

# Fixation Preference for Visual and Auditory Targets in Monkeys with Strabismus

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**PURPOSE.** During binocular viewing, many strabismic subjects choose the eye of fixation depending on the retinotopic location of a visual target. Here, we compare eye choice behavior when orienting to visual and non-visual (auditory) targets.

**METHODS.** Eye movements were measured in two head-fixed exotropic strabismic monkeys in a saccadic task involving either a visual or an auditory stimulus (no visual target information or feedback) during monocular or binocular viewing. The stimulus was one of 21 visual or auditory targets arranged 10° apart in a 7 × 3 array at a distance of 57 cm in an otherwise dark room. Fixation preference was calculated by recording the incidence of using a specific eye to acquire the target at any location.

**RESULTS.** Spatial patterns of fixation preference were observed in both monkeys for both visual and auditory stimuli; targets to the far right were acquired by the right eye, and targets to the far left were acquired by the left eye. For visual targets, the border for a change in fixation preference occurred in between the visual axes of the fixating and deviated eyes (variable in the two animals). In contrast, the border for fixation change remained near the cranio-center during the auditory task. During monocular viewing, fixation switching was observed only at the extremities during visual tasks; during the auditory task, fixation preference was similar to that observed during binocular viewing.

**CONCLUSIONS.** Fixation preference persists for invisible auditory targets. Our data suggest that visual suppression could modify underlying eye choice behavior that functions independently from vision.

**Keywords:** strabismus, non-human primate, fixation, saccades, suppression

Strabismus, most commonly a developmental disorder, is characterized by abnormal alignment of the eyes. At any moment, strabismic subjects use one eye to fixate and acquire information while the other (deviated) eye is non-fixating. Strabismic subjects with amblyopia (reduced visual acuity) prefer to use their non-amblyopic eye to fixate on targets<sup>1-3</sup>; that is, their amblyopic eye is always the deviated or non-fixating eye. However, a subset of strabismic subjects—those with minimal or no amblyopia—are able to take up fixation on a target of interest with either of their eyes depending on where the target is located. In other words, a pattern of fixation preference or eye choice behavior develops depending on spatial target location.<sup>4-6</sup> Within an oculomotor framework, a consequence of fixation preference can be fixation switch (for example, switching from right eye fixation to left eye fixation), which occurs when the target moves from a spatial location habitually preferred by one eye to a spatial location habitually preferred by the other eye. The saccadic eye movement that results in such a switch in fixation is called a fixation switch saccade or an alternating saccade.<sup>4,5</sup>

Several studies investigating this phenomenon propose that visual suppression of specific retinal areas is the driving force leading to fixation preference and fixation switch.<sup>2,6,7</sup> von Noorden and Campos<sup>8</sup> suggested that the peripheral retina of the deviated eye and the fovea are suppressed

to avoid diplopia and visual confusion, respectively. When Economides and colleagues<sup>9</sup> mapped suppression scotomas in exotropic humans, they observed that perception was active in the fovea of the deviated eye and that suppression occurred in the peripheral temporal retina in each eye, not just in the deviated eye. They also noted that the transition between perception and suppression occurred about halfway between the centers of gaze for each eye in the nasal field. Studies in esotropes have found that the nasal hemiretinas of the two eyes are suppressed.<sup>2,6,10</sup> In our lab, we examined fixation preference and alternating saccade behavior in esotropic and exotropic monkeys,<sup>5,6</sup> and we found that saccade behavior and spatial patterns of fixation matched previous proposed areas of suppression. Thus, the eye movement data supported the perception map developed by Economides and colleagues,<sup>9</sup> such that portions of the temporal retina are suppressed in exotropia and portions of the nasal retina are suppressed in esotropia, albeit the fovea, in either case, was not suppressed.

In natural behavior, we make orienting head and eye movements in response not only to visual stimuli but also to non-visual (e.g., auditory) stimuli.<sup>11</sup> The ability of strabismic subjects to orient to non-visual stimuli and, more specifically, the nature of fixation preference when orienting to non-visual stimuli are unknown and, to our knowledge, have never been studied. Consequently, we



FIGURE 1. Stimulus array configuration with LEDs (red dots) and speakers (white circles) that are  $10^\circ$  apart horizontally and vertically.

investigated, in two exotropic monkeys, the spatial pattern of fixation preference when making orienting eye movements to an auditory stimulus, in the absence of any visual target information. Our working hypothesis was that, if fixation preference is a consequence of only visual suppression, then the stereotypical spatial patterns of fixation preference would be absent when the strabismic animals responded to auditory targets (as retinal suppression is not defined without vision). Further, there would be no fixation switch elicited in this condition. On the other hand, if spatial fixation preference and fixation switch were still present when orienting to auditory stimuli, that would suggest that the brain had developed a strategy of fixation preference that is unrelated to the presence of vision. The overall goal of this study, therefore, was to provide insight into how strabismic subjects orient to stimuli of different modalities and how spatial patterns of fixation preference relate to the presence or absence of a visual target. Some of these data have been presented before in abstract form.

## METHODS

### Subjects, Animal Model, and Surgical Procedures

We investigated spatial patterns of fixation in two strabismic non-human primates (NHPs), ages 8 years (monkey 1, M1) and 9 years (monkey 2, M2), that had been reared using optical prisms.<sup>12</sup> In the optical prism-rearing paradigm, infant monkeys wear a lightweight helmet containing Fresnel prisms in front of their eyes starting from day one after birth until they are 4 months of age.<sup>13,14</sup> The animals look through a 20-prism diopter base-in prism over the left eye and a 20-prism diopter base-down prism over the right eye. The prism-rearing method introduces binocular decorrelation that prevents the animals from fusing the images from the two eyes, thereby disrupting the development of binocular vision and eventually leading to strabismus.<sup>15–17</sup> After the 4-month rearing period, the monkeys are allowed to grow without any restriction on their vision. Later in adulthood (>4 years of age), the animals undergo three surgeries to prepare them to be used for behavioral and neurophysiological studies. These surgeries include implanting a titanium post for head stabilization, a titanium recording chamber to be used in later neurophysiological experiments, and binocular search coils to obtain eye position information.<sup>18,19</sup> For our study, all of the surgical procedures were carried out under aseptic conditions using isoflurane anesthesia (1.25%–2.5%). All procedures were performed in strict compliance

with the National Institutes of Health and ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the protocols were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Houston.

### Experimental Paradigm and Training

During testing, the head-fixed monkey was seated 57 cm away from an array of visual and auditory targets made up of 21 red light-emitting diodes (LEDs) for the visual targets and 21 speakers (Scan-Speak Illuminator D2004/602000; Scan-Speak, Videbæk, Denmark) for the auditory targets in an otherwise dark room. The visual and auditory targets were arranged in a  $3 \times 7$  array as shown in Figure 1. The construction of the array was such that the LED was placed at the center of the corresponding speaker and the speaker/LED combination was recessed such that the surface facing the animal appeared to be smooth and uniform (i.e., no visual cues). The visual stimulus was the  $1^\circ$  red LED light, and the auditory stimulus was bandpass white noise (100–20 kHz).<sup>20,21</sup> The visual and auditory stimuli were controlled by custom programs developed using LabVIEW (National Instruments, Austin, TX, USA). The eye coil signal was calibrated at the beginning of each experiment as the animal monocularly fixated the series of LEDs along the horizontal ( $-30^\circ$  to  $30^\circ$ ) and vertical ( $-10^\circ$  to  $10^\circ$ ) meridians. The animal was rewarded with small amounts of juice when viewing within a small region ( $\pm 2^\circ$ ) around the target.

