Impaired Spatial Hearing in Amblyopia: Evidence for Calibration of Auditory Maps by Retinocollicular Input in Humans

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PURPOSE. Evidence from animals and blind humans suggests that early visual experience influences the developmental calibration of auditory localization. Hypothesizing that unilateral amblyopia may involve cross-modal deficits in spatial hearing, we measured the precision and accuracy of sound localization in humans with amblyopia.

METHODS. All participants passed a standard hearing test. Experiment 1 measured sound localization precision for click stimuli in 10 adults with amblyopia and 10 controls using a minimum audible angle (MAA) task. Experiment 2 measured sound localization error (i.e., accuracy) for click train stimuli in 14 adults with amblyopia and 16 controls using an absolute sound localization task.

RESULTS. In Experiment 1, the MAA (mean $\pm$ SEM) was significantly greater in the amblyopia group compared with controls ($2.75 \pm 0.30°$ vs. $1.69 \pm 0.09°$, $P = 0.006$). In Experiment 2, the overall sound localization error was significantly greater in the amblyopia group compared with controls ($P = 0.047$). The amblyopia group also showed significantly greater sound localization error in the auditory hemispace ipsilateral to the amblyopic eye ($P = 0.036$). At a location within this auditory hemispace, the magnitude of sound localization error correlated significantly with deficits in stereo acuity ($P = 0.036$).

CONCLUSIONS. The precision and accuracy of sound localization are impaired in unilateral amblyopia. The asymmetric pattern of sound localization error suggests that amblyopic vision may interfere with the development of spatial hearing via the retinocollicular pathway.

Keywords: amblyopia, auditory localization, cross-sensory calibration

Amblyopia, commonly known as 'lazy eye', is a developmental visual impairment arising from abnormal visual experience during a sensitive period of brain development in early childhood. It typically presents as a unilateral reduction in visual acuity in a structurally healthy eye, and can be attributed to one or more amblyogenic factors—most commonly strabismus (eye misalignment) or anisometropia (unequal refractive error), and more rarely form deprivation—that interfere with normal binocular vision.[1,2] Failure to detect and treat amblyopia in childhood means that its effects are often lifelong. Indeed, amblyopia persists in 3% of adults,[3–5] and remains the single most common cause of unilateral low vision ($\leq20/200$) in adulthood.[6]

In addition to the well-known deficits in spatial vision,[7] amblyopia is also associated with impaired temporal visual processing,[8–10] eye movement control,[11–13] eye–hand coordination,[14–19] reduced reading speed,[20] and abnormal audiovisual multisensory processing.[21–24] Surprisingly, a recent investigation by our laboratory suggested that people with amblyopia may also have greater difficulty localizing sounds, even in complete darkness.[25]

As with spatial acuity in the human visual system, spatial acuity in the auditory system follows a developmental trajectory through childhood. Binaural localization is immature at birth, but improves dramatically during the first several years of life.[26] In developmentally typical infants, the smallest reliably perceptible separation between sound sources, or minimum audible angle (MAA), improves from approximately 20° at 5 months of age,[27] to 4° at 18 months of age, finally reaching adult acuity of 1° to 2° by approximately 5 years of age.[28,29]

Although the concept of impaired sound localization in amblyopia is new, the existence of a cross-modal relation between early visual experience and the developmental calibration of sound localization is well-established in the literature (see King[30] for review). In many instances, early-onset bilateral blindness is accompanied by enhanced sensitivity to auditory spatial cues.[31–35] Sound localization abilities are not always heightened in early-onset blindness, however. Early-blind humans have difficulty perceiving the geometric relationships between sounds.[36] Furthermore, the early-blind who possess residual peripheral vision localize sounds with poorer precision than those who are normally sighted or totally blind.[32] Taken together, these findings suggest a complex interaction between the quality of early vision and the development of auditory spatial abilities.

Animal studies suggest that multisensory interactions in the midbrain may mediate the developmental calibration of sound localization by vision.[37–40] Barn owls reared with prism spectacles mislocalize sounds in the direction of the visual field shift, and show corresponding shifts in the auditory space map of the optic tectum (the avian homolog of the mammalian superior colliculus).[41] After a certain age, restoration of normal visual cues no longer rescues normal spatial hearing in prism-reared owls, indicating that the visually induced sound mislocalization represents permanent alterations crystallized during a sensitive period of brain plasticity.[42] Similar topographic shifts are observed in the auditory map of the superior colliculus in ferrets reared with experimentally induced strabismus,[37] and abnormal spatial tuning in the auditory map is observed in ferrets and guinea pigs deprived of normal visual input during a sensitive period in early life.[38,40]

The superior colliculus has a lamellar and spatiotopic organization. The superficial layers receive direct retinal input[43,44] and show retinotopy similar to that of the striate cortex.[45,46] In contrast to the balanced binocular retinal input to the striate cortex, each superior colliculus receives retinal input primarily from the contralateral eye.[44,45] The superficial map of visual space is topographically aligned with an underlying map of auditory space,[47] permitting auditory and visual stimuli to co-activate neurons at the same site, and enabling multisensory integration of those signals in the deeper layers of the superior colliculus.[48] In primates, this multisensory convergence in the superior colliculus is essential for shifting gaze and attention to salient environmental stimuli,[49,50] and may provide a neural basis for cross-sensory calibration of sound localization by vision.[36]

The present study explores sound localization in adults with unilateral strabismic and anisometropic amblyopia using the following two paradigms: (1) a relative sound localization task to measure the precision of binaural sound localization (i.e., the MAA), and (2) an absolute sound localization task to measure the accuracy of binaural sound localization in the frontal field. We show that unilateral amblyopia involves previously unappreciated deficits in sound localization precision (i.e., increased MAA), and sound localization accuracy (i.e., increased localization error), and propose that the pattern of deficits is consistent with a role for the retinocollicular pathway in cross-sensory calibration of sound localization by vision.

