Compensating for a shifting world: A quantitative comparison of the reference frame of visual and auditory signals across three multimodal brain areas

ABBREVIATED TITLE: Coordinates for auditory space in oculomotor system

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ABSTRACT

Stimulus locations are detected differently by different sensory systems, but ultimately they yield similar percepts and behavioral responses. How the brain transcends initial differences to compute similar codes is unclear. We quantitatively compared the reference frames of two sensory modalities, vision and audition, across three interconnected brain areas involved in generating saccades, namely the frontal eye fields (FEF), lateral and medial parietal cortex (LIP/MIP), and superior colliculus (SC). We recorded from single neurons in head-restrained monkeys performing auditory- and visually-guided saccades from variable initial fixation locations, and evaluated whether their receptive fields were better described as eye-centered, head-centered, or hybrid (i.e. not anchored uniquely to head- or eye-orientation). We found a progression of reference frames across areas and across time, with considerable hybrid-ness and persistent differences between modalities during most epochs/brain regions. For both modalities, the SC was more eye-centered than the FEF, which in turn was more eye-centered than the predominantly hybrid LIP/MIP. In all three areas and temporal epochs from stimulus onset to movement, visual signals were more eye-centered than auditory signals. In the SC and FEF, auditory signals became more eye-centered at the time of the saccade than they were initially after stimulus onset, but

only in the SC at the time of the saccade did the auditory signals become *predominantly* eye-centered. The results indicate that visual and auditory signals both undergo transformations, ultimately reaching the same final reference frame but via different dynamics across brain regions and time.

SIGNIFICANCE STATEMENT

Models for visual-auditory integration posit that visual signals are eye-centered throughout the brain, while auditory signals are converted from head-centered to eye-centered coordinates. We show instead that both modalities largely employ hybrid reference frames: neither fully head- nor eye-centered. In three multimodal regions involved in orienting behaviors (Intraparietal Cortex, Frontal Eye Field and Superior Colliculus) these mixed codes persist in various proportions, shifting towards eye-centeredness both across time and across brain areas. Throughout, visual signals are more eye-centered than auditory signals, until a common predominantly eye-centered code for sound finally emerges during the saccade burst in the Superior Colliculus. In summary, visual and auditory signals reach the same final reference frame but via different dynamics across brain regions and time.

KEYWORDS:

reference frame, multisensory, saccade, Frontal Eye Field (FEF), superior colliculus, (SC), intraparietal cortex, (LIP, MIP), auditory, coordinate transformations

INTRODUCTION

The locations of objects we see or hear are determined differently by our visual and auditory systems. Yet we perceive space as unified, and our actions do not routinely depend on whether they are elicited by light or sound. This suggests that sensory modality-dependent signals ultimately become similar in the lead-up to action. This study addresses how, where, and when this happens in the brain. In particular, we focus on the neural representations that permit saccadic eye movements to both visual and auditory targets.

Differences between visual and auditory localization originate at the sensory organs. Light from different directions excites different retinal receptors, producing an eye-centered map of space that is passed along to thalamic and cortical visual areas. By contrast, sound source localization involves computing differences in sound intensity and arrival time between the two ears, and evaluating spectral cues arising from the filtering action of the outer ear. These physical cues are head-centered and independent of eye movements. However, whether the code for auditory space is head-centered at any stage of the brain is unknown: eye movements affect the auditory transduction apparatus (Gruters et al., 2018), and eye position influences auditory responses in the inferior colliculus and auditory cortex (Groh et al., 2001; Werner-Reiss et al., 2003; Fu et al., 2004; Zwiers et al., 2004; Mullette-Gillman et al., 2005; Porter et al., 2006; Maier and Groh, 2010; Bulkin and Groh, 2012).

In the oculomotor system, visual and auditory stimuli are represented in the intraparietal cortex (LIP/MIP), the frontal eye field (FEF), and the superior colliculus (SC) (Figure 1A, (e.g. Paula-Barbosa and Sousa-Pinto, 1973; Drager and Hubel, 1975; Chalupa and Rhoades, 1977; Palmer and King, 1982; Wise and Irvine, 1983; Fries, 1984; Jay and Sparks, 1984; Middlebrooks and Knudsen, 1984; Meredith and Stein, 1986; Jay and Sparks, 1987a, b; Peck, 1987; Lee and Groh, 2012, 2014); (Russo and Bruce, 1994; Caruso et al., 2016); (Stricanne et al., 1996; Mullette-Gillman et al., 2005, 2009). These areas exhibit bursts of activity in conjunction with saccades (e.g. Sparks, 1978; Bruce and Goldberg, 1985; Jay and Sparks, 1987a; Barash et al., 1991a). Micro-stimulation and lesion studies suggest that they contribute to saccade generation (Robinson and Fuchs, 1969; Robinson, 1972; Schiller and Stryker, 1972; Bruce et al., 1985; Thier and Andersen, 1996, 1998; Constantin et al., 2007; Constantin et al., 2009) (Bisiach and Luzzatti, 1978; Schiller et al., 1980; Schiller et al., 1987; Sommer and Tehovnik, 1997; Dias and Segraves, 1999). Previous studies have shown that in the LIP/MIP auditory locations are not purely eye- or head-centered, but hybrid (Mullette-Gillman et al., 2005, 2009), while in the SC auditory signals are hybrid at sound onset and eye-centered during the saccade motor burst (Jay and Sparks, 1984, 1987a, b; Lee and Groh, 2012). In the FEF, changes in eye position affect auditory signals, but the auditory reference frame has not been characterized (Russo and Bruce, 1994).

In this study, we quantitatively compared auditory and visual coordinates across regions and across time. We found that the coordinates of auditory space in all three areas are mostly hybrid at sound onset, but shift to be predominantly eye-centered in the SC's motor burst. Prior to this point, auditory signals are persistently less eye-centered than visual signals, despite the fact that hybrid visual signals are common in all these areas. In summary, whereas visual coordinates undergo a gradual transition from hybrid to eye-centered, from the parietal cortex to the frontal cortex to the superior colliculus (Caruso et al., 2018a), auditory coordinates remain hybrid in all areas and only become eye-centered during the saccade burst in the SC (Lee and Groh, 2012). The results show that the coordinate transformation for visual and auditory signals reaches the same final format, but via different dynamics through LIP/MIP to FEF to SC.

