions independent of the temporal response profile of the neurons. We discuss the implications of these findings in the context of the vector subtraction model for coordinate transformations (Groh and Sparks 1992).

A preliminary version of this work has appeared (Kelly et al. 2003).

METHODS

Animals and animal care

All procedures were conducted in accordance with the principles of laboratory animal care of the National Institutes of Health (Publication No. 86–23, revised 1985) and were approved by the Institutional Animal Care and Use Committee at Dartmouth. Three adult female rhesus monkeys (*M. X*, and *C*) served in these experiments.

Surgical procedures

All surgical procedures were performed using isoflurane anesthesia and postoperative analgesia (e.g., buprenorphine). Each monkey had a head post for head stabilization and a scleral eye coil for monitoring eye position implanted (Judge et al. 1980; Robinson 1963). After the animals were trained to fixate visual stimuli, a recording cylinder was implanted over a craniotomy. The cylinder was positioned to allow electrodes to approach the IC at a 33° angle from vertical in the coronal plane (see Groh et al. 2003). Data were collected from the left IC in all three animals.

Experimental design

All experimental and behavioral training sessions were conducted in darkness in a single-walled sound-attenuation chamber (Industrial Acoustics) lined with sound-absorbing foam (3-in painted SonexOne, Sonex). We monitored eye position using the scleral eye-coil technique (500-Hz sampling rate) (Judge et al. 1980; Robinson 1963). Sensory stimuli were presented from a stimulus array 1.44 m in front of the monkey. The array contained 8–9 speakers (Audax, Model TWO25V2) with a light-emitting diode (LED) attached to each speaker's face (Fig. 1A). The speaker-LED combinations were placed from 24° left to 24° right of the monkey in 6° increments in one rig (9 locations, $n = 36$ neurons) and from 15° left (ipsilateral) to 20° right in 5° increments in the other (8 locations, $n = 117$ neurons). The responses as a function of both eye position and sound location were assessed using all eight or nine fixation and sound locations in 125 neurons. In an additional 28 neurons, sound location was held constant (at the straight ahead sound location) and only fixation position was varied (using all 8 or 9 fixation positions). The range of eye positions tested closely approximates the portion of the oculomotor range that is not normally accompanied by head movements in monkeys (i.e., $\pm 20^\circ$) (Freedman and Sparks 1997).

The luminance of each LED was ~ 26.4 cd/m². Auditory stimuli were band-pass white noise bursts (rise time: 10 ms, 500 Hz to 18 kHz, 51 dB $\pm$ 2 dB SPL, "A" weighting, Brüel and Kjær, model 2237

FIG. 1. Experimental design in space and time. A: 8 or 9 stimulus locations were used, spaced 5 (8 targets) or 6° (9 targets) apart along the horizontal meridian. B: events of the behavioral task in time. The main spike-counting windows are shown (see METHODS: data analyses for details).

integrating sound level meter and model 4137 condenser microphone).

Behavioral task

In all experiments, monkeys performed a fixation task to probe the effects of eye position on IC activity. While the animal maintained fixation on a randomly chosen LED, a sound was presented from a location that was also selected at random (Fig. 1A). The events of the task are shown in time in Fig. 1B. Each trial began with a 400-ms "spontaneous" period during which eye position and neural activity data were collected, but no stimuli were presented nor were behavioral requirements imposed. From the animal's perspective, the trial began with the onset of the fixation stimulus. The animal was required to make a saccade to the location of the fixation stimulus and maintain fixation for a variable period (600–900 ms), after which the sound was turned on (500-ms duration for most neurons; 200 ms for 7 neurons). After the sound offset, a variable period of continued fixation (300–600 ms) was required (Fig. 1B). Animals received water or juice as reinforcement for maintaining fixation throughout the trial. Trials in which the animal failed to maintain fixation were terminated and discarded from the analysis.

Multiple stimulus repetitions were performed for each combination of sound location and eye position for each recorded neuron (mean of the mean number of repetitions per condition per neuron: 17.6, range 4.9–112.4).

Frequency response functions were assessed for 109 of the 153 units as time and the quality of unit isolation permitted. Tones were presented at a fixed intensity (51 ± 2 dB SPL), usually from a speaker located at 90° contralateral, and covered a frequency range of between 400 Hz to 12 kHz (where the loudspeakers' response functions were fairly flat) in $\sim 1/3$ octave increments. The animals did not perform a behavioral task in this phase of the experiments, although eye position was monitored. Although the lack of control over eye position undoubtedly added variability to the responses, this variability did not appear to impede assessment of frequency tuning properties as all of the neurons that showed eye-position sensitivity during the presentation of tones also showed sensitivity to tone frequency (2-way

ANOVA or ANOVA, with eye position and sound frequency as the factors, with eye position binned in 15° bins).

Recording procedures and strategy

At the start of each recording session, a stainless-steel guide tube was advanced through the dura. Next, a varnish-coated tungsten electrode (FHC, ~ 2 M Ω impedance) was extended into the brain with a hydraulic micropositioner (Narishige, model N-46017). Extracellular neural signals were amplified (Bak Electronics, model MDA-4I), and action potentials from single neurons were isolated using a dual-window discriminator (Bak Electronics, model DDIS-I). The time of occurrence of each action potential was stored for off-line analysis.

Recording locations

The locations of our recording penetrations were identified using MRI at the Dartmouth Brain Imaging Center (GE 1.5-T scanner, 3-dimension T1-weighted gradient echo pulse sequence, 5-in receive-only surface coil). One or more tungsten electrodes were inserted into the brain for the scan; these were readily visible and served as reference points for the reconstruction of other recording locations (e.g., Groh et al. 2003). In *monkey X*, the recording site locations were confirmed histologically (Fig. 2) as well as by MRI. Standard histological techniques were employed: the brain was fixed with formalin and sliced in 50- μ m sections that were stained with cresyl violet. Due to the long period of time over which the recordings took place, we did not attempt to assign specific individual sites to the IC subdivisions that have been identified in other species.

Data analyses

SPIKE COUNTING WINDOWS AND CRITERION FOR INCLUSION OF NEURONS. The number of action potentials occurring within a 500-ms window following stimulus onset (termed the auditory response period) was counted (Fig. 1B). Activity was also assessed during a

FIG. 2. Histological verification of recording sites. A: transverse Nissl preparation of a 50- μ m-thick frozen section through the monkey auditory midbrain. Evidence can be seen of a track (arrowheads in white box) entering at the junction of the superior colliculus (SC) and the brachium of the inferior colliculus (BIC) on the left side, then traversing central nucleus (CN) of the IC en route toward the rostral pole (RP). B: enlarged view of the IC. Mild gliosis denotes the trajectory of the penetration. BSC, brachium of the superior colliculus; Cu, cuneiform nucleus; DL, dorsal nucleus of the lateral lemniscus; IV, trochlear nerve; LC, lateral cortex of the IC; LL, lateral lemniscus; Sa, nucleus sagulum; SCP, superior cerebellar peduncle; Vme, mesencephalic nucleus and tract of the trigeminal. Histology and figure courtesy of D. T. Larue and J. A. Winer.