METHODS

We measured the precision and accuracy of sound localization using a relative localization task (Experiment 1) and an absolute localization task (Experiment 2) in humans with unilateral strabismic or anisometropic amblyopia. All protocols were approved by the Research Ethics Board at The Hospital for Sick Children, and adhered to the tenets of the Declaration of Helsinki.

Experiment 1: Relative Sound Localization Task

Participants. We recruited adults with unilateral amblyopia and normally sighted controls. Participants were excluded if they had any history of neurologic, neurodevelopmental, auditory, or visual disorders other than amblyopia, strabismus, and/or refractive error. Every participant underwent a visual and auditory screening assessment by a certified orthoptist or ophthalmologist. The visual assessment measured refractive correction (automatic lensmeter), eye dominance (Dolman method),[51] distance visual acuity (standard Early Treatment Diabetic Retinopathy Study chart with correction), stereo

acuity (Randot circles test and Titmus fly test), foveal suppression (Worth 4-dot test), ocular motility, and alignment (prism cover test). Amblyopia was defined as an acuity of 0.18 logMAR (20/30) or poorer in the affected eye, and an interocular difference of 0.2 logMAR (2 lines) or more. The auditory assessment ensured reliable detection of low-level pure tones (25 dBA sound pressure level [SPL]) in each ear at 500, 1000, 2000, and 4000 Hz.[52] Amblyopia was classified as anisometropic if the interocular difference in spherical equivalent or cylindrical error was ≥ 1 diopter (D), as strabismic if there was any manifest deviation in the absence of anisometropia, and as mixed if there was a strabismus of ≥ 8 prism diopters (PD) in the presence of anisometropia ≥ 1 D. Normally sighted was defined as visual acuity of at least 0.1 logMAR (20/25) in each eye, stereo acuity of at least 40 second of arc, and no manifest deviation on cover testing.

Ten adults with amblyopia (7 females, mean age [range]: 32 [22–46] years) and 10 normally sighted adults (7 females, mean age [range]: 29 [22–47] years) participated in Experiment 1. The age distribution did not differ significantly between the two groups (2-sample Kolmogorov-Smirnov test, $P = 0.988$). The sample size provided 80% power to detect an effect size of $d = 1.3$ for a two-tailed independent samples t-test at $\alpha = 0.05$.

Demographic and clinical details for participants with amblyopia in Experiment 1 are summarized in Table 1.

Stimuli and Design. All trials were conducted in a darkened, sound attenuating chamber (internal dimensions $2.0 \times 2.1 \times 2.2$ m) lined with 5-cm acoustic wedge foam (Foam Factory, Macomb, MI, USA). The background noise level was 39.0 dBA SPL. Participants were seated with the head stabilized in a chinrest 1 m from a horizontal array of 11 speakers (model CMS0361KLX; CUI Inc., Tualatin, OR, USA) as illustrated in Figure 1. Auditory stimuli consisted of broadband white noise bursts of 32-ms duration, including a 2-ms sigmoid on/off ramp, delivered at 76.5 dBA SPL (output level was verified as between 76.3 and 76.6 dBA SPL for each speaker). A red light-emitting diode (LED) positioned over the central speaker was illuminated between trials to aid maintenance of head alignment with the speaker array. Participants used a wireless gamepad (model F710; Logitech, Newark, CA, USA) to initiate trials and enter responses.

Each trial began with offset of the central fixation LED, followed by a randomized delay of 250 to 400 ms. Two clicks (a reference click and a probe click) were then presented in succession 500 ms apart, and the participant was asked to "indicate whether the second click occurred left or right relative to the first click." The reference click was always presented centrally (0°) and the probe click was presented to the left or right of center (auditory angle $\theta = -15°$, $-12°$, $-9°$, $-6°$, $-3°$, $3°$, $6°$, $9°$, $12°$, or $15°$), but the order of the two clicks was random. Twenty trials were conducted for each of the 10 auditory angles tested. Data were collected in two blocks of 100 trials, with trial order randomized within each block. Participants were given 10 practice trials before data collection began, and instructed to verbally inform the examiner in the event of a response error so that it could be corrected.