The training regimen that we used to train the animals was a modified version of methods reported in studies that successfully trained NHPs to make saccades to auditory stimuli.<sup>22,23</sup> Monkeys tend to orient to novel sounds, and our training paradigm used this behavior initially to help the animals localize auditory stimuli. For the first  $\sim 5$  days of training of the monkeys, which were naïve to auditory stimulation, visual feedback in the form of a visual target was presented at the same location as the auditory stimulus; that is, it was added to the end of the auditory white noise sound burst. After this short period, we continued to train the animals to make saccades to sound stimuli, but visual feedback was not provided. Training without visual feedback continued for approximately 4 months, usually 5 days a week. During the training period, only four out of the 21 possible targets were used:  $(-20, 0)$ ,  $(20, 0)$ ,  $(0, 10)$ , and  $(0, -10)$ . When the monkeys had become proficient in making saccades to the location of the speakers (without visual feedback), we recorded their eye movements to visual

and auditory targets presented at all 21 locations. Because the animals did not receive visual feedback for most of the training and further received training on only a subset of targets, we are confident that their orienting eye movements to the auditory targets during the data collection phase were based on auditory localization mechanisms and were not some sort of visual memory of or associations between the auditory and visual targets.

In the data collection phase, eye position data were collected as each animal performed a saccade task involving the visual or auditory target under both binocular and monocular viewing conditions. In this task, the fixation LED at the straight-ahead location (0, 0) turned on for 1 second. After this fixation period, the eccentric target (either auditory or visual) was presented at a random horizontal ( $\pm 30^\circ$ ) and vertical ( $\pm 10^\circ$ ) location for 2 seconds. This time frame allowed enough time for the monkeys to make saccades to the eccentric location (especially useful for auditory-evoked saccades). At the end of the 2-second time period, the eccentric target was extinguished and was followed by a blank period of  $>1$  second followed by the reappearance of the central LED, signifying the start of the next trial. During auditory trials, the visual target never appeared at the eccentric location, and the cessation of the eccentric auditory stimulus and the subsequent reappearance of the central LED signaled the end of one trial and the beginning of the next trial. Therefore, all auditory trials were executed in the absence of visual target information in the darkened room environment after the central fixation LED was extinguished. Animals were rewarded for looking within a reward window that was  $10^\circ$  square for auditory and  $5^\circ$  square for visual stimuli. This large target acceptance window for the eccentric auditory targets was chosen because previous studies have shown that the error magnitude for auditory targets with the head restrained is larger than with visual targets.<sup>24–26</sup> During binocular viewing, the animals were rewarded regardless of the eye with which they chose to acquire the central fixation LED or the eccentric target, promoting spontaneous eye choice behavior. Blocks of visual and auditory trials were separately acquired.

### Data Analysis

Saccade analysis was partially automated and analyzed using custom software built in MATLAB (MathWorks, Natick, MA, USA). Every trial was visualized, and the investigator had the option of accepting or rejecting the trial. Trials were rejected if the monkey was not fixating on the central fixation spot at the beginning of the trial, the saccade was not in the general direction of the target (e.g., a saccade was generated upwards when the target was presented downwards), or a saccade was not made by the time the eccentric target was extinguished. When a trial had been accepted, the saccade onset and offset were determined automatically by the software using velocity and acceleration criteria that we have previously published.<sup>5,6</sup> The investigator had the option to manually adjust the automatically detected saccade onset and offset, although this was only required in a minority of trials. Depending on the retinal error magnitude with respect to each eye at the start and end of the trial, the software program binned the data into four categories: RR, right eye initially fixating the center fixation spot and right eye obtaining the eccentric target as a consequence of the visual- or auditory-evoked saccade; LL, left eye initially fixating and left eye obtaining the eccentric target; RL, right eye

initially fixating and left eye obtaining the eccentric target; and LR, left eye initially fixating and right eye obtaining the eccentric target. Thus, RL and LR are saccades resulting in a fixation switch, and RR and LL are saccades resulting in no fixation switch. The goal of the analysis was to determine the relationship between the spatial location of either the eccentric visual or auditory target and the eye used to acquire the target. Saccade parameters such as accuracy and main sequence relationships were also analyzed. The Holm–Sidak method (pairwise multiple comparison procedure) at a significance level of 0.05 was used to compare saccade accuracy to different locations.

## RESULTS

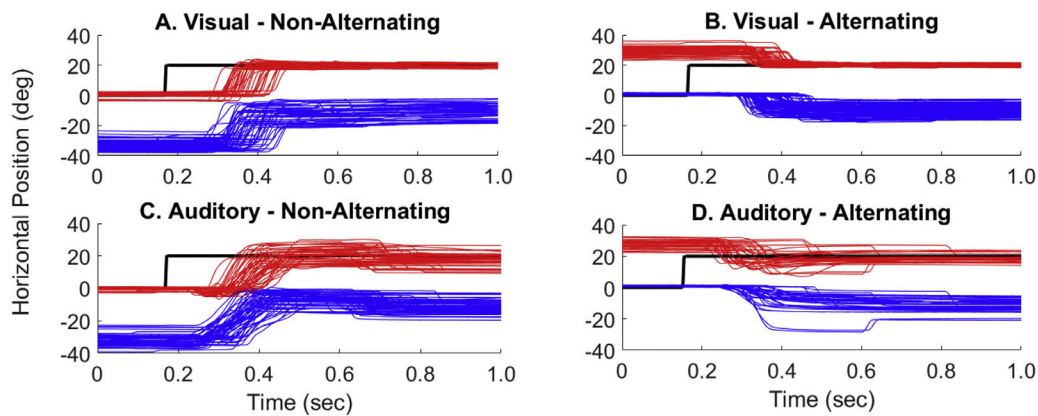
### Properties of Strabismus

The two animals included in the study were both exotropic. Monkey M1 showed an exotropia of  $\sim 30^\circ$  during either eye viewing, and M2 showed an exotropia of  $\sim 30^\circ$  during right-eye viewing and  $\sim 25^\circ$  during left-eye viewing. During binocular viewing conditions, both monkeys presented with small-amplitude downbeat and left-beat manifest fusion maldevelopment nystagmus, typical of infantile-onset strabismus.<sup>17</sup> Animals also underwent monocular contrast sensitivity testing with a psychophysical method that we have described previously.<sup>27</sup> For M1, the high spatial frequency cutoffs for the right eye and left eye, respectively, were 20 and 15 cycles per degree (cyc/deg). For M2, the high spatial frequency cutoffs for the right eye and left eye, respectively, were 14 and 13 cyc/deg. Although some differences in the right and left eye high-frequency cutoff values were noted for M1, closer examination of the contrast sensitivity function (CSF not shown) indicated that the confidence intervals of the functions of the two eyes overlapped significantly, and the CSF values at low spatial frequencies ( $<4$  cyc/deg), at which the sensitivity is the highest, were virtually indistinguishable. Importantly, both animals showed fixation switching behavior, which was the focus of the study.