500-ms window before sound onset (termed the fixation activity period; these windows were 200 ms in duration for the subset of 7 neurons that were tested with a 200-ms sound duration). Neurons were considered auditory and included in the sample if their responses during the stimulus period differed significantly from fixation activity (2-tailed paired *t*-test, $P < 0.05$). Activity was also assessed during a 400-ms period before the onset of the visual fixation stimulus (termed the spontaneous activity period). Spontaneous eye position during this period was defined as the mean of the starting and ending eye positions; trials in which the starting and ending eye positions differed by $>2^\circ$ were discarded from the analysis.

LATENCY. We calculated the auditory response latency for individual neurons by first constructing a peristimulus time histogram of the response with 3-ms bins. The center of the first bin that exceeded the mean baseline response by 3 SD was defined as the auditory response latency.

STATISTICAL ANALYSES OF EYE-POSITION SENSITIVITY. We assessed eye-position sensitivity using several statistical tests and during several periods of time during the trial. During the spontaneous period, eye position was not under experimental control and, therefore varied in a continuous fashion. We used a linear regression relating the horizontal or vertical component of eye position to the activity for

this period (Table 1, lines A, B). The total number of neurons sensitive to eye position during this (and other) time periods was determined using the Bonferroni correction according to the formula

$$p_{\text{individual}} = 1 - (1 - p_{\text{overall}})^{\frac{1}{n}} \quad (1)$$

where p_{overall} is the desired final P value of 0.05, n is the combined number of individual statistical tests, and $p_{\text{individual}}$ is the criterion P value for each individual test. Thus during the spontaneous period, two statistical tests were combined—the horizontal and vertical components of eye position—so that for a desired p_{overall} of 0.05, $p_{\text{individual}}$ was ~ 0.0253 (e.g., Table 1, line C).

During the fixation period, eye-position sensitivity was assessed using a one-way ANOVA (Table 1, line D). During the auditory response period, eye-position sensitivity was assessed with a two-way ANOVA, with eye position and sound location as the two factors (except for the subset of neurons tested with only 1 sound location, in which case, a 1-way ANOVA was used).

Eye-position sensitivity was also assessed during the auditory response period using function fitting: linear regression as well as sigmoidal and Gaussian curve fitting (Table 1, lines I–S). Sigmoids and Gaussians were chosen because they have the same number of degrees of freedom (4 each), which makes it possible to directly

TABLE 1. Statistical analysis of eye position sensitivity

	Statistical analysis	N	% of total
Spontaneous period ($N = 153$)			
A	Horizontal eye position, linear regression ^a	30	19.6%
B	Vertical eye position, linear regression ^a	29	19.0%
C	Horizontal or vertical eye position ^b	36	23.5%
Fixation period ($N = 153$)			
D	ANOVA (1 way) ^a	48	31.4%
Auditory response period, ANOVA (2 way, eye position X sound location, $N = 153$)			
E	Main effect for fixation position ^a	47	30.7%
F	Interaction term ^a	12	7.8%
G	Main or interaction ^a	55	35.9%
H	Main or interaction ^b	48	31.4%
Auditory response period, function fitting, data pooled across all tested sound locations ($N = 153$)			
I	Linear ^a	46	30.1%
J	Sigmoidal ^a	47	30.7%
K	Gaussian ^a	55	35.9%
L	Number of gaussian and not line or sigmoid	7	4.6%
M	Any curve fit ^c	47	30.7%
Auditory response period, function fits calculated separately for each sound location (Total conditions = neurons $\times$ sound locations = 1064)			
N	Linear ^a	196	18.4%
O	Sigmoidal ^a	162	15.2%
P	Gaussian ^a	223	21.0%
Auditory response period, number of neurons with at least one significant individual curve fit ($N = 153$)			
Q	Linear ^d	48	31.4%
R	Sigmoidal ^d	39	25.5%
S	Gaussian ^d	52	34.0%
Combined ($N = 153$)			
T	Spontaneous (H or V) or fixation ^c	55	35.9%
U	Spontaneous (H or V), fixation, or auditory response ANOVA (main or interaction) ^e	63	41.2%
V	Spontaneous (H or V), fixation, or auditory response pooled data linear regression ^f	63	41.2%

Results of different statistical tests for eye position sensitivity during the spontaneous, fixation, and auditory response periods. All P values < 0.05 either individually or after Bonferroni correction as noted. ^a $P < 0.05$; ^b $P < 0.0253$ individually, for a pooled P value < 0.05 ; ^c $P < 0.017$ individually, for a pooled P value < 0.05 ; ^d $P < 0.05$ if tested with 1 sound location, $P < 0.0064$ if tested with 8 sound locations, $P < 0.0057$ if tested with 9 sound locations, for a pooled P value < 0.05 ; ^e $P < 0.0102$ individually, for pooled P value < 0.05 ; ^f $P < 0.0127$ individually, for a pooled $P < 0.05$.

compare their goodness-of-fit. The fitting of sigmoids and Gaussians was performed in Matlab (Mathworks) using the "lsqnonlin" function, which conducts an iterative search to find the parameters yielding the best fit to the data (see Groh et al. 2003 for details). This function fitting was performed on the data pooled across sound location (Table 1, lines I–M), as well as separately for each individual sound location (Table 1, lines N–S).

QUANTITATIVE ANALYSES OF REFERENCE FRAME. To quantify the reference frame in which neurons code sound-location information, we compared each neuron's responses when sound locations were defined with respect to the head versus to the eyes. This comparison was conducted by comparing the dot product of the response functions aligned in a head-centered reference frame at different eye positions versus the dot product of the response functions in an eye-centered reference frame at a subset of three different eye positions (-12 , 0 , and 12 or -10 , 0 , and 10°). The equation for this calculation was

$$dp = \frac{1}{2} \left(\frac{(\vec{R}_{li} - \vec{R}) \cdot (\vec{R}_{ci} - \vec{R})}{\|\vec{R}_{li} - \vec{R}\| \|\vec{R}_{ci} - \vec{R}\|} + \frac{(\vec{R}_{ri} - \vec{R}) \cdot (\vec{R}_{ci} - \vec{R})}{\|\vec{R}_{ri} - \vec{R}\| \|\vec{R}_{ci} - \vec{R}\|} \right) \quad (2)$$

where $\vec{R}_{li}$, $\vec{R}_{ri}$ and $\vec{R}_{ci}$ are the vectors of average responses of the neuron to a sound at location i when the monkey's eyes were fixated at the left (l), right (r), or center (c). This calculation is equivalent to computing an average correlation coefficient between the response functions and will hereafter be referred to as such. The correlation coefficient was calculated once with target locations defined with respect to the eyes (the eye-centered correlation coefficient) and once with target locations defined with respect to the head (the head-centered correlation coefficient). We included only sound locations that existed for all three fixation positions in both head- and eye-centered frames of reference (i.e., sound locations: -12 , -6 , 0 , 6 , and 12° in the apparatus with targets separated by 6° or -5 , 0 , 5 , and 10° with targets separated by 5°). $\vec{R}$ is the average response across all target conditions; subtracting this value makes the distribution of responses symmetric around a value of 0 . The value of the correlation coefficient ranges from -1 to 1 , with a value of 1 indicating that the response functions as measured at the different eye positions showed perfect alignment in the reference frame used for the calculation. A value of 0 would indicate that the response functions at the different eye positions were unrelated. A value of -1 would indicate that the response functions were perfectly anti-correlated with each other.