Data Analysis. Psychometric analysis was performed individually for each participant using custom-written scripts in MATLAB version R2011b (Mathworks, Inc., Natick, MA, USA). The proportion of trials the probe click was "heard left" of the reference click was plotted as a function of the auditory angle θ. A logistic sigmoid function was fit to the psychometric data by the maximum likelihood method (see Supplemental Material for individual data and fitted functions). Fits were unconstrained in position and width, and included a lapse rate parameter, λ (constrained to $0 \leq \lambda \leq 0.06$), as recommended to minimize potential bias from stimulus-independent errors (e.g., response errors).[53,54] The MAA was computed as one-half

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TABLE 1. Clinical Details of Participants With Amblyopia in Experiment 1

ID	Age, y (Sex)	Subtype	Visual Acuity, logMAR		Refractive Correction, D		Alignment at 6 m, PD	Stereo Acuity, arc seconds	Worth 4-Dot Response	Additional Details
			RE	LE	RE	LE				
P1	27 (F)	Strab	0.00	0.48	−6.25 +1.00 × 45	−5.50 +1.25 × 35	LE esotropia 2, LE hypotropia 1	200	Fused	Strab surgery age 9 y
P2	22 (F)	Aniso	0.00	0.48	−1.50 +0.50 × 80	+1.00 +1.25 × 95	LE esotropia 2	200	Fused	
P3	22 (M)	Aniso	1.1	−0.10	−6.00 +0.75 ×174	−4.50 +0.50 ×75	RE esotropia 2	3000	Fused	
P4	23 (F)	Strab	0.20	0.00	+0.50 +0.50 × 28	+1.25 +0.50 × 88	RE esotropia 8, bilateral DVD	Negative	Diplopic	Infantile esotropia, 2 strab surgeries as child
P5	44 (F)	Mixed	0.90	0.00	+6.00 +1.25 × 75	−0.75	RE exotropia 35	Negative	RE suppressed	
P6	37 (F)	Aniso	0.18	−0.10	−3.25 +4.00 × 10	−5.25	RE esotropia 1	70	Fused	
P7	44 (M)	Aniso	−0.10	1.20	−0.25 +2.00 × 98	−2.75 +2.00 ×69	LE esotropia flick	3000	Fused	
P8	46 (F)	Strab	−0.10	0.10	+4.25	+5.00	LE esotropia 25, LE hypotropia 18	Negative	LE suppressed	Esotropia onset age 6–8 mo
P9	28 (M)	Aniso	0.18	−0.10	+2.25	+0.25	Exophoria 2	70	Fused	
P10	26 (F)	Aniso	−0.10	0.18	+0.75	+3.00	LE esotropia 1	140	Fused	

RE, right eye; LE, left eye; F, femal; Aniso, anisometropia; M, male; Strab, strabismus; DVD, dissociated vertical deviation.
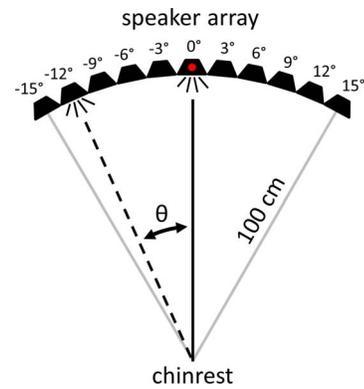
FIGURE 1. Apparatus for Experiment 1, a horizontal array of 11 speakers with a central fixation LED. In each trial, one click was presented at the central reference position and the other was presented a specified angle (θ) to left or right of center.

the difference in θ between the values of 0.25 and 0.75 on the y axis of the psychometric function.[28] A parametric bootstrap with 200 iterations was used to compute the standard error (i.e., reliability) of the estimate of the MAA for each participant.[55]

All statistical tests were computed using IBM SPSS Statistics, version 22 (Armonk, NY, USA). The mean MAA values for the amblyopia and control groups were compared by Welch's t-test. Normality was established by the Shapiro-Wilk test. Associations between the MAA and clinical characteristics in the amblyopia group were assessed using Spearman's rank correlation. Bonferroni correction for multiple comparisons applied where indicated in the text.

Experiment 2: Absolute Sound Localization Task

Participants. Fourteen adults with amblyopia (12 females, mean age [range]: 30 [19–48] years) and 14 normally sighted adults (9 females, mean age [range]: 30 [23–47] years) participated in Experiment 2. Participant screening and classification were the same as for Experiment 1. Five of the participants with amblyopia and four normally sighted controls had also participated in Experiment 1. The age distribution did not differ significantly between the two groups (2-sample Kolmogorov-Smirnov test, $P = 0.558$). Demographic and clinical details for participants with amblyopia in Experiment 2 are summarized in Table 2.

Stimuli and Design. All trials were conducted in an acoustic chamber as described in Experiment 1. Participants were seated with the head stabilized in a chinrest before a large (165-cm diagonal) LED monitor (model E654; NEC, Tokyo, Japan) flanked by stereo speakers (model BR387AA#ABA; HP Inc., Palo Alto, CA, USA) at ear level, illustrated in Figure 2. Auditory stimuli consisted of 32-ms click trains (8 cycles of 4-ms white noise clicks at 62.0 dBA SPL, enveloped with a 2-ms sigmoid on/off ramp), repeating at 3 Hz. The white noise was 2- to 5-kHz bandpass filtered to limit the auditory stimulus to frequencies at which interaural level difference cues predominate for binaural localization.[28] This stereophonic arrangement allowed the generation of phantom (i.e., virtual) sound sources whose location was perceived on the horizontal axis between the two physical speakers according to the principles of amplitude panning and summation localization.[56,57] A small red fixation dot (0.66°) was presented centrally between trials to aid maintenance of head alignment with the stereo speakers. Participants used a wireless mouse with their preferred hand to initiate trials and enter responses.