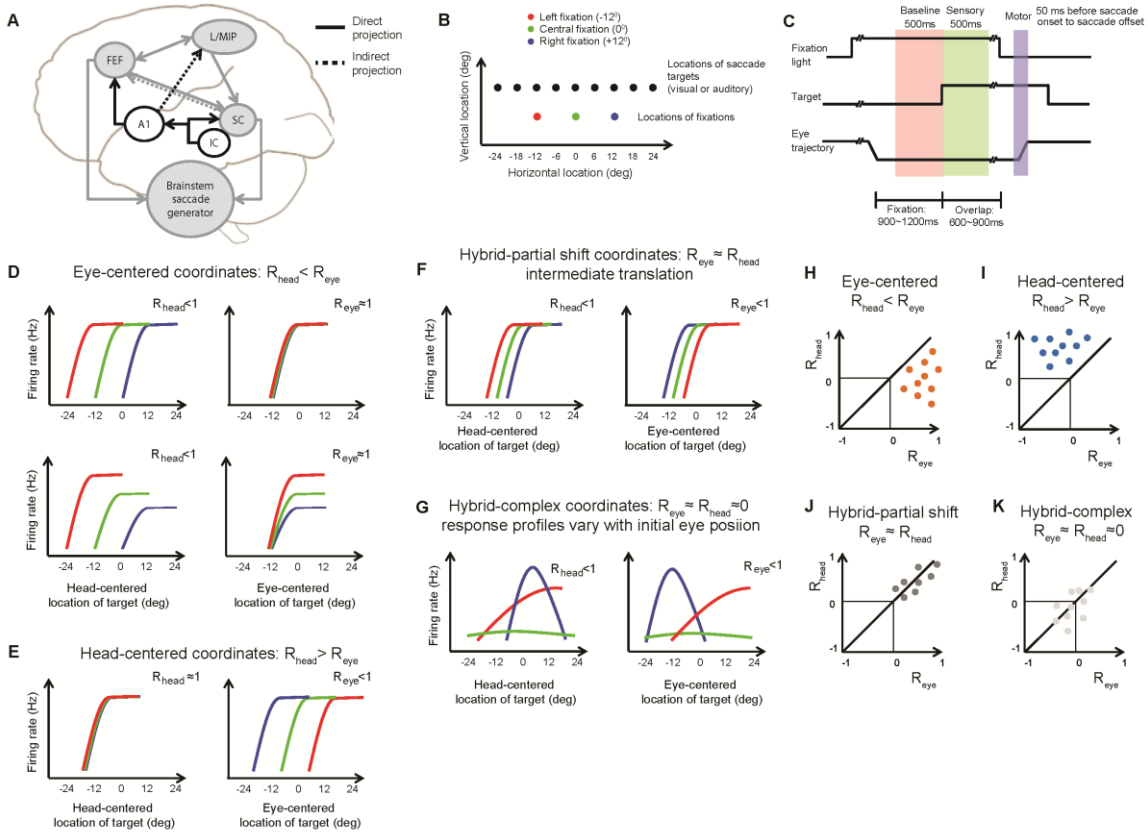

Figure 1: Rationale of the study: the brain areas, stimuli, task and quantification of reference frame. (A) *Anatomical connections and auditory inputs of LIP/MIP, FEF and SC. Whereas FEF and LIP/MIP receive auditory inputs from the primary auditory cortex (A1), SC receives auditory inputs from the inferior colliculus (IC), auditory cortex (AC) and FEF.* ***(B)*** *Locations of stimuli and initial fixations. All visual stimuli were green lights: the different colors of the fixation lights in the schematics serve to distinguish tuning curves constructed from different initial fixations in the following graphs.* ***(C)*** *Task: Each trial starts with the appearance of a light which the monkey is required to fixate. After a variable delay of 900 to 1200 ms, a visual or auditory target is presented. After a second variable delay of 600 to 900 ms, the fixation light disappears and the monkey reports the location of the target by saccading to it. (D-G) Schematics of the relative alignment of three tuning curves from three initial fixation positions plotted in head- and eye-centered coordinates.* ***(D) Eye-centered coordinates****. The three tuning curves align well in eye-centered coordinates (R_{eye}≈1, right panels), and are separated by the distance between the initial eye positions in head-centered coordinates (R_{head}≈0, left-panels). Gain differences across tuning curve do not contribute to the metric chosen to quantify their alignment (lower panels).* ***(E) Head-centered coordinates****. The pattern is the opposite of (D).* ***(F) Hybrid-partial shift coordinates****. The three tuning curves are not perfectly aligned in either head- or eye-centered coordinates, but are separated by less than the distance between the*

fixation locations in both coordinate systems. ***(G) Hybrid-complex coordinates****. Both the shape and the alignment vary with the initial eye location.* ***(H-K) Assessment of reference frame trough the statistical comparison of R_{eye} vs. R_{head} for each cell.*** *The coordinates systems are classified as* ***(H)*** *eye-centered if $R_{eye}>R_{head}$ (orange dots),* ***(I)*** *head-centered if $R_{head}>R_{eye}$ (blue),* ***(J)*** *hybrid-partial shift if $R_{eye}\approx R_{head}\neq 0$ (dark grey),* ***(K)*** *hybrid complex if $R_{eye}\approx R_{head}\approx 0$ (light gray). The quantitative comparison is based on a bootstrap analysis (see Methods).*

MATERIALS AND METHODS

The behavioral task, the neural recording procedures, and the analysis methods were identical for the three brain areas under investigation. We briefly describe the methods here, but for more details see (Caruso et al., 2016, 2018a) (Mullette-Gillman et al., 2005, 2009). All experimental procedures conformed to NIH guidelines (2011) and were approved by the Institutional Animal Care and Use Committee of Duke University or Dartmouth College. Portions of the SC and LIP/MIP data described herein have been previously presented (Mullette-Gillman et al., 2005, 2009; Lee and Groh, 2012; Caruso et al., 2018a).

Experimental Design

Six monkeys (two per each brain area) performed saccades to visual or auditory targets from a range of initial eye locations. The sequence of events in each trial was 1) onset of visual fixation stimulus, 2) saccade to location of fixation stimulus, 3) onset of visual or auditory target stimulus, 4) offset of fixation stimulus, and 5) saccade to visual or auditory target stimulus (Figure 1C). The delay (600-900 ms) between target onset and fixation stimulus offset permitted the dissociation of sensory-related activity from motor-related activity. The targets were placed in front of the monkeys at eye level (0° elevation) and at -24°, -18°, -12°, -6°, 0°, 6°, 12°, 18°, +24° relative to the head along the horizontal direction (figure 1B). The three initial fixation lights were located at -12°, 0°, +12° along the horizontal direction. The elevation of the fixation ranged from -12° to -4° below eye level and from 6° to 14° above eye level, and was chosen specifically for each session to best sample the receptive field of each neuron.

The auditory stimuli consisted of white noise bursts (band-passed between 500 Hz and 18 kHz) produced by Cambridge SoundWorks MC50 speakers at 55 dB spl. The visual stimuli consisted of small green spots (0.55 minutes of arc, luminance of 26.4 cd/m2) produced by light emitting diodes (LEDs).

Recordings

All monkeys (adult rhesus macaques) were implanted with a head holder to restrain the head, a recording cylinder to access the area of interest (LIP/MIP, FEF or SC) and a scleral search coil to track eye movements. In one of the monkeys, a video eye-tracking system (EyeLink 1000; SR Research, Ontario, Canada) substituted the search coil in a minority of

recording sessions (62 over 171,(Caruso et al., 2016)). The recording cylinders were placed over the left and right LIP/MIP (monkeys B and C), over the left or the right FEF (monkeys F and N) and over the left and right SC (monkeys W and P). Locations of the recording chambers were confirmed with MRI scans and by assessment of functional properties of the recorded cells (see (Caruso et al., 2016) (Mullette-Gillman et al., 2005, 2009).