The variance of this metric was calculated with a bootstrap analysis (100 iterations of 80% of data for each sound location/eye-position combination). This allowed us to define a 95% confidence area centered on the mean of the bootstrap distribution.

FREQUENCY SENSITIVITY. We classified the frequency responsiveness in two ways, according to best frequency and with regard to the breadth of tuning. Best frequency was defined as the frequency that produced the largest average response, provided that response was statistically significant according to a t -test, ($P < 0.05$). Best frequencies spanned the entire range of tested tone frequencies. For breadth of tuning, the neural response at each frequency was evaluated using a t -test, with P values Bonferroni-corrected according to the number of tested frequencies. Neurons were classified as either responsive only to low frequencies ($<1,000$ Hz) or responsive to both low and high ($>2,000$ Hz) frequencies. This classification scheme was approximately equivalent to a classification based on bandwidth (i.e., the difference between highest and lowest responsive frequency, expressed in octaves). Broadly responsive neurons had a bandwidth of greater than ~ 2 – 2.5 octaves. Neurons responsive only to high frequencies were too rare to constitute a separate category.

That many neurons were preferentially responsive to low frequencies or both low and high frequencies is consistent with several previous studies that have found low-frequency tails and sharp high-frequency cutoffs in the frequency tuning curves of individual neurons

throughout the mammalian auditory pathway, including the IC (mouse IC: Egorova et al. 2001; Hage and Ehret 2003; Yan et al. 2005; cat primary auditory cortex (A1): Sutter 2000; mouse auditory nerve fibers: Taberner and Liberman 2005). Although many of these studies were conducted by varying both frequency and level, the presence of low-frequency tails implies that more neurons will respond to a low-frequency sound than to a high-frequency sound when sounds are presented at a fixed suprathreshold intensity. It is also possible that the primate IC has an expanded representation of low frequency sounds; most of the characteristic frequencies reported by a prior study in the primate IC were <2 kHz (25 of 27 neurons) (Ryan and Miller 1978).

Temporal response profile

We evaluated the temporal response profile of the neurons in our sample by counting the spikes during two subepochs of the 500-ms stimulus period: 0–100 ms after sound onset, and 100–500 ms after sound onset. We used a paired t -test to determine the significance of responses during these epochs. If a given neuron had significantly more spikes 0–100 ms after sound onset than during the same period immediately before sound onset ($P < 0.05$), it was classified as having a "transient" component to its response. Similarly, neurons with a significant response during the 100–500 ms after sound onset were classified as having a "sustained" response component. These populations were then intersected to yield two mutually exclusive categories. Neurons that only met the test for having a significant response during the 0–100 ms period after sound onset and not during the 100–500 ms time period, were dubbed "transient-only" cells. Neurons that met the test for having a significant response during the 100–500 ms epoch formed the other category, regardless of whether they also met the criterion for having a significant response during the 0–100 ms response epoch. This category was called "sustained (+ transient)" neurons.

RESULTS

Overview

Our sample consisted of a total of 153 IC neurons. In their response latency, sensitivity to tonal stimuli, and temporal response profile these neurons were similar to previously published studies of primate IC neurons (Groh et al. 2001; Ryan and Miller 1977, 1978; Zwiers et al. 2004) and IC cells in other species (e.g., Behrend et al. 2004; Ferragamo et al. 1998; Langner and Schreiner 1988). The mean response latency was 13.1 ms and the median was 8.4 ms. Many neurons, though sensitive to the frequency of tonal stimuli, responded readily to broadband noise. Most neurons (140 of 153 or 91.5%) exhibited a transient on-response immediately after sound onset, and slightly fewer (110 of 153 or 71.9%) had a sustained response as well. An example of a neuron with a predominantly transient response pattern is illustrated in Fig. 3. The response latency was 11.4 ms, and it responded best to an 800-Hz tone; it also responded above the spontaneous rate for other low-frequency tones (Fig. 3C).

The position of the eyes in the orbits affected the responses of 15–41% of the neurons. The exact numbers depended on the response period and statistical test employed (Table 1). When combining the results of different tests for each neuron, the P values for the individual tests were Bonferroni-corrected to yield a final P value of 0.05 as shown in the table. The

FIG. 3. Frequency response properties of an individual IC neuron. *A*: raster plot, sorted by sound frequency. The bar above the raster plot indicates the timing of the sound. *B*: peristimulus time histogram, with sound frequency illustrated in color (bin width: 15 ms). The traces are smoothed by convolving with a filter with points [1/9 2/9 1/3 2/9 1/9] and by averaging with adjacent frequencies. *C*: average discharge rate during the 500-ms sound presentation as a function of sound frequency. Adjacent frequencies are averaged together. ---, activity during the fixation period before the sound was turned on.

horizontal or vertical component of eye position affected the spontaneous activity in 23.5% of the neurons (linear regression, Bonferroni-corrected $P < 0.05$, 36 of 153, Table 1, lines A–C). Activity during the fixation period was affected by eye position in 31% of the neurons (1-way ANOVA, $P < 0.05$, 48 of 153, Table 1, line D). The activity during the auditory response period was affected by eye position in 31% of the neurons (ANOVA, Table 1, lines E–H). Overall, 41.2% of the neurons (63 of 153) showed a significant effect of eye position (Bonferroni corrected $P < 0.05$) in at least one activity period (Table 1, lines U and V). Neurons with responses sensitive to eye position were broadly distributed throughout the IC, as previously noted by Zwiers et al. (2004). A more extensive study of the relationship between eye-position sensitivity and specific IC location is in progress (Werner-Reiss et al. 2005).