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TABLE 2. Clinical Details of Participants With Amblyopia in Experiment 2

ID	Age, y (sex)	Subtype	Visual Acuity, logMAR		Refractive Correction, D		Alignment at 6 m, PD	Stereo Acuity, arc sec	Worth 4-Dot Response	Additional Details
			RE	LE	RE	LE				
P1*	27 (F)	Strab	0.00	0.48	−6.25 +1.00 × 45	−5.50 +1.25 × 135	LE esotropia 2, LE hypotropia 1	200	Fused	Strab surgery, age 9 y
P2*	22 (F)	Aniso	0.00	0.48	−1.50 +0.50 × 80	+1.00 +1.25 × 95	LE esotropia 2	200	Fused	
P3*	22 (M)	Aniso	1.10	−0.10	−6.00 +0.75 × 174	−4.50 +0.50 × 75	RE esotropia 2	3000	Fused	
P4*	23 (F)	Strab	0.20	0.00	+0.50 +0.50 × 28	+1.25 +0.50 × 88	LE esotropia 8, bilateral DVD	Negative	Diplopic	Infantile esotropia, 2 strab surgeries as child
P5*	44 (F)	Mixed	0.90	0.00	+6.00 +1.25 × 75	−0.75	RE exotropia 35	Negative	RE suppressed	
P11	32 (F)	Aniso	−0.10	0.54	Plano	+2.00 +2.00 × 124	Orthotropic	140	Fused	
P12	29 (F)	Mixed	0.00	1.00	Plano	+3.50 +2.00 × 90	LE exotropia 14, LE hypertroia 4	Negative	LE suppressed	Strab surgery, age 4 y
P13	23 (F)	Aniso	−0.10	0.48	−2.25	+0.25 +2.25 × 85	LE esotropia 1	200	Fused	
P14	29 (M)	Aniso	0.10	0.70	−1.50 +1.50 × 100	−3.00 +1.50 × 93	Orthotropic, bilateral DVD	Negative	LE suppressed	
P15	19 (F)	Mixed	0.48	0.00	+3.00 +1.00 × 130	+4.25	RE esotropia 4, RE esophoria 10	3000	Fused	Accom. esotropia, strab surgery as child
P16	29 (F)	Aniso	0.48	−0.10	−5.00	−1.25	RE esotropia 2	3000	Fused	
P17	29 (F)	Strab	0.00	1.00	None	None	LE esotropia 2, bilateral DVD	Negative	LE suppressed	Infantile esotropia
P18	37 (F)	Mixed	−0.10	1.30	−1.00	+6.00 +2.50 × 120	LE exotropia 25	Negative	LE suppressed	Strab, surgery age 23 y
P19	48 (F)	Aniso	0.70	0.00	+2.25 +0.25 × 174	−0.75	RE esotropia 2	3000	Fused	

Accom., accommodative.
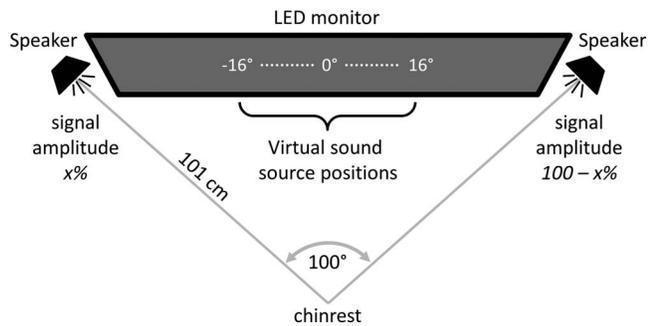* Also participated in Experiment 1.

FIGURE 2. Apparatus for Experiment 2, stereo speakers with LED monitor. Phantom sources were generated at locations on the azimuth (auditory angle θ) between the two physical speakers by amplitude panning. The speakers were driven by coherent signals of independently variable amplitude, such that the signal amplitude gain to the right and left speakers always summed to 1.

Each trial began with the offset of the central fixation dot. After a randomized delay of 250 to 400 ms, a click train was presented at one of nine locations on the azimuth ($-16°$, $-12°$, $-8°$, $-4°$, $0°$, $4°$, $8°$, $12°$, or $16°$), all within the area of a typical binocular field. Two seconds after onset of the click train, a visual cursor (vertical white line) appeared on the monitor. Participants aligned the cursor with the perceived direction of the sound and clicked a mouse button to enter their localization response. The click train continued at 3 Hz until a response was entered. To mitigate the potential effect of visual capture by the visual cursor, participants were asked to make their judgment during the 2 seconds of darkness before the cursor appeared. Additionally, the initial horizontal location of the visual cursor was jittered randomly between $-40°$ and $40°$ on every trial. Participants were instructed to hold their head still in the chinrest during trials, but eye movements were unconstrained. Five trials were conducted for each of the nine sound source locations. Data were collected in one block of 45 trials, with trial order randomized within each block. Participants were given 10 practice trials before data collection began, and instructed to verbally inform the examiner in the event of a response error so that it could be corrected.