The behavioral paradigm, and the recordings of eye gaze and of single cell spiking activity were directed by the Beethoven program (Ryklin Software). The trajectory of eye gaze was sampled at 500Hz. Extracellular activity of single neurons was acquired with tungsten micro-electrodes (FHC, 0.7 to 2.5 MOhm at 1 kHz). A hydraulic pulse microdrive (Narishige MO-95) controlled the electrodes position. A Plexon system (Sort Client software, Plexon) controlled the recordings of single neurons spiking activity.

FEF dataset

The basic auditory properties and the visual reference frame of the FEF data set have been previously described (Caruso et al., 2016, 2018a). The analysis of the auditory reference frame is novel. In total, we analyzed 324 single cells from the left and right FEF of two monkeys (monkey F, male, and monkey P, female).

LIP/MIP and SC datasets

The data from LIP/MIP and SC have been previously described (Mullette-Gillman et al., 2005, 2009) and are re-analyzed here to permit comparison between all three brain regions. In total, we re-analyzed 179 single cells from the left and right SC of two monkeys (monkey W, male, and monkey P, female), and 275 single cells from the left and right LIP/MIP of two other monkeys (monkey B, male, and monkey C, female).

Statistical Analysis

All analyses were carried out with custom-made routines in Matlab (the MathWorks Inc.). Only correct trials were considered. Responsiveness, spatial selectivity and reference frame were quantified in the same way in all datasets. These analyses have been described in detail in (Mullette-Gillman et al., 2005), (Lee and Groh, 2012; Caruso et al., 2018a), here we describe them briefly.

Spatial selectivity analysis. For all brain areas (FEF, LIP/MIP, SC), we defined three analysis windows: **baseline,** comprising the 500 ms of fixation before the target onset, **sensory period,** comprising the first 500 ms after target onset (this includes both the transient and sustained responses to visual and auditory targets) and **motor period**, from a variable time (150 ms for the LIP/MIP data, 50ms for the FEF, and 20ms for the SC) before saccade onset to saccade offset. The length of the motor period was varied across areas to sample the saccade related burst, which has a different temporal profile across areas. Saccade onset and offset were measured as the time in which the instantaneous speed (sampled at 2ms resolution) of the eye movement crossed a threshold of 25°/s. In addition to these three analysis windows, we also analyzed the entire interval between target onset and saccade using sliding windows of 100 ms, as shown in figures 4 and 5.

Neurons were considered **responsive** in the visual/auditory modality and sensory/motor periods, if a two-tailed t-test between their baseline activity and sensory/motor activity was significant. Neurons were considered **spatially selective** if the target locations modulated their firing rate during sensory/motor periods and in the visual/auditory modality. Operationally, this was measured for each period and modality, with 2 two-way ANOVAS (one in head-centered and one in eye-centered coordinates). Neurons were classified as spatially selective if either ANOVAs yielded a significant main effect for target location (5 locations, from -12° to +12° in 6° increments, defined in head- or eye-centered coordinates), or a significant interaction between the target and fixation locations (3 locations, -12°, 0°, +12°). As all these tests served as an inclusion criterion for subsequent analyses, statistical significance was set at an uncorrected level of 0.05.

Reference frame analysis. To determine the reference frame of visual and auditory signals, we quantified the relative alignment between the tuning curved computed in eye-centered or head-centered coordinates. To be specific, for each cell and modality, we computed the three response tuning curves for the three initial fixations twice: once with target locations defined in head-centered coordinates, and once with target locations defined in eye-centered coordinates. For each triplet of tuning curves, we quantified the relative alignment by defining a **reference frame index** (akin to an average correlation coefficient) according to equation 1. (Mullette-Gillman et al., 2005).

$$R = \sum_i \frac{1}{2}\left(\frac{(\overrightarrow{r_{L,i}}-\bar{r})\cdot(\overrightarrow{r_{C,i}}-\bar{r})}{|\overrightarrow{r_{L,i}}-\bar{r}|\cdot|\overrightarrow{r_{C,i}}-\bar{r}|} + \frac{(\overrightarrow{r_{R,i}}-\bar{r})\cdot(\overrightarrow{r_{C,i}}-\bar{r})}{|\overrightarrow{r_{R,i}}-\bar{r}|\cdot|\overrightarrow{r_{C,i}}-\bar{r}|}\right) \quad (1)$$

In equation 1, $r_{L,i}$, $r_{C,i}$, and $r_{R,i}$ are the vectors of the average responses of the neuron to a target at location *i* when the fixation location was left (L), right (R), or center (C). Only 5 target locations (-12, -6, 0, 6, and 12°) were included in the analysis, as these were present for all fixation positions in both head- and eye-centered frames of reference. This is a critical aspect of any reference frame comparison because unbalanced ranges of sampling can bias the results in favor of the reference frame sampled with the broader range. In the current study, this bias would have favored an eye-centered reference frame.

The **reference frame index (R)** measures the relative translation of the three tuning curves, and is relatively invariant to changes in gain as long as the sampling captures part of the receptive field. This is ensured here by including only responses classified as spatially selective in the ANOVA analysis as noted above: flat responses that do not vary with target location were not considered. The index values vary from -1 to 1, with 1 indicating perfect alignment, 0 indicating no alignment and -1 indicating perfect negative correlation (Mullette-Gillman et al., 2005; Porter and Groh, 2006; Mullette-Gillman et al., 2009).

The reference frame for each set of tuning curves was assessed by statistical comparison between the head- and eye-centered reference frame indices at the 0.05 level of significance, i.e. indices are statistically different if their 95% confidence intervals do not overlap. The

95% confidence intervals were computed with a bootstrap analysis, with 1000 iterations of 80% of data for each target/fixation combination. The classification of reference frames was as follows (Figures 1 and 3): **eye-centered**: the eye-centered reference frame index was statistically greater than the head-centered reference frame index ($R_{eye} > R_{head}$); **head-centered**: opposite pattern ($R_{head} > R_{eye}$); **hybrid-partial shift**: the two reference frame indices were both statistically greater than zero but not different from each other ($R_{eye} \approx R_{head} \neq 0$); **hybrid-complex**: the two reference frame indices were not statistically different from zero ($R_{eye} \approx R_{head} \approx 0$);

The reference frame analysis was performed during the sensory and motor periods. To compare the evolution of the reference frame in time for visual and auditory responses, we also considered the entire time range between target onset and saccade, by using a sliding window (100ms wide, sliding with steps of 50ms, see figure 3 and 4).

RESULTS

1. Overview

We compared neural activity along three dimensions, modality, brain area, and time, through an approach that integrated new with previously reported results (Mullette-Gillman et al., 2005, 2009; Lee and Groh, 2012) (Caruso et al., 2016) (Caruso et al., 2018a). We will first present the new data concerning the auditory reference frame in FEF in comparison with the visual reference frame, then turn to how visual and auditory signals change across brain areas and across time.