Figure 2 shows raw data from M2 illustrating saccade behavior to a visual (Figs. 2A, 2B) or auditory (Figs. 2C, 2D) target presented at a horizontal eccentricity of right  $20^\circ$  during binocular viewing conditions. Thus, when the right eye is initially viewing (left eye deviated to the left by  $\sim 30^\circ$ ) and the target appears in the nasal retina of the right eye, fixation switch never occurs regardless of whether the target is visual (Fig. 2A) or auditory (Fig. 2C). On the other hand, when the left eye is initially viewing and the target appears in the near temporal retina of the right eye, fixation switch always occurs regardless of whether the target is visual (Fig. 2B) or auditory (Fig. 2D). Note that, for the auditory target presentations, no visual feedback was provided to the animal, so the animal could not have simply matched the auditory stimulus with the presentation of the visual target in the same spatial location. Figure 2, therefore, illustrates that the monkey can indeed generate saccades with (right panels) or without (left panels) fixation switch to either a visual or an auditory target at a specific spatial location.

### Saccade Metrics for Visual and Audio Elicited Saccades

Prior to mapping spatial fixation preference behavior for all target locations, saccade metric parameters, such as



**FIGURE 2.** Raw data from exotropic monkey M2 illustrating fixation preference behavior during saccades made under binocular viewing conditions to a visual (A, B) or auditory (C, D) target presented at  $+20^\circ$ . Each line shows data from a single trial, and trials are aligned on target onset. **A** (visual) and **C** (auditory) illustrate target presentations that elicited no fixation switch for either a visual or an auditory target; that is, the right eye fixated the central target and acquired the eccentric target. **B** (visual) and **D** (auditory) illustrate target presentations for which every trial resulted in a fixation switch; that is, the left eye fixated the central target, and the right eye acquired the eccentric target. Rightward eye positions are positive, and leftward eye positions are negative. *Red*, right eye position; *blue*, left eye position; *black*, target position.

accuracy and amplitude-peak velocity relationships for visual and auditory saccades, were calculated and compared to ensure that the animals were making reasonable saccadic eye movements in response to the auditory stimulus. Accuracy was evaluated by calculating the error at the end of the saccade (including any catchup saccades) to the visual or auditory targets (Fig. 3). As expected from the raw data shown in Figure 2 and from previously published work in normal animals,<sup>22</sup> saccades to visual targets were more accurate (mean value close to target position) and precise (smaller standard deviation) than saccades to auditory targets. Although saccades to auditory targets have greater errors, one-way ANOVA followed by post hoc testing (Holm-Sidak method) showed that there was a statistically significant difference ( $P \leq 0.001$ ) between the mean values of all the saccade endpoints in the horizontal plane for both monkeys. There was also a significant difference in saccade endpoints in the vertical plane, except for 2/21 locations for M1 only. These data show that, despite the increased errors, the saccade behavior in response to the different auditory target locations is sufficiently distinct and therefore allows unequivocal conclusions about spatial patterns of fixation preference.

Figure 4 shows the amplitude versus peak velocity main sequence plots for M1 for the visual and auditory targets. As described in previous studies of normal monkeys,<sup>28-31</sup> saccades to auditory targets tend to show more variability in peak velocities (for similar amplitudes) and lower asymptotic peak velocities when compared to visually guided saccades. Regardless of these differences in the saccade metrics, the data show that the monkey is able to make saccadic eye movements to localize both auditory and visual targets.

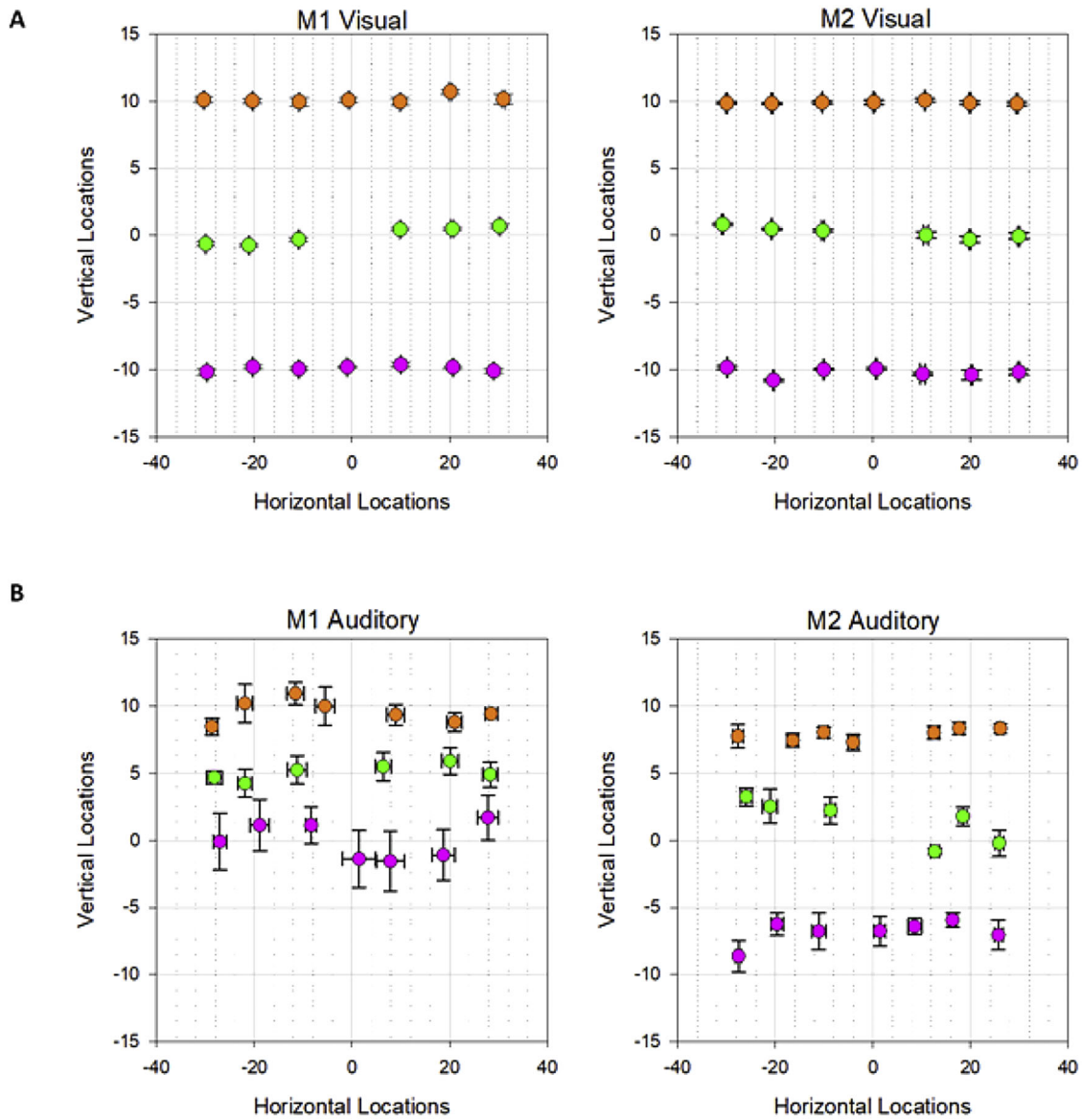
### Fixation Preference Maps During Binocular Visual Versus Auditory Stimulus Presentation