Data Analysis. By convention, location data were signed relative to the side of each participant's amblyopic or nondominant eye. Positive values indicate locations in the auditory hemispace ipsilateral to the amblyopic eye (or the nondominant eye for normally sighted controls), and negative values indicate locations in the contralateral auditory hemispace. For participants with amblyopia, these auditory hemispaces were termed the amblyopic eye hemispace and the fellow eye hemispace, respectively. For normally sighted control participants, these auditory hemispaces were termed the nondominant eye hemispace and the dominant eye hemispace, respectively.

Overall localization bias toward or away from the amblyopic eye (or nondominant eye for controls) was computed for each participant as the intercept of the linear regression of sound source position (i.e., specified sound position) on sound localization (i.e., perceived sound position). The mean localization bias within each group was compared with the expected values of $0°$ using a one-sample t-test.

The magnitude of sound localization error at each sound source position was computed for each participant as the absolute value of the mean error. The mean error was computed as the difference between the perceived sound position and the specified sound position, averaged across all five trials. Absolute mean error was compared between groups using a 2 (group) × 9 (position) mixed-design ANOVA with
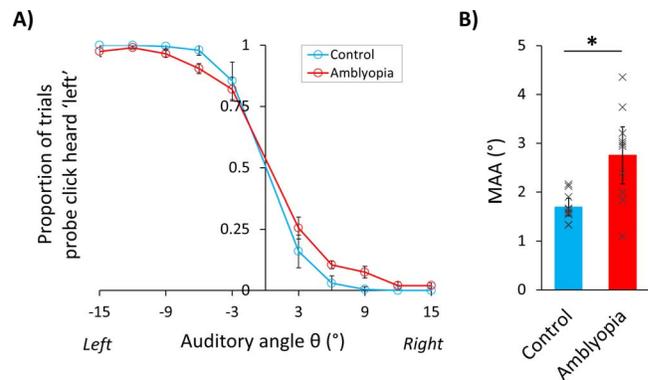
group as the between-subjects factor, and position as the within-subjects factor. Within each group, absolute mean error was compared between auditory hemispaces across sound source eccentricities using a 2 (hemispace) × 4 (eccentricity) repeated-measures ANOVA. For mixed-design ANOVAs, the assumption of equality of covariance matrices was satisfied according to Box's M test. For mixed-design and repeated-measures ANOVAs, the assumption of sphericity was assessed using Mauchly's test, and where violated, the conservative Greenhouse-Geisser correction was applied. Associations between sound localization error and clinical characteristics in the amblyopia group were assessed using Spearman's rank correlation.

FIGURE 3. Relative sound localization performance on a horizontal speaker array. *Error bars* indicate ± 1 SEM. **(A)** Mean psychometric data for the minimum audible angle task. Negative and positive auditory angles represent sounds presented to the left and right of the central click, respectively. **(B)** The mean minimum audible angle (MAA). The *symbols* ($\times$) represent individual MAA values. The mean MAA was significantly larger in the amblyopia group compared with the control group ($*P = 0.006$).

RESULTS

Experiment 1: Relative Sound Localization Task

Performance on the relative sound localization task is illustrated in Figure 3A. The MAA, illustrated in Figure 3B, was significantly larger in the amblyopia group (mean $\pm$ SEM: $2.75 \pm 0.30°$) compared with the control group (mean $\pm$ SEM: $1.69 \pm 0.09°$), indicating poorer sound localization precision in the amblyopia group ($t_{(10.623)} = -3.389$, $P = 0.006$, $d = 1.52$). Within the amblyopia group, the MAA showed no significant correlation with visual acuity in the amblyopic eye ($R_s = 0.295$, $P = 0.407$) or with stereo acuity ($R_s = 0.285$, $P = 0.425$). The bootstrapped standard error of the estimate of the MAA ranged from $0.41°$ to $0.80°$ (mean $0.62°$) for control group participants and from $0.31°$ to $0.92°$ (mean $0.62°$) for amblyopia group participants.