Format of the eye-position signal

Neurons with eye-position sensitivity usually had monotonic eye-position signals. Figure 4 shows two neurons that had a statistically significant influence of eye position on their auditory responses (ANOVA main effect for eye position, $P < 0.05$). In these two example neurons, sound location had minimal impact (ANOVA, main effect for sound location, $P > 0.05$), and the effect of eye position was consistent across the different sound locations. This is apparent in Fig. 4, *D* and *I* where the activity of the neurons (in color) appears as a function of eye position (*y* axis) and sound location (*x* axis). There was little change in the activity with changes in sound location, but a sizeable, monotonic change in activity with changes in eye position.

Because monotonicity is the hallmark of a rate code, it is important to evaluate monotonicity in a quantitative fashion. We have previously used a comparison between sigmoidal and Gaussian curve fits as a statistical assay for monotonicity (Groh et al. 2003). Our reasoning was that nonmonotonic sensitivity to a parameter will likely require a nonmonotonic function such as a Gaussian, whereas monotonic sensitivity can in principle be well fitted both by monotonic functions such as sigmoids as well as by functions that are only partially monotonic, such as Gaussians. Thus evidence for nonmonotonicity would consist of Gaussian fits that are substantially better than sigmoidal fits; whereas equivalent sigmoidal and Gaussian fits suggest monotonicity. The two cells illustrated in Fig. 4 each show monotonic sensitivity to eye position because both Gaussian and sigmoidal functions fit the responses about equally well (Fig. 4, *C* and *H*).

Figure 5 shows the auditory responses of six additional representative neurons as a function of sound location and fixation position. Much like the neurons in Fig. 4, these neurons were insensitive to sound location but were sensitive to eye position. These neurons all showed predominantly monotonic sensitivity to eye position, with one showing increased activity for ipsilateral fixation positions (Fig. 5*A*) and the others for contralateral fixation positions (Fig. 5, *B–F*).

Figure 6 shows an example of a neuron sensitive to both eye position and sound location. Pooling across sound locations, the sensitivity to eye position was monotonic with a preference for ipsilateral eye positions (Fig. 6*A*). This eye-position sensitivity was evident both during the auditory response and prior to sound onset as can be seen in the PSTH showing the response at three different eye positions in color (Fig. 6*B*). The mean response of the neuron (Fig. 6*C*, in color) as a function of sound location and eye position was greatest when the eyes were fixating an ipsilateral position and the sound was located in a contralateral position (i.e., the response rate is the highest in the lower right corner of this plot). Figure 6*D* shows the sigmoidal and Gaussian curve fitting of eye-position sensitivity at each sound location separately as well as when the data are pooled across eye positions. Statistically significant curve fits were obtained at several different individual sound locations as well as when the sound locations were pooled. The eye-position curves resemble, but are not identical, to one another at different sound locations. For example, at sound locations 0 and +5°, the eye-position signal is nonmonotonic and prefers ipsilateral eye positions, whereas at sound locations –15 and

FIG. 4. Response patterns for 2 neurons as a function of eye position and sound location. *A* and *E*: raster plot for trials organized as a function of eye position (left y axis). Within the delineated subregions, the trials are sorted according to sound location, although neither neuron is particularly sensitive to sound location. The bars on top of the raster plots indicate the timing of the sound. *B* and *F*: peristimulus time histogram as a function of eye position, pooled across all sound locations (bin width: 10 ms, smoothing as in Fig. 3). *C* and *H*: mean spike rates $\pm$ SE during the 500 ms after sound onset as a function of eye position, pooled across all sound locations, with sigmoidal and Gaussian fits. *D* and *I*: mean discharge rate in color as a function of sound location and eye position. The neuron on the right is the same as the neuron shown in Fig. 3.

+15° it is more monotonic but still favors ipsilateral eye positions.

Temporarily setting aside the issue of how typical it is for the eye-position signal to vary with sound location, we conducted the curve fitting for the population of neurons both ways: i.e., by pooling across sound location, and by treating sound location as an independent variable so that each neuron would be tested for eye-position sensitivity once for each sound location (Table 1, lines N–S) and once for all sound locations pooled together (Table 1, lines I–M).

The overall pattern of results is similar for data pooled across sound locations and when curves are fitted independently for each sound location. The proportion of neurons sensitive to eye position in the pooled condition (Table 1, lines I–M) is 30–36%, while significant eye-position sensitivity is slightly less prevalent when the curve fits are conducted sep-

arately for each sound location (15–21%, Table 1, lines N–P). This could reflect the fact each fit involves only a small fraction of the data (1/8 or 1/9 of the trials) when conducted separately for each sound location, thus weakening the power of the statistical test. The proportion of neurons sensitive to eye position in at least one (Bonferroni corrected) sound location is 25–34% (Table 1, lines Q–S).

For most neuron sound-location combinations, the sigmoidal goodness of fit was similar to the goodness of fit of the Gaussian curve fit. Figure 7 shows the Gaussian correlation coefficients plotted against the sigmoidal correlation coefficients. Most of the statistically significant Gaussian functions were also successfully fit by sigmoidal functions (red dots), and the two types of curves captured the response pattern about equally well: the dots cluster along the unity slope line. Gaussian-only fitting was more unusual (blue squares). This

FIG. 5. Response patterns for 6 additional neurons as a function of eye position and sound location. The grid lines indicate the sampling density for eye position and sound location, which was from 15° ipsilateral to 20° contralateral in 5° increments for these neurons.

pattern of results is overall quite similar to our previous findings concerning sound-location sensitivity in IC neurons (Groh et al. 2003) and supports the view that the predominant pattern of eye-position sensitivity is monotonic.

How does the overall pattern of eye-position sensitivity vary across the population of IC neurons? This question is important for predicting the results of future experiments using methods

such as local field potentials, evoked potentials, or fMRI, which are all sensitive to the average pattern of activity in a population of neurons occupying a particular volume of neural tissue. The population profile of the eye-position sensitivity is shown in Fig. 8. *Panel A* shows the family of statistically significant sigmoidal fits, computed separately for each sound location and normalized to the peak response. The curves show

FIG. 6. Responses of an individual neuron as a function of eye position and sound location. *A*: average response as a function of eye position pooled across all sound locations. *B*: peristimulus time histogram of activity in color as a function of eye positions for a subset of 3 of the 8 eye positions tested. *C*: activity in color as a function of eye position and sound location for the full dataset. Eye position and sound location were tested at 8 positions from 15° ipsilateral to 20° contralateral. *D*: sigmoidal and Gaussian curve fits for this neuron, conducted separately for each sound location as well as pooled. Individual fits that were statistically significant ($P < 0.05$) are highlighted in red.

FIG. 7. Correlation coefficient of Gaussian vs. sigmoidal fits for curve fitting performed separately for each sound location. The total number of attempted curve fits was 1,064. In general, Gaussian fits did not provide much of an advantage over sigmoidal fits.

a clear contralateral bias. The averages of these curves are shown in *panel B*. The contralateral bias produces a more than twofold increase in average activity for the most contralateral eye position relative to the most ipsilateral eye position. This pattern of results suggests that eye-position signals present in individual IC neurons do not cancel out at the population level and should therefore be detectable with methods that assess the combined activity of larger pools of neurons.

