Individual similarities and differences in eye-movement-related eardrum oscillations (EMREOs)

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Abstract

A unique type of low-frequency otoacoustic emission (OAE) time-locked to the onset (and offset) of saccadic eye movements was recently discovered in our laboratory (Gruters et al., 2018). The specific underlying mechanisms that generate these eye-movement-related eardrum oscillations (termed EMREOs) and their possible role in auditory perception are unknown. Clues to both the drivers of EMREOs and their purpose can be gleaned by examining responses in normal hearing human subjects. Do EMREOs occur in all individuals with normal hearing? If so, what components of the response occur most consistently? Understanding which attributes of EMREOs are similar across participants and which show

more variability will provide the groundwork for future comparisons with individuals with hearing abnormalities affecting the ear's various motor components. Here we report that in subjects with normal hearing thresholds and normal middle ear function, all ears show (a) measurable EMREOs, (b) a phase reversal for contra- versus ipsilaterally-directed saccades, (c) a large peak in the signal occurring soon after saccade onset, (d) an additional large peak time-locked to saccade offset and (e) evidence that saccade duration is encoded in the signal. We interpret the attributes of EMREOs that are most consistent across subjects as the ones that are most likely to play an essential role in their function. The individual differences likely reflect normal variation in individuals' auditory system anatomy and physiology, much like traditional measures of auditory function such as auditory-evoked OAEs, tympanometry and auditory-evoked potentials. Future work will compare subjects with different types of auditory dysfunction to population data from normal hearing subjects.

Introduction

Eye movements are critical to linking vision and spatial hearing. Sounds create spatial cues across the head and ears while visual stimuli are detected based on patterns of light impinging on the eye (e.g. e.g. Groh and Sparks, 1992; Blauert, 1997; Groh, 2014). Every eye movement shifts the relative relationship between the visual and auditory reference frames. Thus, information about angle of the eye with respect to head/ears is crucial for integrating the locations of auditory and visual stimuli. However, exactly how this occurs is not yet known.

We previously identified a unique type of otoacoustic emission that may play a role in this process (Gruters et al., 2018; Murphy et al., 2020; Lovich et al., 2022). Unlike traditional otoacoustic emissions that can occur spontaneously or in response to auditory stimuli, eye movement-related eardrum oscillations (EMREOs) are time-locked to the onset and show phase resetting at the offset of saccadic eye movements. Both initial eye position and change

in eye position parametrically impact the magnitude and phase of EMREOs (Gruters et al., 2018; Murphy et al., 2020; Lovich et al., 2022). Therefore, eye-movement-related information is present at the auditory periphery, providing the auditory system early access to signals necessary for communication with visual maps of space. The mechanism(s) underlying such signals may alter auditory transduction in an eye-movement dependent fashion and could contribute to previous neurophysiological observations of eye-movement-related modulation of the auditory pathway (Groh et al., 2001; Werner-Reiss et al., 2003; Fu et al., 2004; Zwiers et al., 2004; Porter et al., 2006; Maier and Groh, 2010; Bulkin and Groh, 2012a, b; O'Connell et al., 2020).

Our initial study suggested that there are individual differences in the precise nature of this signal (Gruters et al., 2018). Given that all individuals with normal or corrected-to-normal vision, hearing, and eye movements are confronted with the same computational challenge of achieving spatial perceptual stability between vision and hearing across eye movements, the similarities and differences in the EMREOs observed across normal participants can provide clues as to what particular aspects of these signals are relevant to that underlying computational process. Furthermore, like conventional OAEs, EMREOs could eventually have clinical relevance for diagnosing the nature of hearing deficits or auditory-visual integrative dysfunction. Accordingly, in this work, we seek to ascertain which aspects of the EMREO signal are most consistent across normal hearing individuals and which exhibit the most variability. An overarching goal is to establish norms for EMREO data collection and analysis and set the stage for future clinical research in this area.

We report here that certain basic properties of EMREOs were present in all participants: specifically, varying phase and amplitude based on the direction and amplitude of the associated eye movement. Generally, EMREOs are larger when saccades are made to the hemi-field contralateral to the recorded ear than to the ipsilateral field. Individuals varied in the maximum amplitude of their EMREO signals. There was also a slight jitter in the latency of the

maximum peaks of the EMREO across normal hearing individuals, but the pattern of latency changes in the EMREO relating to saccade length/duration is maintained within individual subjects' responses. Finally, there is greater response variability across subjects for ipsilateral compared to contralateral saccades.