Experiment 2: Absolute Sound Localization Task

Performance on the absolute sound localization task is illustrated in Figure 4A. The relation between the perceived and specified sound source positions was linear for all participants in the control group (mean $R^2 = 0.98$) and the amblyopia group (mean $R^2 = 0.96$). The mean linear regression intercept did not differ significantly from the expected value of $0°$ for the control group (mean $\pm$ SEM: $0.09 \pm 0.66°$, $t_{(13)} = 1.37$, $P = 0.893$, $d = 0.04$) or the amblyopia group (mean $\pm$ SEM: $0.67 \pm 1.08°$, $t_{(13)} = 0.627$, $P = 0.542$, $d = 0.17$),
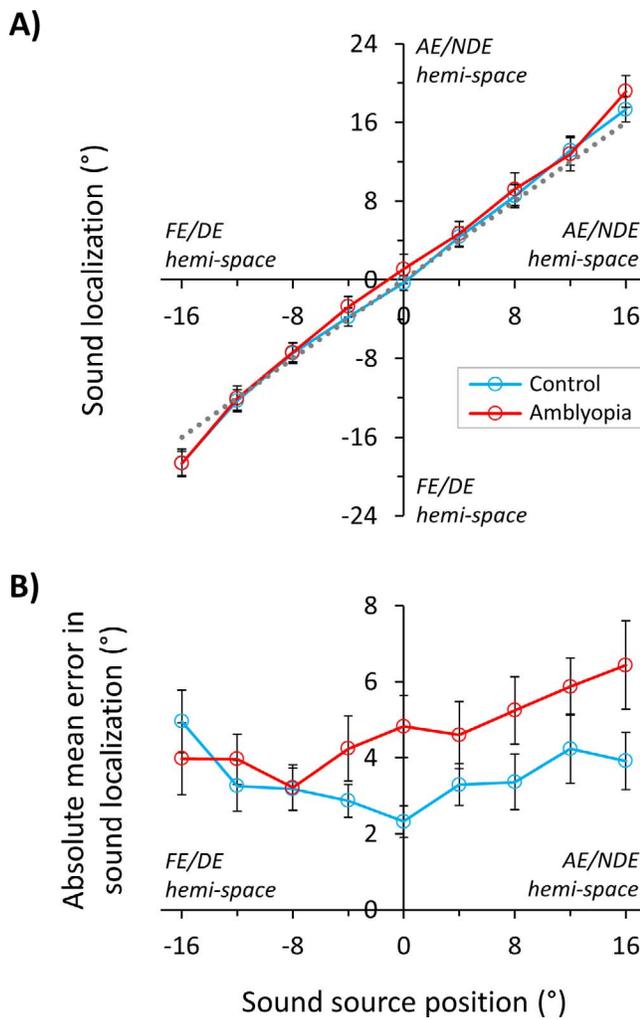
A)

B)

FIGURE 4. Absolute sound localization performance. Positive coordinates indicate positions in the auditory hemispace ipsilateral to the amblyopic eye (or the nondominant eye in controls). *Open circles* represent mean responses for the control group (*blue*) and the amblyopia group (*red*). *Error bars* represent ± 1 SEM. AE, amblyopic eye; NDE, nondominant eye; FE, fellow eye; DE, dominant eye. (**A**) Mean perceived sound location for each sound source position. The *dashed line* represents the expected performance as predicted by linear amplitude panning. There was no significant systematic spatial bias in either group. (**B**) Absolute mean error in sound localization for each sound source position. The magnitude of sound localization error was significantly greater in the amblyopia group compared with controls ($P = 0.047$).
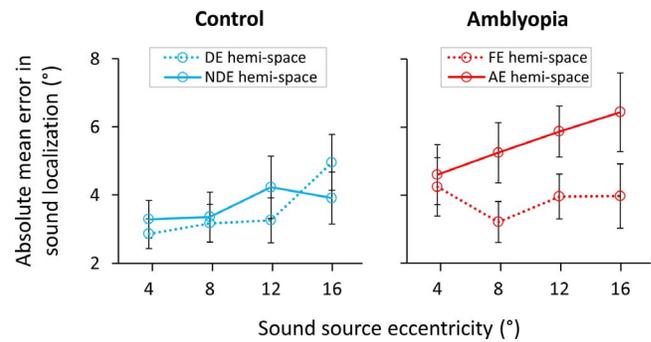

FIGURE 5. Comparison of sound localization error between the two auditory hemispaces. *Open circles* represent the mean responses. *Error bars* represent ± 1 SEM. In the control group (*blue*), there was no significant difference in absolute mean error in sound localization between the DE hemispace and the NDE hemispace. In the amblyopia group (*red*), the absolute mean error was significantly greater in the AE hemispace compared with the FE hemispace ($P = 0.036$). Correlations between the magnitude of clinical deficits in amblyopia and absolute mean error at each sound source position are illustrated in Figure 6 (see Supplementary Fig. S3 for correlation plots). The clinical deficit in stereo acuity and the magnitude of sound localization error were significantly correlated within the amblyopic eye hemispace at the 8° sound source position ($R_s = 0.67$, $P = 0.036$, Bonferroni correction for multiple comparisons). There were no significant clinical correlations with amblyopic eye acuity.

indicating that there was no systematic horizontal spatial bias in sound localization in either group.

The absolute mean error in sound localization is illustrated for each group at sound source position in Figure 4B. A 2 (group) × 9 (position) mixed-design ANOVA yielded a significant main effect of group ($F_{(1,26)} = 4.343$, $P = 0.047$, $\eta^2 = 0.143$), no significant effect of sound source position ($F_{(4.587,119.250)} = 2.070$, $P = 0.80$, $\eta^2 = 0.074$), and no significant interaction between group and sound source position ($F_{(4.587,119.250)} = 1.397$, $P = 0.234$, $\eta^2 = 0.051$). This indicates that mean magnitude of sound localization error was greater in the amblyopia group (i.e., impaired accuracy) compared with the control group.