Relationship between eye-position sensitivity and sound-location sensitivity

Here we return to the question of how the eye-position and sound-location signals relate to each other. First, we considered whether the prevalence of eye-position sensitivity was correlated with sound-location sensitivity. To address this question, we subdivided our sample into sound-location-sensitive neurons (2-way ANOVA, main effect for sound location, $P < 0.05$, $n = 63$) and neurons insensitive to sound location ($P > 0.05$, $n = 61$) and assessed the eye-position sensitivity in these subpopulations. The prevalence of eye-position sensitivity was highest in the sound-location-insensitive neurons (Table 2, lines E–M, columns b and c). Eye-position sensitivity occurred in 22–32% of the sound-location-sensitive neurons, and in 46–56% of the sound-location-insensitive neurons. These differences were statistically significant (χ^2 , $P < 0.05$, bold). Thus there is some segregation of eye-position and sound-location sensitivity into different subpopulations of IC neurons.

Second, we investigated the similarity of the eye-position sensitivity for different sound locations by fitting Gaussian eye-position sensitivity functions to the data pooled across all but one sound location (referred to as the “pooled $n-1$ sounds”),

and then determining how well that Gaussian captured the pattern of eye-position sensitivity at the excluded sound location. We repeated this process for each sound location for each neuron (Fig. 9). The r values of eye position fits calculated from the pooled $n-1$ sound locations and evaluated at the excluded location were significantly skewed toward positive values (1-tailed t -test, $P < 0.001$), for both sound-location-sensitive and sound-location-insensitive neurons (Fig. 9B, histogram) and tended to be larger when the r value of the eye position fit to the pooled $n-1$ sound data were larger as illustrated by the regression lines, which are statistically significant ($P < 0.001$). (Cases were excluded from the analysis if the curve fit to the pooled $n-1$ sound data was not itself statistically significant.)

Reference frame

In a prior analysis of the reference frame employed by IC neurons (Groh et al. 2001), we concluded that the eye-position signal in the IC tends to disrupt the “head-centeredness” of neural response patterns but usually does not create eye-centered receptive fields that shift in space as the eyes move. The analytic method involved comparing the average difference in responsiveness across eye positions as a function of sound location defined in head- versus eye-centered reference frames. This analysis, while useful for assessing the reference frame employed by individual neurons, had several disadvantages: it provided only a relative metric of how the two reference frames compared with each other in capturing the response pattern without a more absolute measure of the efficacy of either reference frame in describing the response pattern, and we did not estimate the confidence intervals

FIG. 8. Family of significant curve fits. *A*: sigmoidal curves for cases in which at least a sigmoidal function successfully fit the eye-position sensitivity pattern. *B*: average of curves in *A* with SE bars.

around these values. In short, this analysis, although quantitative, was not statistical in nature.

To correct these deficiencies, we have adopted a new method of analyzing reference frame (Mullette-Gillman et al. 2005). For this analysis, we computed the correlation coefficient between the response patterns across three eye positions as a function of target location defined with respect to either the head or the eyes (see METHODS for details). A value of 1 indicates perfect alignment, a value of 0 indicates no correlation between the response functions, and a value of -1 reflects a perfect negative correlation between them. We also calculated 95% confidence intervals using a bootstrap algorithm to estimate the SD of the estimates of this metric for each neuron.

Figure 10*A* illustrates the results of this analysis for the 125 neurons in which both sound location and eye position were varied. As noted previously, the mode of the distribution is neither head- nor eye-centered but lies between these possibilities. Based on the confidence intervals, we could classify specific neurons as head-centered, eye-centered, or neither. For

a neuron to be classified as head-centered, for example, the head-centered correlation coefficient had to be larger than the eye-centered correlation coefficient, and the confidence interval had to exclude both zero and the line of slope 1. Neurons that did not meet this test for one or the other reference frame were classified as being neither head- nor eye-centered. About 25% of the neurons were classified as either more head- or more eye-centered: 16% ($n = 20$) were more head- than eye-centered, 8.8% ($n = 11$) were more eye- than head-centered, and 75.2% ($n = 94$) were neither. This analysis revealed a pattern consistent with our earlier analysis method in that most of the neurons did not have a head- or eye-centered response pattern.

How difficult is it to “read” this representation of sound location and eye position? Two-layer networks can solve problems that are linearly separable, whereas three-layer networks are required if the problem is not linearly separable (for review, see Anderson and Rosenfeld 1988). The monotonic nature of the eye position and sound location coding in the IC would suggest that the task of reading this representation is linearly separable. Indeed, we previously modeled the feasibility of deriving a signal of sound location in an eye-centered reference frame from the mean responses of the population of IC neurons (Groh et al. 2001) with a two-layer network. However, that simulation did not take into account response variability, which could have an impact on the success of the exercise. Also, we did not compare read-out accuracy for both head- and eye-centered signals of sound location. Accordingly, we conducted a refined version of this simulation, taking into account not only the means but also the variability in neural responses (see for example Mullette-Gillman et al. 2005). Using neurons in our sample as the input neurons in a two-layer network (Fig. 10*B*), we sought to create a signal of target location in either head- or eye-centered coordinates in the output unit. Weights were established by optimizing the performance of the network on a set of training trials created from the measured responses of the sampled neurons. Specifically, for each neuron $\times$ sound location $\times$ eye position combination, we calculated the mean and SD of the neural responses, then drew 100 trials from normal distributions with those same means and SDs and fit the weights using this training set. Finally, we tested the performance of the network by using the means of the each neuron’s actual responses

A network “trained” to produce a signal of target location defined with respect to the head (Fig. 10*C*) and a network trained to produce a signal of target location with respect to the eyes (Fig. 10*D*), both performed successfully, although the performance was slightly better for the head-centered model ($r^2 = 0.84$ for the head-centered output and $r^2 = 0.63$ the eye-centered output). Together the results support the view that IC cells have the information essential to extract sound location from the population and that the eye position modulation can be either successfully ignored to derive a signal of target location with respect to the head, or it can be incorporated to create a target location signal with respect to the eyes. The latter computation is likely more challenging, and may require more neurons or a more complex network to be calculated accurately.