Identifying and quantifying aspects of EMREO signals that are similar across normal hearing subjects as we have done here will ultimately allow comparisons to responses in individuals with different types of auditory system dysfunction. These comparisons should provide insight into the mechanisms that generate and/or modulate the EMREO response as well as provide a means for assessing the feasibility of the EMREO as a future clinical measure of auditory-visual integration.

Methods

Subjects: This work is part of a larger study that has tested approximately 40 normal hearing subjects. Using ER-10B+ microphones coupled with ER-10 foam ear tips, we have successfully recorded EMREOs in all normal hearing individuals who completed a visual saccade task (~40 subjects). There were a few instances where subjects were sleepy or unable to remain focused on the task long enough to collect sufficient data for analysis during the typical number of recording sessions. Whenever possible, we asked subjects to return for additional testing at a later date. In all cases where adequate data was collected, we were able to observe EMREOs.

In this study, a total of 10 subjects (20 ears, 6 female, 4 male, 18-39 years old) completed the horizontal-vertical task (Figure 1). All study procedures involving subjects were approved by the Duke Institutional Review Board and all subjects received monetary compensation for their participation in the study. All subjects had hearing thresholds within normal limits (air conduction thresholds < 25 dB HL @250, 500, 1k, 2k and 4kHz, determined

through pure tone audiometry using a Maico-25 screening audiometer) and normal middle ear function based on standard 226Hz probe tone tympanometry and acoustic reflexes (Maico touch Tymp MI-24). Screening audiograms, baseline tympanograms and acoustic reflexes were obtained prior to or on the first day of testing and middle ear function was assessed with tympanometry on each day of data collection. For all subjects, no significant variation in tympanograms were noted during the testing window.

Tasks: Data are presented here from a visually guided saccade task involving a central fixation point and targets arrayed in the horizontal and vertical dimensions. Targets were spaced 3° apart and spanned a range of +/- 18° horizontally and +/- 12° vertically (Figure 1). As previously (Lovich et al 2022, Murphy et al 2020), the fixation point was illuminated for 750ms (until the target appeared). In turn, the green target stayed on for a further 750ms before turning red, signally the end of the trial. No external sounds were presented at any time during data collection.

Subjects performed this task while seated in a darkened sound-insulated booth (Acoustic Systems). The stimuli were presented on a monitor positioned 70cm away; head position was stabilized using a chin rest. Eye position and ear canal microphone data were recorded simultaneously (see Equipment) while subjects performed the saccade task. Data collection occurred on multiple days, typically over two one-hour sessions per subject. Recordings were made in blocks of ~125 trials each, presented pseudorandomly. Each test session consisted of 5-6 blocks, with breaks offered between blocks. Recording time for each block was approximately five minutes and each test session lasted approximately one hour, including instructions, eye calibrations, microphone assessments, and rest periods. Data were combined across blocks and sessions.