A comparison of absolute error in sound localization between the two auditory hemispaces across sound source

eccentricities is illustrated for each group in Figure 5. For the control group, a 2 (hemispace) × 4 (eccentricity) repeated-measures ANOVA showed no main effect of auditory hemispace ($F_{(1,13)} = 0.075$, $P = 0.864$, $\eta^2 = 0.002$), a significant main effect of sound source eccentricity ($F_{(2.098,27.272)} = 3.710$, $P = 0.029$, $\eta^2 = 0.234$), and no significant interaction of auditory hemispace and sound source eccentricity ($F_{(1.923,25.005)} = 1.447$, $P = 0.254$, $\eta^2 = 0.100$). For the amblyopia group, the same analysis showed a significant main effect of auditory hemispace ($F_{(1,13)} = 5.443$, $P = 0.036$, $\eta^2 = 0.295$), no significant main effect of sound source eccentricity ($F_{(3,39)} = 0.724$, $P = 0.544$, $\eta^2 = 0.053$), and no significant interaction of auditory hemispace and sound source eccentricity ($F_{(3,39)} = 0.804$, $P = 0.499$, $\eta^2 = 0.058$). This indicates that in the amblyopia group, but not in the control group, there was a significant horizontal spatial asymmetry in the magnitude of sound localization error, with greater error in the auditory hemispace ipsilateral to the amblyopic eye.

DISCUSSION

Our novel findings show deficits in the precision and accuracy of sound localization in adults with unilateral amblyopia. The deficits in sound localization precision and accuracy were apparent as increases in the MAA and absolute mean error in sound localization, respectively, within the frontal region of space. Listeners with unilateral amblyopia also showed an asymmetric pattern of sound localization error, with greater magnitude of error in the auditory hemispace ipsilateral to the amblyopic eye. Moreover, within the auditory hemispace ipsilateral to the amblyopic eye, the magnitude of sound localization error was positively correlated the severity of the amblyopic deficit in stereo acuity.

Unlike people who have lost all vision in one or both eyes at an early age,[32,34,58] our results indicate that people with amblyopia do not exhibit enhanced auditory spatial perception to compensate for their deficits in visual acuity. Rather, the sound localization deficits in unilateral amblyopia more closely
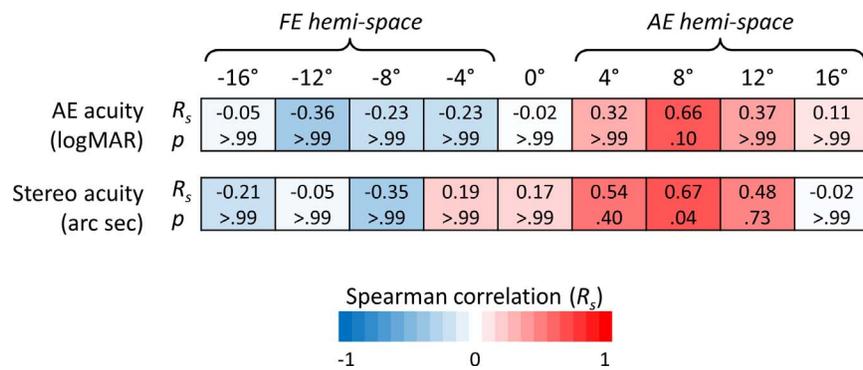
		FE hemi-space				AE hemi-space			
		-16°	-12°	-8°	-4°	0°	4°	8°	12°	16°
AE acuity (logMAR)	R_s	-0.05	-0.36	-0.23	-0.23	-0.02	0.32	0.66	0.37	0.11
	p	>.99	>.99	>.99	>.99	>.99	>.99	.10	>.99	>.99
Stereo acuity (arc sec)	R_s	-0.21	-0.05	-0.35	0.19	0.17	0.54	0.67	0.48	-0.02
	p	>.99	>.99	>.99	>.99	>.99	.40	.04	.73	>.99

Spearman correlation (R_s)

-1   0   1

FIGURE 6. Correlations between clinical measures of amblyopia and sound localization error across sound source positions. The magnitude of stereo acuity deficit was significantly correlated with magnitude of sound localization error at one position (8°) in the auditory hemispace ipsilateral to the amblyopic eye. All P values adjusted by the Bonferroni method.

resemble those observed in early-blind people who retain residual vision in both eyes.[32] This indicates that discordant binocular vision caused by amblyogenic factors can disrupt the developmental calibration of auditory localization, and that normal visual acuity in the fellow eye is not adequate to rescue this cross-sensory process. More generally, the results reported here support the view that it is the quality of visual input, rather than its absence, that has the stronger influence on the visual calibration of auditory space maps during development.

Comparing our findings with the normal trajectory of MAA improvement through childhood, auditory spatial acuity in adults with amblyopia is similar to that of children between 1.5 to 5 years of age.[26] This age range corresponds roughly to the age of onset for the most common forms of amblyopia,[59,60] raising the possibility that amblyopia or its etiological factors (e.g., strabismus or anisometropia) interfere with the visually guided maturation of auditory localization abilities, leaving the binaural system in a persistently juvenile state. Alternatively, it may result from a loss of auditory spatial acuity, in which anomalous visual input during a later sensitive period in auditory system development causes regression in the MAA to the level of a normal 1.5- to 5-year old.