The examples in Figure 2 show data for a single visual or auditory target location. Data were collected from 21 target locations to establish the spatial pattern of fixation

preference in both of the monkeys. During binocular viewing for M1, we analyzed 943 saccades during the visual task and 775 saccades during the auditory task. During binocular viewing for M2, we analyzed 1180 saccades during the visual task and 743 saccades during the auditory task. The animals were free to assume central fixation of the LED at the start of the trial with either eye (juice reward provided for either eye), and the blank period before the appearance of the central fixation spot further promoted spontaneous choice of eye for central fixation. M1 assumed initial fixation with the left eye on 67% of the trials (auditory and visual trials combined), and M2 assumed initial fixation with the left eye on 57% of trials. Although there is an imbalance in the number of trials starting with left or right eye fixation, the large number of trials collected for each eccentric target allowed the development of reliable spatial maps of fixation preference. As we have done in previous studies,<sup>5,6</sup> spatial patterns of fixation were analyzed by calculating the incidence of using either the right or left eye to acquire the eccentrically located auditory/visual targets at each location. Figure 5 shows the pattern of fixation preference for M1 developed from all 21 locations for visual targets (Figs. 5A, 5B) and auditory targets (Figs. 5C, 5D). If the left eye acquired a target at a specific eccentric spatial location on 100% of the trials, then this area was coded as blue; conversely, if the right eye acquired the target on 100% of the trials, then this area was coded as red. A color that is intermediate between blue and red denotes an intermediate percentage of choosing the left or right eye. Both similarities and differences were noted in comparing the animal's orientation behavior to eccentric visual and auditory targets.

A fundamental observation from Figure 5 (also observed in the raw plots in Figure 2 for one target location) regarding the patterns formed in response to visual and auditory stimuli at all 21 target locations is that fixation preference behavior occurs regardless of target modality. Targets on the far right are generally acquired by the right eye and targets on the far left are generally acquired by the left eye for both visual and auditory targets. Our results for visual targets for M1 (Fig. 5) match those from previous studies<sup>6,32</sup> and show that visual targets presented on the nasal retina of the





**FIGURE 3.** Mean saccade end points for M1 and M2 in response to visual (A) and auditory (B) stimuli. On the *x*-axis are the horizontal locations and on the *y*-axis are the vertical locations. The color of the circles indicates saccade endpoints for targets presented at three vertical locations (orange,  $y = +10^\circ$ ; green,  $y = 0^\circ$ ; pink,  $y = -10^\circ$ ). Error bars are horizontal and vertical standard error.

fixating eye are acquired by the same eye, whereas presenting visual targets on the nasal retina of the deviated eye results in fixation switch. Previous studies attributed this behavior to a visual stimulus falling on the suppressed portions of the retina of the previously fixating eye, causing NHPs and humans to switch fixation.<sup>5,6,9,32</sup> Data from this study modify this understanding by showing that fixation preference patterns and fixation switch behavior is also elicited in response to an auditory stimulus without any visual feedback.

The fixation preference maps for visual and auditory stimuli for M1 show broad agreement with some differences. For example, when the monkeys were presented with auditory targets at the same far eccentric locations ( $\pm 30^\circ$ ), the areas of 100% fixation switch and 100% no-fixation switch overlapped with that of the visual target map. For both visual and auditory targets, fixation preference changes gradually from

left eye to right eye as horizontal target position is varied from left to right (change in the map color from predominantly blue to predominantly red or vice versa). There appears to be no specific pattern associated with vertical target position for either visual or auditory target. However, there are also some important points of difference between the visual and auditory target maps. For visual targets, a change in fixation preference occurs in between the gaze axes of the two eyes, confirming the observation from our previous study.<sup>6</sup> In contrast, for auditory stimuli, this border is more centralized and passes very close to horizontal zero. Also noteworthy is the fact that the border is fairly narrow for visual stimuli but is significantly more widespread for the auditory stimuli.

The data for M2 (Fig. 6) show some similarities and differences compared to the data for M1. The primary finding of the study (i.e., that fixation preference and fixation

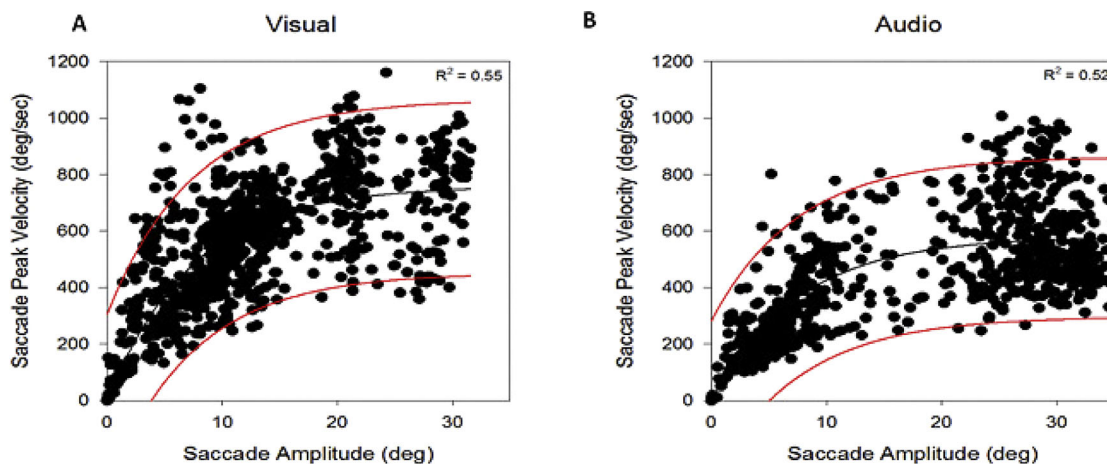


FIGURE 4. Amplitude versus peak velocity main sequence plots from binocular viewing saccade data obtained for monkey M1 in response to visual (A) and auditory (B) targets. Also plotted are the nonlinear regressions (black lines) and 95% prediction intervals (red lines).