The task and recording techniques were the same across all brain areas: single unit recordings in 2 monkeys performing saccades to visual or auditory targets at variable horizontal location and from different initial eye positions. Figure 1B-C shows the location of the target stimuli and the timeline of the task (see Methods, (Mullette-Gillman et al., 2005, 2009; Lee and Groh, 2012) (Caruso et al., 2016) (Caruso et al., 2018a)).

Figure 1D-K shows a summary of possible reference frames exemplified by three hypothetical tuning curves (color coded by the initial gaze direction and plotted in head-centered or eye-centered coordinates). Eye-centered tuning curves align well in eye-centered coordinates (figure 1D), while head-centered tuning curves align in head-centered coordinates (figure 1F). We show two possible ways in which cells deviated from this schema. Namely, we define a *hybrid-partial* shift frame, in which tuning curves with similar shapes are not perfectly aligned in eye- or head-centered coordinates (figure 1E), and a *hybrid-complex* frame, in which tuning curves vary in shape and location when the initial fixation changes (figure 1G). This classification was performed by measuring and comparing the relative alignment of each cells' three tuning curves in head- and eye-centered coordinates with the reference frame indices, R_{head} and R_{eye}, as shown in Figures 1H-K. In eye-centered representations R_{eye} is statistically greater than R_{head}; in head-centered representations the opposite relation holds ($R_{head} > R_{eye}$); in hybrid-partial shift representations, the two indices were both statistically greater than zero but not different

from each other ($R_{eye} \approx R_{head} \neq 0$); and in hybrid-complex representations the two indices were not statistically different from zero ($R_{eye} \approx R_{head} \approx 0$).

All analyses were performed on responses modulated by target presence (t-test comparing relevant response period to baseline) and by target location (spatial selectivity test; see Methods). In other words, we included single neuron responses only if we were able to sample at least part of the receptive field during the recordings.

2. FEF individual response patterns are heterogeneous

Individually, neurons in the FEF could show considerable heterogeneity of responses patterns, for different sensory modalities and for different periods of time. Figure 2 shows the responses of 5 example cells to visual and auditory targets in the sensory and motor periods, encompassing the scope of similarities and differences.

Figure 2A-B-C shows three cells that responded to both visual and auditory targets. In these examples, the visual activity is eye-centered during both the sensory and motor periods, while the auditory activity varies across cells and in time. In the first cell, figure 2A, auditory sensory signals are head-centered (compare R_{head} and R_{eye}: 0.88 vs. 0.1) and motor signals are classified as hybrid-partial shift (R_{head}=0.60 vs. R_{eye}=0.51). In figure 2B, the auditory sensory activity is hybrid-complex, while the auditory motor activity is eye-centered. Finally, in figure 2C, both sensory and motor activities are head-centered.

Figure 2 D-E shows two cells that fired in conjunction to both visual and auditory saccades, although with different strength, but did not respond to the mere presence of a target. Such motor activity was eye-centered in both modalities for the cell in Figure 2D. For the cell in figure 2E, the reference frame was classified as hybrid-partial shift during the auditory saccades, but it was not quantified in the visual modality, as the activity during visual saccades was un-tuned (did not vary with target location).

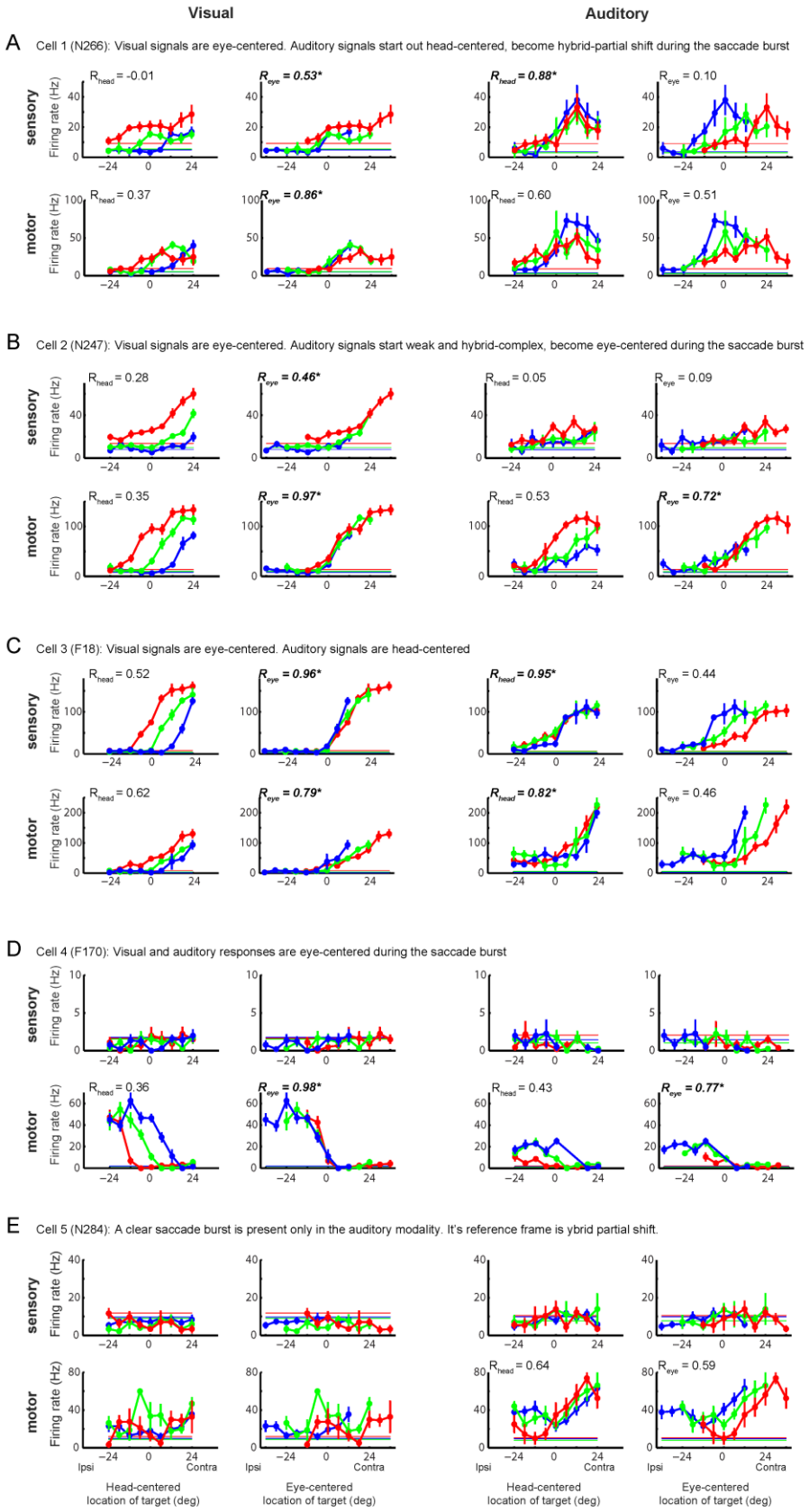
Visual
Auditory
A
Cell 1 (N266): Visual signals are eye-centered. Auditory signals start out head-centered, become hybrid-partial shift during the saccade burst
sensory
motor
Firing rate (Hz)
R_head = -0.01
R_eye = 0.53*
R_head = 0.88*
R_eye = 0.10
R_head = 0.37
R_eye = 0.86*
R_head = 0.60
R_eye = 0.51
B
Cell 2 (N247): Visual signals are eye-centered. Auditory signals start weak and hybrid-complex, become eye-centered during the saccade burst
R_head = 0.28
R_eye = 0.46*
R_head = 0.05
R_eye = 0.09
R_head = 0.35
R_eye = 0.97*
R_head = 0.53
R_eye = 0.72*
C
Cell 3 (F18): Visual signals are eye-centered. Auditory signals are head-centered
R_head = 0.52
R_eye = 0.96*
R_head = 0.95*
R_eye = 0.44
R_head = 0.62
R_eye = 0.79*
R_head = 0.82*
R_eye = 0.46
D
Cell 4 (F170): Visual and auditory responses are eye-centered during the saccade burst
R_head = 0.36
R_eye = 0.98*
R_head = 0.43
R_eye = 0.77*
E
Cell 5 (N284): A clear saccade burst is present only in the auditory modality. It's reference frame is ybrid partial shift.
R_head = 0.64
R_eye = 0.59
Ipsi
Contra
Head-centered
location of target (deg)
Eye-centered
location of target (deg)