TABLE 2. *The relationship between eye-position sensitivity, frequency sensitivity, and temporal response*

	Full Dataset	Spatial Sensitivity		Frequency Sensitivity				Temporal Profile					
	a	b	c	d	e	f	g	h	i	j	k	l	m
		Spatial	Nonspatial	Low best frequency	High best frequency	Low only	Broad	Sustained cells	Sustained cells	Transient cells	Transient cells	Transient only	Sustained (+transient)
Number of neurons	153	63	61	32	13	19	30	110	110	140	140	32	108
Response period, with respect to sound onset (ms)	0–500	0–500	0–500	0–500	0–500	0–500	0–500	0–500	100–500	0–500	0–100	0–100	0–500
Auditory response period, ANOVA (2 way, eye position X sound location)													
	%	%	%	%	%	%	%	%	%	%	%	%	%
E Main effect for fixation position ^a	30.7	23.8	45.9	18.8	46.2	26.3	23.3	31.8	30.0	31.4	30.7	28.1	32.4
F Interaction term ^a	7.8	7.9	11.5	0.0	15.4	0.0	3.3	4.5	7.3	7.9	9.3	12.5	3.7
G Main or interaction ^a	35.9	31.7	50.8	18.8	53.8	26.3	26.7	35.5	35.5	36.4	34.3	31.3	35.2
H Main or interaction ^b	31.4	23.8	47.5	12.5	53.8	21.1	23.3	30.9	26.4	32.1	26.4	25.0	31.5
Auditory response period, function fitting, data pooled across all tested sound locations													
I Linear ^a	30.1	22.2	45.9	12.5	38.5	21.1	23.3	30.0	27.3	29.3	22.9	28.1	29.6
J Sigmoidal ^a	30.7	22.2	49.2	15.6	38.5	26.3	20.0	31.8	27.3	30.0	23.6	21.9	31.5
K Gaussian ^a	35.9	27.0	66.7	16.6	46.2	31.6	23.3	28.2	32.7	35.7	29.3	34.4	37.0
L Number of gaussian and not line or sigmoid	4.6	3.2	6.6	0.0	7.7	5.3	0.0	5.5	5.5	5.0	5.0	9.4	5.6
M Any curve fit ^c	30.7	23.8	47.5	15.8	38.5	26.3	20.0	31.8	30.0	30.0	26.4	28.1	31.5

Results of statistical tests for eye position sensitivity on different subpopulations of IC neurons. The line labels (E–M) correspond to the lines with the same labels from Table 1; column a reports the same data as lines E–M of Table 1. All P values < 0.05 either individually or after Bonferroni correction as noted. ^a P < 0.05; ^b P < 0.0253 individually, for a pooled P value < 0.05; ^c P < 0.017 individually, for a pooled P value < 0.05. Adjacent pairs of proportions that differed significantly at the P < 0.05 level according to a χ^2 test are highlighted with boldface font (e.g., line E, columns b and c).

Eye-position sensitivity, frequency sensitivity, and temporal response profile

We next asked whether eye-position-sensitivity correlates with other aspects of IC responsiveness. IC neurons vary in their patterns of frequency sensitivity and temporal response profiles (for review, see Winer and Schreiner 2005). As noted in the METHODS, many of the neurons in our sample appeared to have low-frequency “tails” in their response functions, biasing responsiveness to low frequencies. We classified frequency sensitivity according to best frequency (the frequency eliciting the largest response) and by the breadth of tuning (responsive to low frequencies only versus responsive to both low and high frequencies). The incidence of eye-position sensitivity was higher among neurons with high best frequencies than in those with low best frequencies (Table 2, columns d and e), although this difference did not always reach statistical significance (χ^2 tests, P < 0.05). There was no difference as a function of breadth of tuning (Table 2, columns f and g, χ^2 tests, P > 0.05).

Temporal response profile was not correlated with eye-position sensitivity. Neurons were classified as having a sustained response component if their response exceeded the baseline (fixation period) firing during the 100–500 ms after sound onset. Neurons were classified as having a transient component if the response exceeded baseline in the 0–100 ms after sound onset. Individual neurons could therefore show both transient and sustained response components. We investigated the eye-position sensitivity both by neural category and within different time periods of the responses (Table 2). Neurons with sustained firing patterns showed

little difference in eye-position sensitivity in the 0–500 ms versus 100–500 ms time windows (Table 2, columns h vs. i). Similarly, eye-position sensitivity in the 0–100 ms period for neurons with transient responses was similar to that of the entire 0–500 ms response period (Table 2, columns j vs. k). These analyses demonstrate that assessment of eye-position sensitivity is not critically dependent on the time period of the response that is used or on the interaction between that time window and the temporal response profile of the neuron. In general, these findings are consistent with a previous study in primate auditory cortex using current source density analysis, which also concluded that eye-position modulation occurs over an extended time frame (Fu et al. 2004).

χ^2 testing was not done on the preceding comparisons because the involved data overlapped, i.e., the spikes included in the 100–500 ms window for a cell are a subset of those in the 0–500 ms window, and the category of transient cells overlaps with the category of sustained cells. To form mutually exclusive categories, we classified cells as “transient only,” i.e., satisfying only the criterion of a transient and not a sustained response, and “sustained (+transient),” i.e., cells showing at least a sustained response component. We used the 0–100 ms time window for assessing eye-position sensitivity in the transient-only cells, and 0–500 ms in the sustained (+transient) cells. There was little difference between the proportions of eye-position sensitivity observed in these two subcategories of IC neurons (Table 2, columns l vs. m; χ^2 , P > 0.05).

FIG. 9. Variance accounted for by Gaussian curve fit calculated from all but 1 sound location on the eye-position sensitivity pattern for the excluded sound location. A Gaussian function was fit to the responses as a function of eye position, pooling across all but 1 sound location, for each neuron-sound location combination. If that fit was itself statistically significant, then the goodness-of-fit (correlation coefficient) of that curve was calculated using the excluded sound location. The results are illustrated separately for neurons with a significant effect of sound location (ANOVA main effect for sound location or interaction term, $P < 0.05$) vs. those that were insensitive to sound location (same test, $P > 0.05$).

DISCUSSION

Comparison with previous studies concerning eye-position sensitivity in the auditory pathway

This study confirms and extends the findings of four previous studies on the influence of eye position on activity in the auditory pathway: IC (Groh et al. 2001; Zwiers et al. 2004) and auditory cortex (Fu et al. 2004; Werner-Reiss et al. 2003). Despite differences in methodology, all have found statistical evidence for an effect of eye position on responses of auditory neurons.