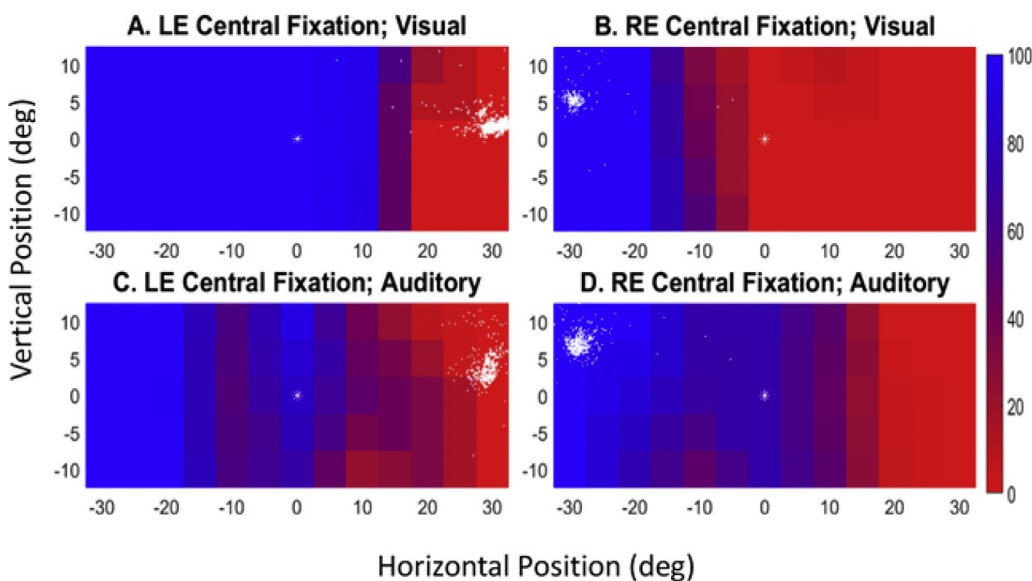
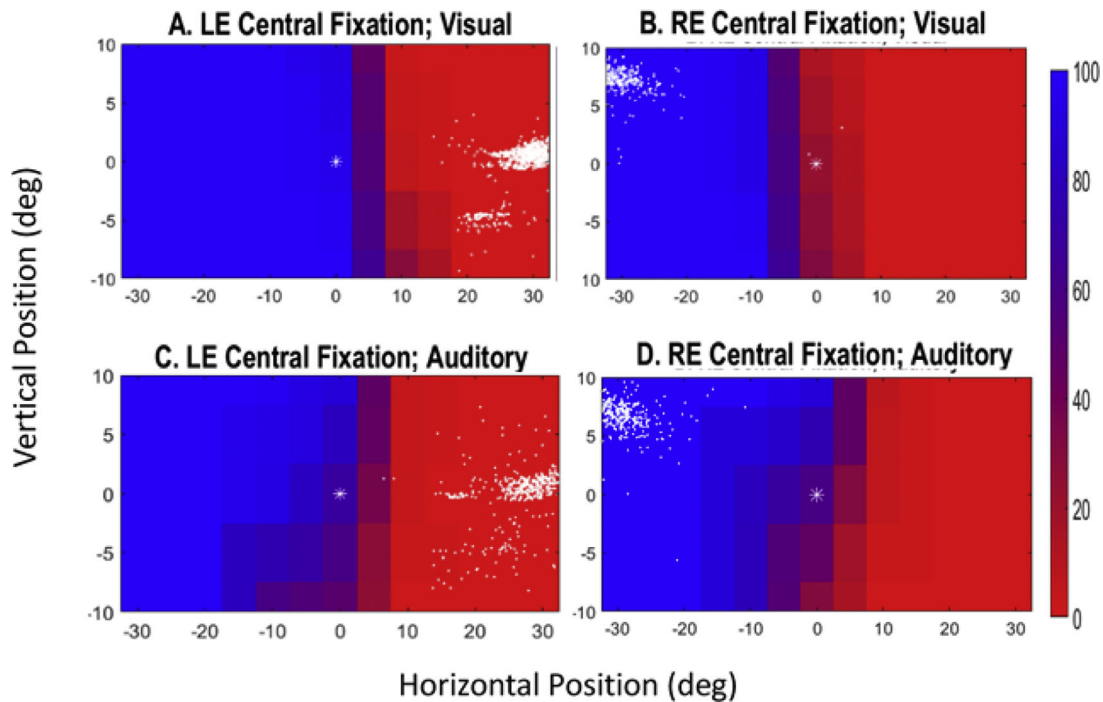


FIGURE 5. Filled surface plots developed from binocular viewing saccade data for monkey M1 indicating eye choice behavior to visual (A, B) or auditory (C, D) targets. A and C include only trials where the left eye was initially fixating the central target, and B and D include only trials where the right eye was initially fixating the central target. The x-axis is the horizontal position of the eccentric target, and the y-axis is the vertical position of the eccentric target. The position of the initially fixating eye is indicated by a \* sign and is located at 0°. The position of the initially non-fixating eye is shown as dots and is variable from trial to trial. Eccentric visual or auditory target locations where the left eye acquired the final target 100% of the time are shown in blue, and eccentric visual or auditory target locations where the right eye acquired the target 100% of the time (equivalent to left eye acquiring the eccentric target 0% of the time) are shown in red. Intermediate percentages of eye choice behavior based on left eye (0%–100%) are represented by the color scale shown next to the plot.

switching are observed for auditory targets) is replicated in M2. Fixation preference for far eccentric horizontal targets and a lack of association with vertical target position for both visual and auditory targets were also observed in M2, as in M1. The border of fixation switching for auditory targets for M2 is close to cranio-center, as for M1. A point of difference between M2 and M1 lies in the border of fixation switching for visual targets. For M1, the border of fixation switching for visual targets was approximately half-way between the gaze axes of the two eyes, but for M2 the

border of fixation switching for visual targets appears shifted only a few degrees from the position of the initially viewing eye, which was viewing a straight-ahead target. Therefore, the difference in the border of fixation preference for visual and auditory targets observed for M1 is less apparent for M2. This issue is considered in greater detail in the section on analysis of the border between right and left eye fixation preference, and possible implications are offered in the Discussion section. It should be noted that spatial patterns of fixation preference for visual targets can differ



**FIGURE 6.** Filled surface plots developed from binocular viewing saccade data for monkey M2 indicating eye choice behavior to visual (A, B) or auditory (C, D) targets.

widely among subjects and may account for the differences in where the border occurred for visual targets for the two monkeys used in this study. M2 also showed quite a bit of variability of strabismus angle on a trial-to-trial basis, as can be deduced from the dispersion of the position of the deviated eye (white dots) in Figure 6. This variability can also affect estimating the point of fixation switch for visual targets.

### Fixation Preference Maps During Monocular Visual and Auditory Stimulus Presentation

As a control experiment, we also investigated spatial patterns of fixation preference under monocular viewing conditions (Fig. 7). For visual targets, monocular viewing should not elicit suppression, so the viewing eye would be expected to acquire the target at all locations. This prediction was accurate for all target locations except the most eccentric ( $\pm 30^\circ$ ), where the occluded eye still initially attempted to acquire the target, followed by a larger saccade that brought the viewing eye onto the target. These responses are examples of the crossover saccades described by Economides and colleagues.<sup>9</sup> In the auditory target trials, the monkey initially fixated the central target monocularly; however, when the central fixation target disappeared and the eccentric auditory stimulus was presented, the animal was in complete darkness, so the viewing condition at this time was basically the same as during auditory trials under binocular viewing. The finding during the monocular testing was that the fixation preference map for auditory targets during monocular viewing was relatively similar to the maps formed during binocular viewing. Thus, with initial monocular viewing, preference for right eye for right auditory targets and left eye for left auditory targets is maintained.