How could amblyopia interfere with auditory spatial development when the brain has access to high-resolution visual spatial information from the fellow eye? The disconnect between impaired binaural spatial acuity and normal binocular visual acuity may represent physiological differences between the retinocollicular pathway involved in aligning and calibrating the auditory space map, and the retinogeniculostriate pathway responsible for pattern vision. Under binocular viewing conditions, perceptual dominance of the fellow eye is a function of suppression of the signal from the amblyopic eye.[61,62] Amblyopic suppression is mediated, however, by inhibitory interactions in the primary visual cortex.[63] If visual calibration of auditory space occurs in the superior colliculus, as suggested,[30] the usual cortical mechanisms for amblyopic suppression are likely bypassed. Without an independent midbrain mechanism to suppress signals from the amblyopic eye, signals from both eyes would be equally salient in their collicular representation of visual space. In this way, anomalous visual input from one eye may disrupt the calibration of the auditory space map in the midbrain, despite normal-acuity input from the fellow eye.

Eye movement abnormalities associated with amblyopia may also interfere with the development of spatial hearing. Saccades are mediated by the superior colliculus,[49,50] and in amblyopia, primary saccades to visual targets are less precise, even under binocular viewing conditions.[64] If the efferent

signal from an anomalous saccade is used to calibrate auditory spatial perception, increased variability in that signal may contribute to a widened MAA in amblyopia. However, this amblyopic increase in saccadic variability is relatively small (<0.2°), and therefore unlikely to account for the entire MAA effect.

Anomalous visual input from factors, such as strabismus and anisometropia, are widely posited to exert their amblyogenic effects at the level of the primary visual cortex by derailing the normal process of experience-depending maturation during a sensitive period (see Barrett et al.[65] for review).[66,67] Because the superior colliculus predominantly receives visual input directly via the retinocollicular pathway rather than via the retinogeniculostriate pathway, however, it is likely unaffected by the cortical maldevelopment responsible for amblyopia as commonly defined. This anatomic distinction in the retinal input to the superior colliculus and striate cortex suggests that the loss of auditory spatial acuity may be an auditory analog of amblyopia caused by the same amblyogenic factors, but arising de novo in the retinocollicular pathway. A similar pathologic mechanism involving direct retinocollicular input has been previously proposed to explain the abnormally long saccadic latencies observed in amblyopia.[11]

Clinical markers of visual impairment, namely, visual acuity in the amblyopic eye and stereo acuity, did not correlate significantly with the width of the MAA among the participants with amblyopia. While the relevant predictors of the amblyopic deficit in MAA remain to be determined, the width of the MAA may depend on historic factors, such as age of onset, age at treatment, and duration of patching, that are generally not known or documented. Furthermore, the lack of correlation between MAA and clinical markers of amblyopia may reflect a relatively short sensitive period for recovery of MAA compared with that for visual acuity. Indeed, another amblyopic deficit possibly mediated by the superior colliculus—prolongation of saccadic latency—can persist despite successful visual rehabilitation.[11]

It is important to note that the smallest auditory angle tested (3°) exceeded the MAA measured for most participants. Therefore, estimation of the MAA often relied on interpolation between data points concentrated in the high-performance tails of the psychometric functions. Although bootstrap analysis demonstrated reasonable reliability of our estimates of MAA, tighter sampling intervals would have improved the reliability of the data.

In addition to widening of the MAA, people with amblyopia also showed greater error in sound localization in the auditory hemispace ipsilateral to their amblyopic eye. This pattern of

auditory localization deficits is remarkable because it does not match the spatial distribution of visual spatial or oculomotor deficits observed in amblyopia.[64,68,69] Although participants localized sounds using a visually guided cursor, the task was done with both eyes open, and the specified click locations were well within the field of view of the fellow eye even for the most eccentric auditory targets at 16° left and right of the midline. Furthermore, the accuracy of visual localization with both eyes open, as measured by saccade amplitude, is normal in adults with anisometropic amblyopia[64] and strabismic amblyopia.[70] The asymmetry in sound localization error therefore cannot be attributed to difficulty seeing the visual cursor or visuomotor dysfunction. Furthermore, the pattern does not reflect the functional anatomy of the retinogeniculo-striate pathway, because the left and right primary visual cortices receive equal input from each eye, ensuring that monocular visual loss does not cause blindness in half of the visual field (i.e., homonymous hemianopia). Rather, the hemi-spatial asymmetry in sound mislocalization is suggestive of the functional anatomy of the retinocollicular pathway, because retinal input to each superior colliculus is largely crossed from the contralateral eye.[44,45] Simply stated, the left superior colliculus 'sees' the right visual hemifield predominantly through the right eye, and 'hears' the right auditory hemispace. A right eye visual impairment may therefore affect cross-sensory calibration of sound localization in the right auditory hemispace (i.e., a sound localization deficit ipsilateral to the amblyopic eye). That the magnitude of sound localization error in the amblyopic eye hemispace also correlated with the severity of amblyopic deficit in stereo acuity provides additional evidence that amblyopia and amblyopia-associated auditory deficits may be etiologically related. The observed pattern of deficits is largely consistent with a speculated mechanism of impaired cross-sensory calibration of auditory spatial maps in the superior colliculus, driven by anomalous retinocollicular input during early childhood.

Acknowledgments

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