Clearly, the precise methods used likely affect the proportion of neurons with statistically significant eye-position sensitivity. The prevalence of eye-position sensitivity has ranged from 29% in a single-unit recording study in the IC (Zwiers et al. 2004) to 83% of electrode penetration sites using multiple-contact electrodes and current source density analysis (Fu et al. 2004) in auditory cortex. There are also differences in the statistical approaches that have been employed in past studies driven in part by differences in the sampling of eye position. In our previous IC study (Groh et al. 2001), we sampled only three eye positions, and we relied only on ANOVA for detecting eye-position sensitivity in auditory-evoked activity, which

was found in ~33% of the neurons. In the IC, Zwiers et al. (2004) sampled 13 eye positions in both the horizontal and vertical dimensions, with three stimulus repetitions per fixation position. A categorical test such as ANOVA did not reveal eye-position sensitivity, but a regression analysis found eye-position sensitivity in 29% of the neurons. The success of the linear regression was likely due to the benefit derived from the larger set of sampled eye positions, whereas the ANOVA was likely unable to detect a significant effect with so few data points per condition. In our present study, we sampled many eye positions with many repetitions per condition, and we were therefore able to use both ANOVA and linear regression to detect eye-position sensitivity. We found that both were about equally successful at identifying eye-position sensitivity. This suggests that the difference between the results of Zwiers et al. (2004) and Groh et al. (2001) are probably due to sampling differences. When the sampling is adequate for both linear regression and ANOVA, both methods will produce similar results.

Another unresolved issue from our previous study was whether eye-position sensitivity was present at all times and in all subtypes of IC neurons. In that study (Groh et al. 2001), we adjusted the response period to each neuron, whereas in the present study, we used consistent response periods for all the neurons in our sample. The results were very similar for the two methods. In the prior study, we found little eye-position sensitivity during the fixation period before sound onset, and we did not assess spontaneous activity. In the present, more extensive, investigation, there was evidence for eye-position sensitivity in both periods. Because we had more stimulus conditions in the present study, we recorded more trials for each neuron, and this would have tended to improve our chances of detecting eye-position sensitivity during the fixation and spontaneous periods.

In short, eye-position sensitivity can be detected using a variety of statistical tests and during a range of temporal epochs. We conclude that such sensitivity is present in all of the physiologically defined subtypes of IC neurons with approximately equal frequency with the most-interesting exception being sound-location-sensitive neurons. We found eye-position sensitivity less often in neurons that are sensitive to sound location. This parallels earlier reports that found no positive correlation between the degree of modulation due to eye position and sound location in individual neurons (Groh et al. 2001; Zwiers et al. 2004).

Compared with eye-position sensitivity in single core auditory cortex neurons, IC neurons with eye-position sensitivity show some quantitative differences. First, in single neurons, such sensitivity is more common in IC than in core auditory cortex (ANOVA main or interaction term, $P < 0.05$, no Bonferroni correction, IC: 36 vs. AC: 23% of neurons) (Werner-Reiss et al. 2003). Second, eye-position sensitivity is more monotonic in the IC than in auditory cortex. Most of the IC neurons in our sample that could be fitted by Gaussians could also be fitted by sigmoidal functions. In our previous study of auditory cortex, the ratio of Gaussian to sigmoidal fits was ~2:1, indicating the presence of a neural population whose eye-position sensitivity could be fitted only by Gaussian functions. Similarly, evaluations of the current-source density profile in primate auditory cortex suggested a rather even distribution of preferred eye positions with the most frequently

FIG. 10. Analysis of reference frame and simulated read-outs of population of IC neurons. *A*: correlation coefficients between the responses evoked at a leftward (-12 or -10), central (0), or rightward (10 or 12°) fixation position when plotted as a function of the head-centered location of sounds vs. the eye-centered locations of sounds. The crosses indicate 95% confidence intervals. See METHODS for details. *B*: design of network simulation. The neurons in the sample served as the inputs of a 2-layer network. *C* and *D*: performance of the network when the desired output was the head-centered or eye-centered location of the sound.

preferred eye position occurring centrally (Fu et al. 2004). Such a finding is more consistent with a nonmonotonic coding format because in a monotonic format the most frequently preferred eye position would be located more eccentrically.

Thus there is some evidence for differences in the degree and nature of eye position influences as signals progress along the auditory pathway. Previous laminar profile studies in primate auditory cortex have suggested that these eye-position signals may be fed back along the pathway (Fu et al. 2004). Our results do not shed any particular additional light on this question as the differences in proportion of neurons in the IC versus auditory cortex could be achieved either by convergence or divergence of projections from sites with either more or less eye-position sensitivity. As for differences in the shape of eye-position sensitivity at different sites along the pathway, these could be the result of signal transformations in either direction, as it is certainly feasible to transform signals from either a monotonic to a nonmonotonic format or vice versa (e.g., Groh 2001; Groh et al. 2003).

Computational significance: reference frames and gain fields

The orbital position of the eyes determines the spatial relationship between the retina and the ears. When determining whether a sound and a sight coincide in space, it is necessary to integrate three pieces of information: eye position, the location of the sound with respect to the head/ears, and the retinal locus of the object. Before signals can be combined, it

may be useful to encode them in a common format for computational purposes.

In this study, we tested the hypothesis that the format of the representation for eye position in the IC forms a rate code. A rate code for eye position has intrinsic advantages stemming from the fact that the eyes can be in only one position at a time. Use of the same format as sound location is a second potential advantage, and we and others had previously shown that information concerning sound location is predominantly monotonic (in azimuth) in the mammalian IC (Aitkin and Martin 1987; Aitkin et al. 1984, 1985; Bock and Webster 1974; Delgutte et al. 1999; Groh et al. 2003; Ingham et al. 2001; McAlpine et al. 2001; Moore et al. 1984; Palmer 2004). Our results support the eye-position rate code hypothesis: monotonic functions such as lines or sigmoids were in general as accurate as nonmonotonic functions in fitting the eye-position sensitivity. As was the case for sound-location sensitivity (e.g., Groh et al. 2003), there was a contralateral bias with increasing activity levels for progressively contralateral eye positions.

The format for the IC eye-position signal is consistent with the near-linear effect of eye position on the discharge rate of brain stem oculomotor nuclei during fixation (Fuchs and Luschei 1970; Keller 1974; Luschei and Fuchs 1972; Sylvestre and Cullen 1999). Besides these brain stem structures, a predominately monotonic (linear, or, in 2 dimensions, planar) format of eye-position signals has been observed in many visual, oculomotor and movement related (or sensorimotor) pathways (posterior parietal cortex: Andersen et al. 1990;

FIG. 11. Revised partial circuit from the "vector subtraction" model of Groh and Sparks (1992), and relation to populations of IC neurons. The original model called for 2 input signals, head-centered sound location and eye position. The head-centered sound-location information was originally conceived of as being encoded in a place code but has been re-envisioned as a rate code here. The pie chart indicates the proportions of IC neurons sensitive to sound location (red), eye position (blue), both (purple), and neither (gray; numbers equivalent or complementary to Table 2, line M and columns b and c). The neurons sensitive to both eye position and sound location but not encoding sound location with respect to the eyes (purple) are not a required signal of the model, but can be incorporated into it, as illustrated by the inset.

frontal eye field: Bizzi 1968; premotor cortex: Boussaoud et al. 1998; extrastriate motion-sensitive areas MT and MST: Bremner et al. 1997b; supplementary eye field: Schlag et al. 1992; thalamic internal medullary lamina: Schlag-Rey and Schlag 1984). However, it was not a forgone conclusion that eye-position sensitivity in the IC would be monotonic because there is evidence in some visual areas for both monotonic and nonmonotonic eye-position-sensitive subsystems, specifically in the LGN, V1, V2, and V4 (Bremner 2000; Guo and Li 1997; Lal and Friedlander 1990b; Rosenbluth and Allman 2002; Weyand and Malpeli 1993).