Figure 2: Examples of responses in the FEF*. Each panel shows the tuning curves for an example cell during the sensory and motor period and in the visual and auditory modalities. The tuning curves are plotted in head-centered coordinates (left) and eye-centered coordinates (right). Note that sensory and motor panels have different scales. The horizontal lines indicate the baseline firing rate. The reference frame indexes* R_{head} *and* R_{eye} *are indicated. See main text for a full description.*

3. FEF auditory responses are predominantly hybrid

Figure 3 shows the reference frames of the visual and auditory signals in the FEF during the sensory and motor period (A-E) and in time (F-G). While individual cells could be found anywhere along the spectrum from head-centered to eye-centered (figure 2, figure 3A-D), auditory signals were for the most part hybrid, whereas visual signals were for the most part eye-centered (compare panels 3A and 3C for sensory, and 3B and 3D for motor periods). The proportion of eye-centered auditory responses increased in the motor period (from 15 to 30%), but was still only about half of the prevalence of visual eye-centered responses (59%), while the overall proportion of non-pure reference frames (hybrid-partial shift and hybrid-complex) remained stable (66 and 60%). Furthermore, the average magnitude of R_{eye} was statistically higher than R_{head} for visual signals (Figure 3E, the difference $R_{eye} - R_{head}$ was positive). For auditory signals, the difference between R_{head} and R_{eye} was not significant in the sensory time, and very small in the motor period (Figure 3E).

The analysis of reference frame at a finer time scale during the trials yielded the same results. Figures 3F and 3G plot the average population values of R_{eye} and R_{head} across time (100 ms bins). Visual responses were predominantly, though not fully, eye-centered from target onset to saccade completion, while auditory responses only slightly shifted towards eye-centeredness at the time of a saccade.

In summary, whereas visual signals in the FEF were consistently but weakly eye-centered over the course of a trial, auditory signals remained hybrid over time, with a minimal change during the saccade to the location of the sound.