### Analysis of Border Between Right and Left Eye Fixation Preference

The data show that fixation preference is a feature along the horizontal plane but not along the vertical plane. Therefore, we collapsed the pseudo-color spatial maps (Figs. 5, 6) along the vertical plane and performed a sigmoidal fit to the data (Fig. 8), in order to quantitatively capture how the change in fixation preference from one eye to the other occurred in response to visual and auditory stimuli during binocular viewing. In order to create the plots shown in Figure 8, the incidence of a specific eye obtaining the target at any horizontal position was averaged across the different vertical positions. Data points and sigmoid curve-fits in the figure show the incidence of the right or left eye acquiring the target as a function of only horizontal target position for the two monkeys. The 50th percentile on the  $y$ -axis is denoted as the fixation switch mark and the spatial width over which fixation switch occurs is estimated as the range of horizontal target positions between the 10th and 90th percentile mark.

The Table shows the values of 50% location and 10% to 90% width for each condition. Although the differences between the visual and auditory target data are much more dramatic for M1 (Table, Fig. 8), the general observations are, in fact, similar. For binocular visual data (solid colored line), the switch in fixation preference occurred at locations in between the gaze axes of each eye (M1:  $+15^\circ$  for left eye fixating,  $-10^\circ$  for right eye fixating; M2:  $+7^\circ$  for left eye fixating,  $-4^\circ$  for right eye fixating). For the binocular auditory data (solid black line), the fixation switch occurred closer to cranio-center (M1:  $+4^\circ$  for left eye fixating,  $+6^\circ$  for right eye fixating; M2:  $+2^\circ$  for left eye fixating,  $+1^\circ$  for right eye fixating) compared to the visual target condition and does not lie in between the gaze axes for right eye fixating conditions for either animal. Note also that the width over which

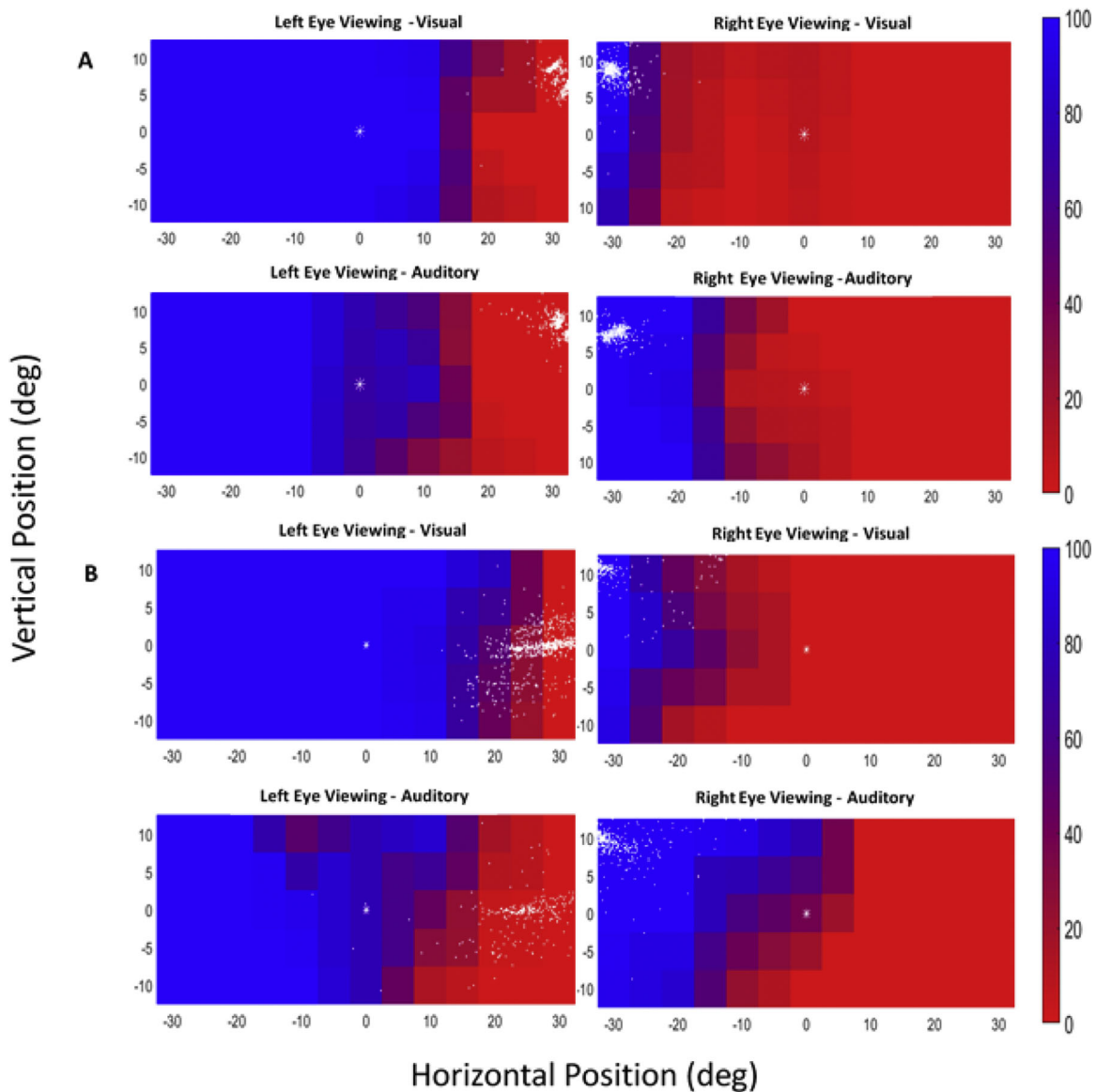


FIGURE 7. Filled surface plots developed from monocular viewing saccade data for monkey M1 (A) and M2 (B) indicating eye choice behavior to visual (top two panels in each section) or auditory (bottom two panels in each section) targets.

TABLE. Fixation Switch Location and Width Parameters Derived from Sigmoid Fits

	M1				M2			
	Binocular		Monocular		Binocular		Monocular	
	OD	OS	OD	OS	OD	OS	OD	OS
Fixation Switch (50% locations)								
Visual	-10.0	15.4	-25.3	16.4	-4.1	6.5	-20.6	20.9
Auditory	6.1	4.0	-12.2	8.9	1.2	2.1	-5.4	7.5
Border width (10%–90% locations)								
Visual	2.3	8.0	10.8	9.1	9.0	7.5	16.6	9.4
Auditory	27.7	44.5	10.1	25.8	17.4	12.7	29.5	20.4