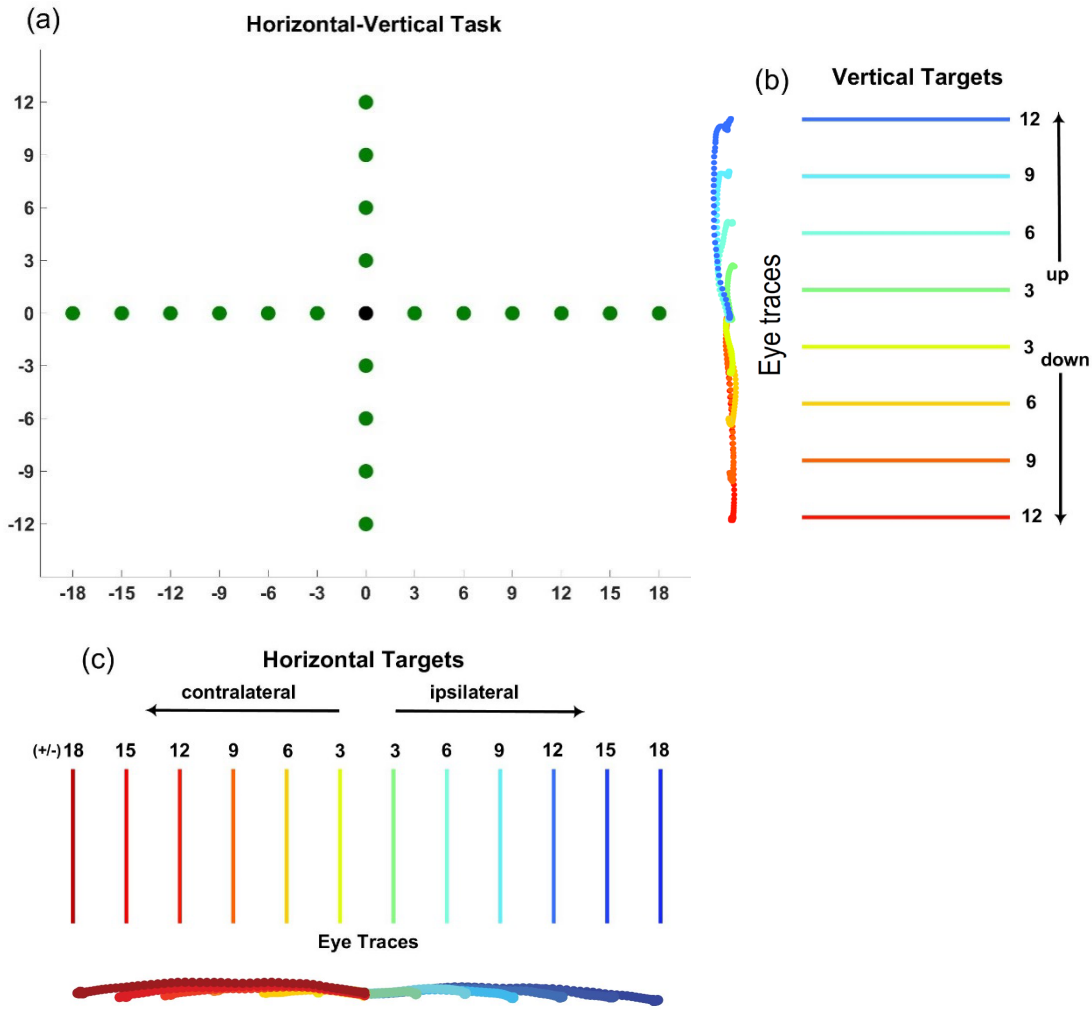

Figure 1. (a) Schematic of horizontal-vertical task and color schemes for subsquent presentation of results as a function of visual target locations. Subjects were asked to fixate on a center point on the screen (black dot) until it disappeared and a target (green dot) appeared. Subjects then saccaded to the target and held fixation until the target turned red, signaling the end of the trial. (b, c) The color code represents saccade direction to target locations. For vertical targets (b), the color code for saccade direction indicates either upward or downward movement and does not change between left and right ear recordings. For horizontal targets (c), the color code for saccade direction is relative to the ears, not to visual space. Contralateral targets are in the hemi-field opposite the ear canal recording and ipsilateral targets are in the same hemi-field as the ear canal recording. Data will be plotted according to this color scheme for Figures 4 and 5.

Data collection equipment: The entire data collection process was managed through Matlab 2017b and Psychtoolbox on a Mac Pro computer.

Microphone recordings were obtained in both ear canals simultaneously during all testing sessions using Etymotic Research ER10B+ Low Noise Microphone Systems, coupled with ER-10 foam ear tips. A Focusrite Scarlett 2i2 low-latency audio interface provided audio capture and playback at 48 kHz sampling rate through the Etymotic system. Microphone data were downsampled from 48 kHz to 2 kHz prior to analysis to reduce processing time. This is well above the Nyquist frequency for the range of interest (<100Hz). Each subject's microphone recording values are Z-scored or expressed in units of standard deviation relative to the variability observed in a 20-30ms baseline window at least 40ms prior to saccade onset; see Gruters et al., 2018 for an evaluation of EMREO magnitude in units of dB SPL.

To ensure stable microphone function across all testing sessions, the Etymotic ER-2 earphones were evaluated using a sequence of tones prior to each test session as well as before each test block (pure tone sweeps from 10-1600Hz: 10Hz steps for 10-200Hz, 100Hz steps for 300:1000Hz, 200Hz steps for 1200-1600Hz). Before the subject arrived, we assessed the function of the microphone system using a device to simulate average ear canal volume (A 3 ml syringe tip was cut off and replaced with an ear tip typically used with the microphone system. The syringe stopper was pulled to a volume of 1.25 cm^3 and a small amount of cotton wadding (.25 cm^3) was added to simulate the soft tissue of the ear canal.). Microphone measurements were considered valid if the input-output of the tone sequence during this pre-testing evaluation routine matched the standard set for all pre-testing evaluations.

The tone sequence also played prior to each test block, with microphones placed in the subject's ears, to evaluate microphone response stability throughout the testing session.

Microphone output recorded during the tone sweeps was monitored. Any changes (e.g., indicating the possibility an earbud had become dislodged) caused the associated recording block to be discarded.

Eye tracking information was recorded with the SR Research Eyelink 1000 system at a 1kHz sampling rate. Eye tracking was calibrated at the beginning of each test session using the Eyelink 1000 calibration program and again if the subject moved position or paused for a break in data collection.