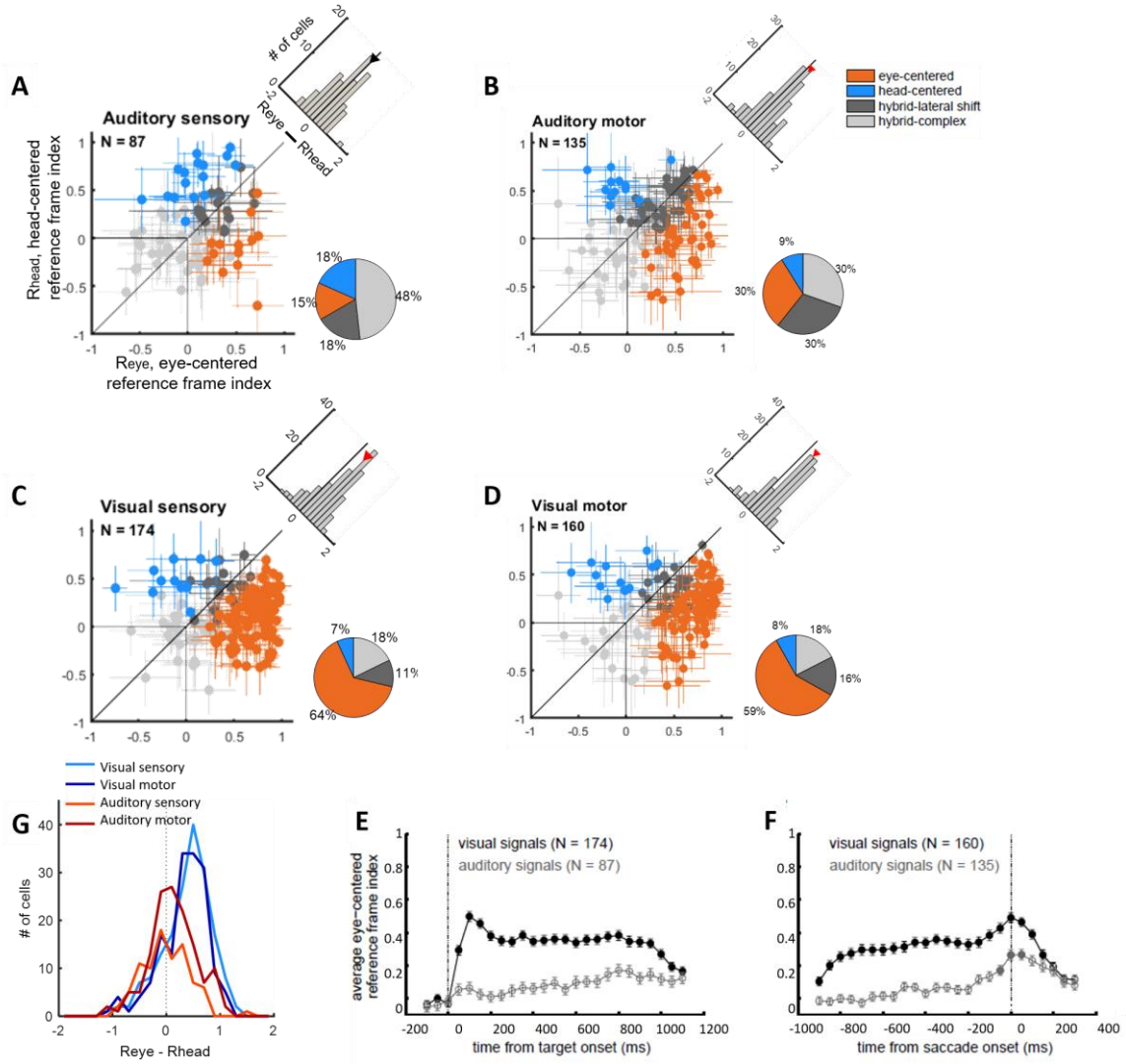

Figure 3: FEF auditory and visual reference frame (A-D) *The reference frame indexes in head-centered and eye-centered coordinates (R_{head} and R_{eye}) are plotted in each modality and time window:* ***(A)*** *auditory sensory,* ***(B)*** *auditory motor,* ***(C)*** *visual sensory,* ***(D)*** *visual motor. Responses are classified and color coded as eye-centered, head–centered, hybrid-partial shift and hybrid-complex, based on the statistical comparison between their R_{eye} and R_{head} (see Methods). The pie charts summarize the proportion of responses in the different classes. The histogram inserts show the difference ($R_{eye} - R_{head}$) for the populations of cells (positive values mean stronger eye-centered representations across the population). The triangles indicate the mean values of the distributions (in red if significant: ttest, p-value <0.05)* ***(E)*** *Distributions of the difference ($R_{eye} - R_{head}$) for all modalities and time windows (same data as the histogram inserts in A-D, replot to allow visual comparison).* ***(F-G)*** *Time course of the average (mean ± SE) reference frame index*

*in eye-centered coordinates (R_{eye}) for the visual and auditory populations, aligned to target onset **(E)** and saccade onset **(F)**. The R_{eye} are calculated in bins of 100ms, sliding with a step of 50ms. Filled circles indicate bins in which R_{eye} was significantly different from R_{head} (as assessed with a t-test, p-value <0.05). Visual data were previously presented in Caruso et al. 2018*

4. Comparison with LIP/MIP and SC

To investigate the evolution of the coordinates for auditory space across the areas that contribute to saccade generation, we compared the auditory reference frame in the FEF to those in the LIP/MIP and SC. We used the evolution of the visual reference frame across the same three regions as benchmark for the pattern of results found in the auditory modality.

Figures 4 and 5 show the reference frame of neurons in the LIP/MIP and SC during the sensory periods and during the saccade related bursts, similar to Figure 3 for the FEF. In the LIP/MIP, the auditory signals are predominantly hybrid in both time windows. In contrast, in the SC the proportion of purely eye-centered auditory signals increases during the motor period to more than 60%.

Figure 6 shows the time course of the average eye-centered reference frame index R_{eye} across all areas. As described in (Caruso et al., 2018a), the visual reference frame in the FEF is persistently intermediate between the strong eye-centered coding in the SC and the hybrid coding in the LIP/MIP (Mullette-Gillman et al., 2005, 2009; Lee and Groh, 2012). This pattern is clear in Figure 6A: the FEF data persistently lie between the SC and LIP/MIP. The auditory reference frame differs from the visual reference frame in the way it unfolds across areas and over time (figure 6B). Contrary to the visual modality, in the auditory modality there is a prevalence of hybrid representations in all regions until the saccade burst. Only during the saccade burst and only in the SC, we observed a clear shift towards eye-centered coordinates, while the LIP/MIP and FEF displayed only negligible changes and remained largely hybrid (figure 6B right side). To give a measure of the eye-centeredness of auditory signals in the SC, Figure 6C shows a comparison of the average R_{eye} for visual and auditory signals in the SC and FEF: auditory signals in the SC underwent a considerable shift in time from being hybrid to eye-centered, eventually becoming more eye-centered than visual signals in the FEF.

In summary, the coordinate transformation for visual and auditory signals appear to reach a final eye-centered format via different dynamics through LIP/MIP and FEF to SC: visual signals gradually shift from hybrid to eye-centered, while auditory signals remain hybrid throughout the two cortical levels and only become eye-centered at the SC's motor command stage.

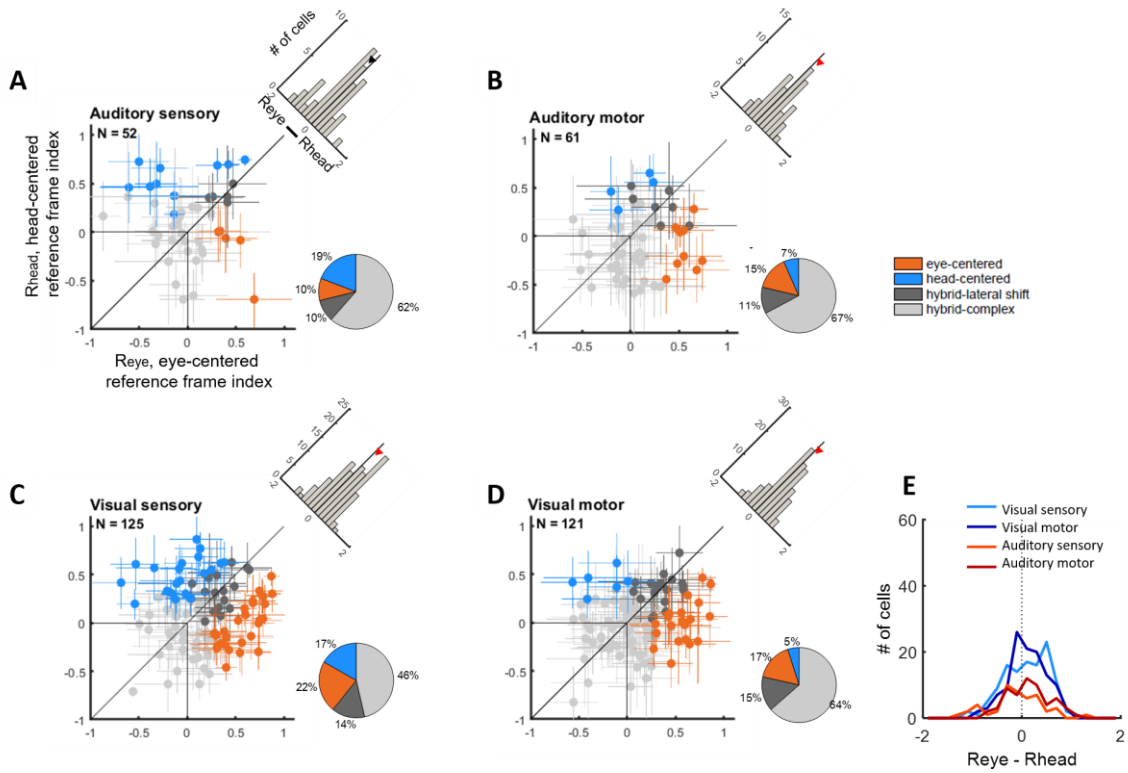

Figure 4: LIP/MIP auditory and visual reference frame. *Same as figures 3 and 4 but for signals in LIP/MIP. Data originally reported in (Mullette-Gillman et al., 2005, 2009).*