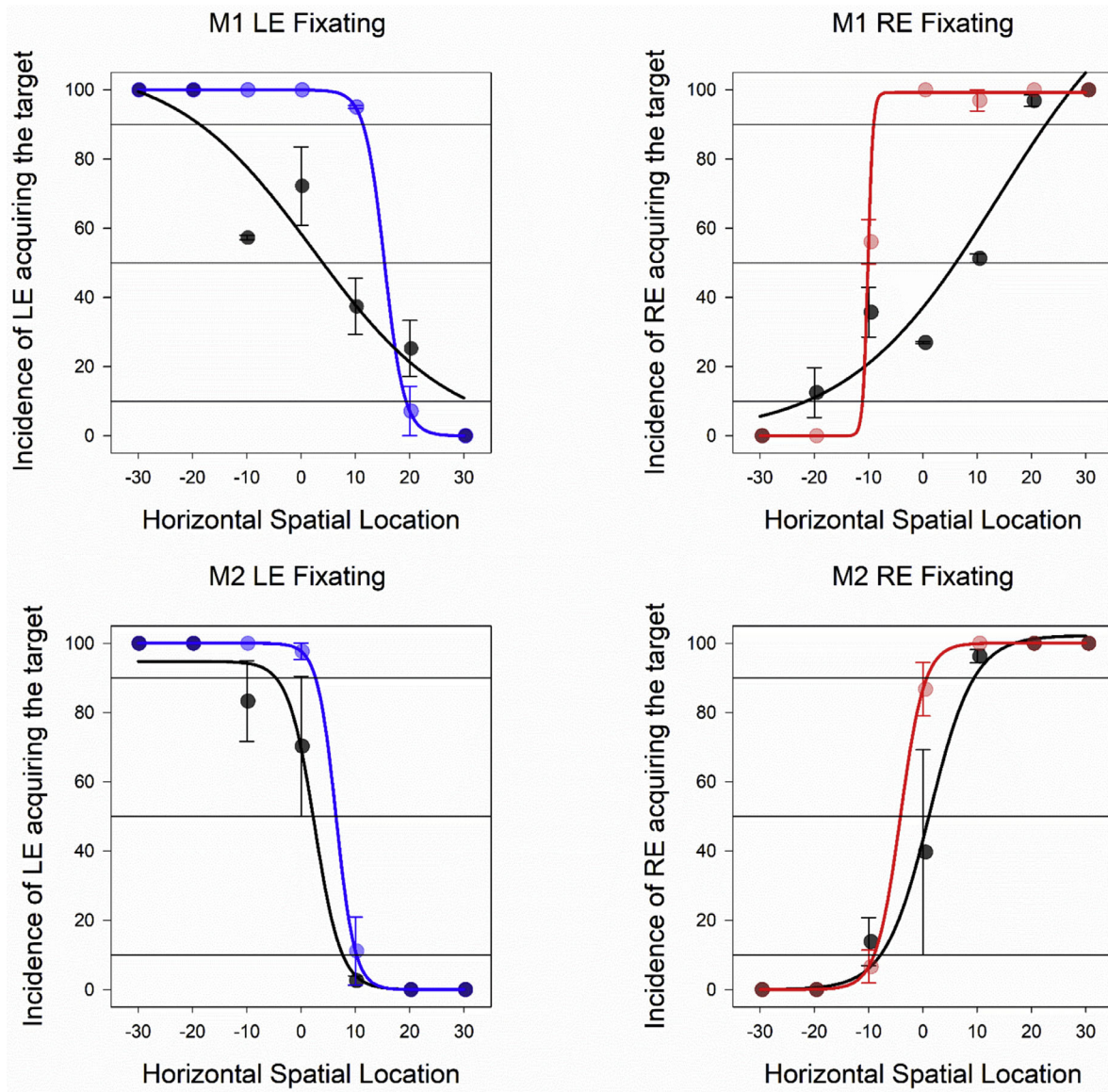
fixation switch occurred is significantly larger for the auditory target condition compared to the visual target condition. Another way to consider the difference between the visual

and auditory target conditions is that the fixation switch point changed by  $\sim 11^\circ$  for M2 when comparing right and left eye viewing conditions for visual targets, but it changed by only  $0.9^\circ$  when comparing right and left eye viewing conditions for auditory targets (Table). These differences are even more magnified in M1, with a fixation switch point change between right and left eye viewing of  $\sim 25^\circ$  for visual targets and only  $\sim 2^\circ$  for auditory targets.

### DISCUSSION

The phenomenon of fixation switch and the spatial patterns of fixation preference is a unique property observed in humans and monkeys with strabismus. This strabismus property has provided insight into visual processing mechanisms in strabismus, specifically the possible suppression of certain parts of the visual field. In this study, we evaluated saccade responses to visual and non-visual (auditory)





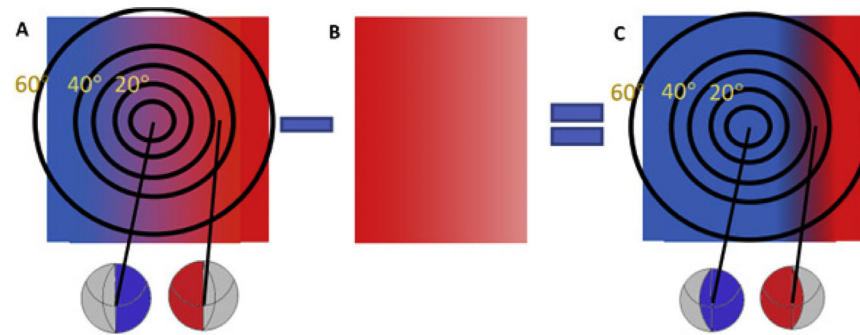
**FIGURE 8.** Sigmoid fit graphs of M1 (top row) and M2 (bottom row) eye choice data for horizontal target locations under binocular viewing conditions. The y-axis is the incidence (%) of either the left eye (LE) or the right eye (RE) acquiring the target. Data for the visual targets are shown in *blue* and *red* for the LE and RE, respectively; data for the auditory targets are shown in *black*.

stimuli and found that fixation switch behavior occurred for both visual and auditory stimuli and that the spatial patterns of fixation showed some major similarities and some differences for the two stimulus modalities.

**Comparing Spatial Fixation Maps for Visual and Auditory Stimuli During Binocular Viewing**

It had previously been thought that, during binocular viewing in exotropes, spatial patterns of fixation preference are elicited as a result of visual suppression of parts of the temporal retina in each eye.<sup>8</sup> In this scenario, eye choice for auditory targets is not readily apparent because retinal suppression in darkness is not defined. A priori predictions could have been that eye choice to auditory targets would be completely random, with no discernible spatial pattern

of preference maps, or, perhaps, would be determined by the eye that was fixating at the start of the trial. Our data suggest, however, that our animals adopted neither of these two options; rather, they adopted a spatial pattern that was only broadly similar for both visual and auditory targets with important differences. Therefore, it appears that visual suppression is not the only reason why spatial patterns of fixation preference are developed and that the property of eye choice to orient to external visual and non-visual stimuli and the associated property of the stereotypical spatial map of fixation preference in exotropia are at least partially hardwired into the oculomotor system. Note that we do not suggest that fixation preference is devoid of the influence of vision and visual suppression, because there were indeed differences in the spatial auditory maps and the spatial visual maps, as was apparent for M1. The border that is developed for visual stimuli, which is shifted toward a location between



**FIGURE 9.** Sample framework for fixation preference during visual and non-visual tasks when exotropic subjects initially viewed with the left eye (LE). **A** is the default fixation preference map for non-visual (auditory) stimuli. For visual targets, visual suppression of the deviated right eye (**B**) acts additionally to shift fixation preference towards the left eye (**C**). In **B**, the depth of suppression was graded (greater to the left for the right eye) and is shown as subtractive to illustrate that the signal from the right eye (RE) was reduced.

the visual axes of the two eyes, as per the current and previous studies,<sup>6</sup> did not hold true for auditory targets in this study, where the border was approximately at cranio-center. Our data also show that this border was not as sharply defined for auditory targets when compared to visual targets, as shown by the gradual transition of colors between A and B compared to C and D in [Figures 5 and 6](#) and in the [Table](#).