We only evaluated eye-position sensitivity for eye positions spanning a range of approximately $\pm 20^\circ$, which is the range of eye excursions that occurs naturally when monkeys are free to move their heads (Freedman and Sparks 1997). Given this, we cannot exclude the possibility that testing beyond this range might produce some evidence for nonmonotonicity. However, to meet the definition of a place code, the peaks of any orbital receptive fields would have to be reasonably evenly distributed across the full range of possible eye positions. The dearth of neurons with peaked orbital receptive fields in the natural oculomotor range strongly suggests that eye-position information in the IC is not place coded.

There are advantages and disadvantages inherent to monotonic rate coding. The main benefit is efficiency: individual neurons can, in theory, unambiguously encode eye position, whereas in a nonmonotonic place code the discharge pattern of

an individual neuron is inherently ambiguous—save at the precise center of the tuning function—because the same discharge level can correspond to more than one parameter value. The main cost of a monotonic representation is that it becomes ambiguous when more than one parameter value must be encoded simultaneously. As noted earlier, this is not a problem for eye position because the eyes occupy only one position at a time, making a monotonic code effective and parsimonious in representing eye position.

As noted in the preceding text, eye-position sensitivity was more prevalent among neurons insensitive to sound location. This suggests that eye-position and sound-location signals in the IC are partially segregated from one another. Perhaps the neurons with conjoint sound-location and eye-position sensitivity reflect the convergence of inputs from eye-position- and sound-location-only sources. Viewed as a whole, the reference frame of the entire population of recorded IC neurons spans a continuum from head-centered to more eye-centered with most neurons lying between.

One previous model for coordinate transformations, the "vector subtraction" model of Groh and Sparks (1992), suggested that an efficient way to compute a coordinate transformation would be to subtract a vector representing the position of the eyes in the orbits from a vector representing sound location with respect to the head. If these vectors were embodied monotonically in neural firing patterns (in Cartesian coordinates), then subtracting an appropriately weighted eye-posi-

tion signal from the sound-location signal would produce a signal representing the location of the sound with respect to the eyes.

Figure 11 revisits this model and illustrates how the observed signals in the IC might relate to the different components of the computation. The neurons that represent sound location¹ and eye position separately (colored red and blue) can be conceived of as the inputs to the circuit. Neurons sensitive to both eye and sound location (purple), but that do not encode eye-centered sound location, are not a required feature of this model, but they can certainly be incorporated into it as an intermediate stage of processing (*inset*).

Thus it is possible to fit much of our data into this model with minimal modification. However, some caveats do apply. In particular, it is difficult to see what advantage is conferred by encoding information in a fashion that is ambiguous with respect to reference frame, especially when it would appear to be a simple matter to perform a full and accurate coordinate transformation based on the available eye and sound-location signals. And yet, the very simplicity of the computation suggests that there is probably no great cost associated with this ambiguity in reference frame as it should be possible to complete the coordinate transformation readily even from these ambiguous response patterns. Indeed, our simulation involving a simple two-layer network suggested that it is possible to extract eye-centered sound-location information from the activity patterns of the IC neurons that we recorded, a point that others have made as well (e.g., Pouget and Sejnowski 1997).

In other brain areas, the combined influences of the sensory stimulus (usually visual) and eye position have been conceived of as forming a “gain” field (for review, see Salinas and Thier 2000). In the broadest formulation of this idea, there is thought to be a signal derived from the external sensory stimulus and a signal derived from eye position, and these two signals are then combined in some fashion (additive, multiplicative, both, or perhaps neither) to produce the neuron’s activity pattern. This simple model makes some predictions that are not fully born out by our results in the IC. Chiefly, it predicts that if one holds one parameter constant and varies the other, the general shape of the response function should not change. In short, the eye-position signal sampled at one sound location should resemble the eye-position signal sampled at other sound locations. To some extent, this was true in our study: the curve fits to the eye-position signal for a pool of $n-1$ sound locations, did capture some of the variance of the eye-position signal evaluated at the excluded sound location (e.g., Fig. 9). However, there was also evidence that the eye-position signal varies with sound location in some neurons, producing a more complex pattern of interaction (e.g., Figs. 6 and 9).

If the component signals are both monotonic and if the weighting between them is appropriate, then the “gain” field can be equivalent to a coordinate transformation. In particular,

if the eye-position input of a neuron is monotonic and prefers contralateral eye positions, and the head-centered sound location input has a similar shape and dynamic range, then subtracting the eye-position signal from the sound-location signal will cause that neuron to respond monotonically as a function of the eye-centered location of the sound. Thus when perfectly calibrated, a suitable eye-position gain field can produce an eye-centered signal of sound location.

Currently, it does not appear that any calculation producing a prominent signal of sound location with respect to the eyes is completed within the auditory pathway proper, but this computation could be accomplished as signals are “read out” from the IC by areas outside the classical auditory pathway, such as the superior colliculus (SC). The SC does not have a purely eye-centered frame of reference for sound location either, but it does have receptive fields that shift systematically when the eyes move (Hartline et al. 1995; Jay and Sparks 1984, 1987; Peck et al. 1995; Populin et al. 2004; Zella et al. 2001). This pattern is closer to being an eye-centered representation than the pattern found in the IC.

Clearly, many issues concerning eye-position information and coordinate transformations remain to be worked out. The simple models discussed here are undoubtedly gross oversimplifications of the computations performed by the brain to create joint visual and auditory representations and produce behavioral responses to such stimuli. A more complete view of this process will require incorporating not only eye-position information but also head position information, given that gaze shifts normally involve coordinated movements of the eye and head together. Furthermore, thus far our experiments concerning eye-position and sound-location sensitivity have reduced this complex issue to a single dimensions. Extending these findings into two dimension and ultimately additional dimensions (e.g., torsional rotation) will be necessary to achieve a thorough understanding of how the brain combines information from different sources to produce a percept of where sights and sounds are located in space.

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¹ For the purposes of this figure, we somewhat arbitrarily chose to use the statistical tests in Table 2 rather than the reference frame analyses of Fig. 10 to provide a count of neurons that might encode the head-centered location of the sound because the former analysis provides a separate count of neurons that are sensitive only to eye position. The “sound-location-only”-sensitive neurons likely include both neurons that are predominantly head-centered in the reference frame analysis and neurons that are actually sensitive to both sound location and eye position but for which the eye-position sensitivity does not reach statistical significance.

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