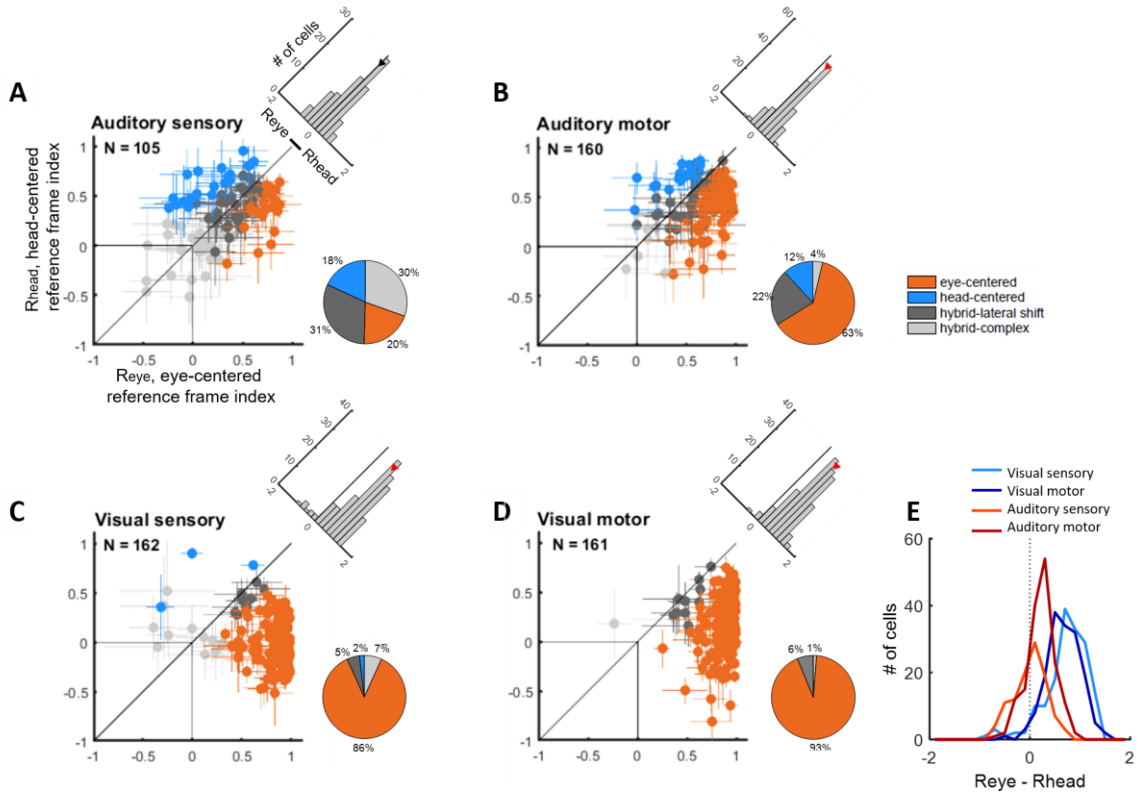

Figure 5: SC auditory and visual reference frame. *Same as figures 3 and 4 but for signals in SC. Data originally reported in (Lee and Groh, 2012).*

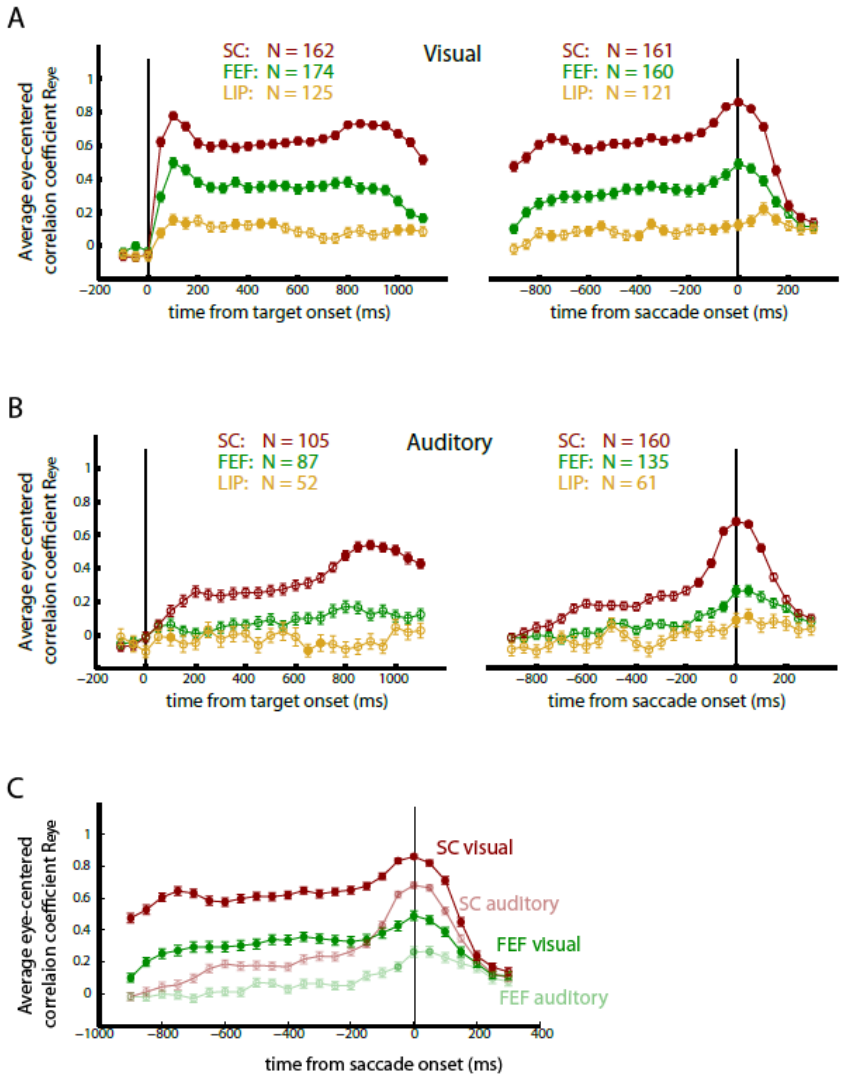

Figure 6: Time course of the eye-centered reference frame indexes in LIP/MIP, FEF, SC. *The average eye-centered reference frame index, R_{eye} (mean ± SE) was computed in 100ms bins (sliding with a step of 50ms). Filled circles indicate that R_{eye} was statistically larger than R_{head} (see Methods).* ***(A)*** *Visual signals, aligned to the target onset (left) and to the saccade onset (right).* ***(B)*** *Auditory signals, aligned to the target onset (left) and to the saccade onset (right).* ***(C)*** *Comparison of visual and auditory signals in the FEF and SC aligned to the target onset. Same data as in panel A and B, reproduced to permit visual comparison.*

DISCUSSION

We investigated how the reference frames for auditory and visual space unfold across three monkeys' brain areas (LIP/MIP, FEF, and SC), and across time during a sensory guided saccade task. In all areas considered, most neurons did not encode auditory sensory signals in neat eye-centered or head-centered reference frames, but rather employed hybrid codes in which the neural responses are modulated by both head-centered and eye-centered locations. To a lesser degree, this was also true of visual sensory responses, although they were more eye-centered than auditory signals. During the auditory saccade burst, the proportion of eye-centered signals increased in the SC and the FEF, but only in the SC and only at the time of a saccade, auditory signals were primarily eye-centered, yielding a code similar to visual motor signals in the same area. In short, both visual and auditory signals converge to a common eye-centered code in the SC, but with different dynamics across time and brain area.