Another interpretation of our data could be that downstream effects of suppression, elicited by fixation of the central target by one of the eyes, on oculomotor target selection and saccadic centers of the brain such as the superior colliculus, persist for some time even after the disappearance of the central stimulus. However, the presence of crossover saccades (i.e., saccades where the covered eye appears to acquire the target during monocular viewing) does not support this mechanism because retinal suppression should be absent during monocular viewing. It is likely that neurophysiological investigations of oculomotor areas (e.g., superior colliculus) while animals perform visual or auditory tasks will help test these hypotheses.

### Possible Framework for Eye Choice Behavior to Visual and Non-Visual Targets

In our natural environment, the overarching strategy of fixation preference could be seen as economic and energy saving in strabismic subjects; they tend to make the smallest saccade to get there more quickly and save energy. However, our previous study with only visual targets and the current study with auditory targets suggest that the underlying mechanism is more complicated, and the smallest saccade prediction must be qualified. In a previous publication that used only visual targets (see figure 5 in Agaoglu et al.<sup>6</sup>), we analyzed the relationship between instantaneous retinal error and eye choice and did not find a consistent relationship. In the current study, if this smallest saccade prediction were true, we would have expected auditory targets presented in the area between  $+10^\circ$  and  $-10^\circ$  to be acquired by the fixating eye, as both monkeys had relatively large deviations. However, [Figures 5 and 6](#) show that either eye could acquire the auditory target presented at these locations.

We suggest a possible framework for fixation preference during both visual and non-visual tasks that accounts for the similarities and the observed differences ([Fig. 9](#)). In this

framework, the eye choice map for non-visual stimuli is the default representation that is built into the oculomotor system of a strabismic individual ([Fig. 9A](#)). This map is based on craniotopic coordinates and is fairly imprecise in that either eye could be used to saccade onto the non-visual target for a range of target locations around the straight-ahead position. Possibly noisy spatial localization within auditory structures of the brain is a contributing factor. When a strabismic subject partakes in a visual task, visual suppression acts as an additional influence ([Fig. 9B](#)), modifying the default eye choice behavior. Because visual suppression acts in a graded manner (i.e., depth of visual suppression varies with eccentricity), the net effect is that the border (location at which fixation preference switches from right to left eye or vice versa) is rendered sharper and is also shifted to between the gaze axes of the two eyes in exotropia ([Fig. 9C](#)). For subjects who have moderate amounts of amblyopia, the visual suppression map ([Fig. 9B](#)) is modified to further suppress the amblyopic eye and therefore shifts the spatial fixation preference map further. This hypothetical framework suggests an emergent property that can be tested experimentally; that is, the default map is independent of the visual capability (i.e., presence of amblyopia) of the subject.

The above hypothetical framework fits well for the data for M1 but less so for the data for M2 because the differences in visual and auditory patterns for M2 are not as marked as those for M1. The additional effect of visual input and visual suppression is therefore still not fully resolved in this framework because there is quite a bit of variability between subjects in the spatial patterns developed for visual targets.<sup>6,32</sup> Perhaps the visual suppression map ([Fig. 9B](#)), shown here to be gradually changing with eccentricity, is in fact irregular, leading to variability in the position of fixation switch. The similar visual and auditory maps for M2 also leave open the possibility that visual suppression plays a smaller role in some subjects. It was also a little odd that M1 used his left eye to assume central fixation on a larger percentage of trials, even though contrast sensitivity testing suggested that the high spatial frequency cutoff of the left eye was lower than that of the right eye. However, confidence intervals of the CSF overlapped significantly for the two eyes, especially at lower spatial frequencies at which the sensitivity is the highest. We also believe the difference in high spatial frequency cutoff is perhaps not so relevant in our testing because the visual stimulus was a bright LED against a dark background. Moreover, studies in humans by

Economides and colleagues<sup>32,33</sup> have shown that a strong preference for fixation of the central cross does not influence the choice of eye used to acquire eccentric visual targets. Future testing of fixation preference using near-threshold stimuli could be used to investigate this issue further and test the framework more effectively.

### Comparing Spatial Fixation Maps for Visual and Auditory Stimuli During Monocular Viewing

The monkeys were also tested during monocular viewing, and spatial patterns of fixation preference were compared for saccades made to visual and auditory stimuli. The notable result is that, although there is a significant difference between monocular and binocular viewing conditions for visual targets, indicating an effect of different states of visual suppression, there are relatively minor differences between monocular and binocular viewing for the auditory trials. This finding reinforces our findings for binocular viewing conditions that fixation switching mechanisms do not depend on the presence of a visual target. One possible explanation for the small differences between the monocular and binocular auditory target tasks in our study is that the initial fixation condition, using a central LED, may have affected the overall development of fixation preference, even when making a saccade to non-visual modalities.

### Comparing Saccade Metrics for Visual and Auditory Stimuli

For the most part, there were broad similarities among the two monkeys in saccade metrics. Previous studies have shown that saccades to auditory targets are on average slower than saccades made to visual targets,<sup>28–30</sup> and we found the same (Fig. 4). Saccades to auditory targets also tend to be less accurate than saccades to visual targets,<sup>22,34</sup> another finding that was replicated in this study. Additionally, for M1, there was a significant upward bias in the localization of the auditory targets. Because the change in fixation preference occurred in the horizontal plane, the upward bias of M1 (Fig. 3) did not affect interpretation of the fixation preference maps.

### Methodological Considerations

The sample size in this study is low and typical of studies utilizing non-human primates. Therefore, behavioral studies in larger human strabismic sample populations should be conducted to verify our main finding that fixation preference is also observed for non-visual targets and to test our hypothetical framework for fixation preference to visual and non visual targets (Fig. 9). Most animal studies on normal auditory-oculomotor localization have used head-fixed monkeys very effectively, but one previous study has suggested that auditory localization in head-fixed monkeys is poor when compared to results in head-unrestrained monkeys.<sup>35</sup> So, a potential concern at the outset of our study was that poor auditory localization could distort the fixation preference map, interfering with our ability to interpret and compare spatial fixation preference between visual and auditory tasks. However, the data suggest that this was not a problem. Figure 3, which shows the accuracy of performing the auditory task, indicates that a naïve head-fixed monkey can be trained such that there is a clear statistically signifi-

cant difference between the targeting movements to the left and right auditory targets, even without any visual feedback. Further, the fixation maps developed for the visual and auditory tasks (Figs. 5, 6) unequivocally show that fixation preference is a feature of auditory stimuli, as well; that is, noise in auditory localization did not defocus the maps to the extent that we are unable to identify a left-right difference in fixation preference for far eccentric stimuli. Essentially, a lack of fixation preference for auditory targets could be considered to be uninterpretable because of poor auditory localization, but the opposite is not true—poor auditory localization cannot manufacture fixation preference. Although the basic eye choice effect for auditory stimuli is unequivocal, it is possible that poor auditory localization may have induced some errors in the estimates of the 50% level at which fixation switch occurs and the differences in spatial width between visual and auditory stimuli (Fig. 8). Perhaps this is the reason for the large difference in spatial width of fixation switch for visual versus auditory targets between M1 and M2. Further experiments in larger samples that directly assesses both auditory localization and the equivalent oculomotor response will help address these issues.

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