To quantify single neuron reference frames, we adopted a correlation approach and measured the degree to which neural signals were anchored to the locations of the eye or the head when these locations were experimentally misaligned. We focused primarily on measures of effect size and proportions of the neural population, in addition to statistical significance at the level of individual neurons. To avoid bias in the estimates of single neurons' reference frame, we sampled space symmetrically in both coordinate systems, eliminating any "extra" locations that existed in one reference frame but not the other. Without such balanced sampling, the estimate would be erroneously high in favor of the more extensively sampled reference frame. For example, early studies in intraparietal cortex concluded that visual representations were eye-centered with an eye position gain modulation (e.g. (Andersen et al., 1985)) but a later study suggested that this finding may have been due to inadequate sampling in a head-centered frame of reference (Mullette-Gillman et al., 2009).

The limitations of our approach are related to the possibility that systematic changes in neural responses across populations and task conditions might affect measures of neural signals' alignment. For example, low response strength, high trial-to-trial variability, and low spatial selectivity would each reduce the correlation measures in both coordinate systems, resulting in more hybrid estimates. Any such hypothetical difference occurring systematically between brain areas or sensory modality could contribute to the effect size of the measured differences in reference frames. However, they could not fully explain the observed pattern of results, as we did characterize strong eye-centered and head-centered representations in all regions and modalities, indicating that multiple reference frames were active, beyond hybrid signals. Indeed, there is consensus in the literature that eye movements or changes in eye position affect visual and auditory signals in all of the areas we tested here (Van Opstal et al., 1995; Klier et al., 2001; DeSouza et al., 2011; Lee and Groh, 2012; Sadeh et al., 2015), (Jay and Sparks, 1984, 1987b, a), (Cassanello and Ferrera,

2007) (Sommer and Wurtz, 2006; Zirnsak and Moore, 2014; Zirnsak et al., 2014).(Keith et al., 2009; Sajad et al., 2015; Sajad et al., 2016). (Russo and Bruce, 1994), (Andersen and Mountcastle, 1983; Andersen et al., 1985, 1987; Andersen and Zipser, 1988; Zipser and Andersen, 1988; Andersen et al., 1990; Barash et al., 1991a, b; Duhamel et al., 1992; Colby et al., 1993; Stricanne et al., 1996; Batista et al., 1999; Cohen and Andersen, 2000; DeSouza et al., 2000; Berman et al., 2005; Colby et al., 2005; Heiser et al., 2005; Mullette-Gillman et al., 2005; Heiser and Colby, 2006; Berman et al., 2007; Mullette-Gillman et al., 2009)).

Differences in how spatial information is coded across sensory systems pose problems for the perceptual integration of the different sensory inputs that arise from a common source, such as the sight and sound of someone speaking. Since the discovery of auditory response functions that shift with changes in eye position (Jay and Sparks, 1984), the model for visual-auditory integration has been that visual signals remain in eye-centered coordinates and auditory signals are converted into that same format. Some experimental results however cannot be explained under this view. In particular, "pure" reference frames, representations in which the responses are clearly better anchored to one frame of reference over all others, have proved surprisingly rare. In the experiments described here, only the SC contains strongly eye-centered representations, for visual signals during both sensory and motor periods, and for auditory signals only in the motor period. All other observed codes appear to be at least somewhat impure, with individual neurons exhibiting responses that are not well captured by a single reference frame as well as different neurons employing different reference frames across the population. Hybrid, intermediate, impure or otherwise idiosyncratic reference frames have also been observed in numerous other studies (Stricanne et al., 1996; Avillac et al., 2005; Mullette-Gillman et al., 2005; Schlack et al., 2005; Mullette-Gillman et al., 2009; Chang and Snyder, 2010; Chen et al., 2013).

A possible explanation for such hybrid states is that coordinate transformations might be computationally difficult to achieve and hybrid codes represent intermediate steps of a coordinate transformation that unfolds across brain regions and time. Our results lend empirical support to this notion of a gradual, transformative process. However, why such a transformation should unfold across time and brain areas is unclear from a theoretical perspective, since there exist computational models of coordinate transformations in one step (Groh and Sparks 1992). Thus, the computational or evolutionary advantages of such a system remain unclear. Regardless, hybrid codes contain the necessary information to keep track of where targets are with respect to multiple motor effectors, and may therefore facilitate flexible mappings of multiple behaviors or computations on the same stimuli in different contexts (Bernier and Grafton, 2010; Crespi et al., 2011). In this scenario, it is plausible that visual and auditory signals become maximally similar in the SC at the moment in which a particular behavioral response, namely a saccade, is executed, as the SC is a key control point in the oculomotor system, encoding not only target location in

abstract, but also controlling the time profile and dynamic aspects of saccadic movements (Stanford et al., 1996; van Opstal and Goossens, 2008).

The exact mechanism by which auditory signals become predominantly eye-centered in the SC is unknown. Our data do not resolve whether a coordinates' transformation unfolds locally within the SC, or whether it reflects preferential sampling of eye-centered auditory information through mechanisms of gating or selective read-out. Indeed, the SC gets auditory inputs primarily from FEF and Inferior Colliculus (IC), both containing a variety of simultaneous auditory representations, from head-centered to eye-centered (see figure 3 and (Porter et al., 2006)).

Apparent mixtures of different reference frames could also be a consequence of the use of different coding formats across time, with individual neurons switching between different reference frames for different individual epochs of time. Response measures that involve averaging across time and across trials would yield apparently hybrid or intermediate reference frames when in reality, one reference frame might dominate at each instant in time. We recently presented evidence that neurons can exhibit fluctuating activity patterns when confronted with two simultaneous stimuli and suggested that such fluctuations may permit both items to be encoded across time in the neural population (Caruso et al., 2018b). Similar activity fluctuations might permit interleaving of different reference frames across time, with the balance of which reference frame dominates shifting across brain areas and across time. At the moment, this hypothesis is difficult to test because the statistical methods deployed in (Caruso et al., 2018b) require being able to ascertain the responses to each condition in isolation of the other, but every reference frame exists concurrently. Novel analysis methods, perhaps relying on correlations between the activity patterns of simultaneously recorded neurons, are needed to address this question.

A possible clue that activity fluctuations may be an important factor comes from studies of oscillatory activity. If neural activity fluctuates on a regular cycle and in synchrony with other neurons, the result is oscillations in the field potential. Indeed, studies of the coding of tactile stimuli in saccade tasks provide evidence for different reference frames encoded in different frequency bands, in different brain areas and at different periods of time. In the context of saccade generation, oscillations could allow the selection of one reference frame by adjusting the weights of spatial information received from different populations, in essence flexibly recruiting eye-centered populations (Buchholz et al., 2011; Haegens et al., 2011; Buchholz et al., 2013, 2014).

In summary, our results suggest that new ways of thinking about how visual and auditory space are integrated, beyond simplistic notions of a single pure common reference frame and registration between visual and auditory receptive fields are needed.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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