Analysis: As in earlier work (Lovich et al., 2022; Murphy et al., 2020), we smoothed the eye tracking data using a lowpass discrete filter with a 7ms window. Microphone recordings were synchronized with eye tracking data at saccade onset and offset, defined based on the third derivative of eye position, or jerk. The point where change in eye acceleration was greatest was marked as saccade onset while the point where change in eye deceleration was greatest was marked as saccade offset. Trials were first excluded based on saccade performance and then on quality of the microphone recordings. For eye tracking, trials were excluded if subjects made more than a single saccade to reach the target, if eye tracking signal was lost during the trials (e.g., from blinks), if eye movement was significantly slower than an average saccade, or if the saccade curved more than 4.5^{o}. Finally, a minimum fixation of 200ms before and after the saccade was required in order to include a trial in analysis. In the horizontal-vertical task, the majority of trials that did not meet criteria for inclusion were due to issues with eye tracking, eliminating 19% of trials. This number is slightly higher than previously reported from our lab, likely due to the specifics of this task (visual targets for the horizontal-vertical task are more closely spaced, with only 3° separation, compared to earlier tasks with 6° target separation). Once the criteria for eye tracking were met, a modest number of trials (1%) were excluded based on integrity of microphone recordings. Individual trials were excluded when the whole trial RMS value was +/-10 SD or greater than the average RMS value for the entire trial block. Following application of exclusion criteria, there were between 20-60 trials per target for each

subject (average of ~40 trials per target for each subject). The Z-scoring of the microphone values described above under "Data collection equipment" was computed after these exclusion criteria were applied.

Statistical evaluation.

"To statistically evaluate EMREOs in individual subject ears, we fit the microphone data for each ear using the following regression equation:

$$Mic(t) = B_{\Delta H}(t)\ \Delta H + B_{\Delta V}(t)\ \Delta V + C(t) \qquad \text{Eq 1}$$

where ΔH and ΔV correspond to the respective changes in eye position associated with a given trial and were measured in degrees. The slope coefficients $B_{\Delta H}$ and $B_{\Delta V}$ are time-varying and reflect the dependence of the microphone signal on the respective eye movement parameters and have units of standard deviation per degree. The term $C(t)$ contributes a time-varying "constant" independent of eye movement metrics, with units of standard deviation. It can be thought of as the best fitting average oscillation across all eye movements. We used the measured values of change in eye position for this analysis rather than the associated fixation and target locations so as to incorporate trial-by-trial variability in fixation and saccade accuracy" (Lovich et al., 2022).

We determined whether an individual subject's ear exhibited a statistically significant EMREO in a two-stage process. First, we evaluated the time-varying p-values of the regression fits (p(t)) during a window starting 5ms before saccade onset and ending 70ms after saccade onset; this corresponds to 149 data points given the downsampling of the microphone data. These data points are not independent of one another, so conventional Bonferroni correction would not be appropriate. Accordingly, we evaluated whether the proportion of p-values less than 0.05 was greater than the 5% that would be expected by random chance. We adopted a criterion of 10%, i.e. if more than 10% of these p-values were below 0.05, we considered the subject ear to have a statistically significant EMREO. This 10% threshold was

adopted because a binomial test to evaluate whether one proportion is larger than another reaches a significance level of $p<0.01$ when considering 10% vs. 5% in a sample size of 149 values.

Results

Statistical significance of individual EMREOs via regression

All subjects tested in this study showed statistically significant EMREOs per the test described in *Methods: Statistical evaluation*. Briefly, this involved assessing the influence of the horizontal and vertical displacement of the eyes on the recorded microphone signal via time-varying regression (Eq 1). We evaluated the time varying p-values of this regression ($p(t)$) during a window of -5 to 70ms, when aligned to saccade onset. Any ear that exhibited $p(t)<0.05$ for more than 10% of this time window was considered statistically significant. As shown in Table 1, all 20 ears in 10 subjects exhibited statistically significant EMREOs when aligned to saccade onset (range 22-85%). A similar process was adopted to evaluate saccade offset-aligned EMREOs, with an evaluation window of -25 to 50ms before/after saccade offset. The range of observed values was 18-83%, again reaching significance for all 20 ears. (Table 1).

	Onset-aligned		**Offset-aligned**	
	Left Ear	Right Ear	Left Ear	Right Ear
S05	85.23	38.15	83.22	51.01
S15	53.02	46.99	23.49	33.56
S17	53.69	26.51	69.13	21.48
S24	51.68	19.68	46.98	51.01
S45	55.71	39.76	41.61	35.57
S49	55.69	32.53	28.19	40.27
S50	63.76	61.45	53.02	35.57
S52	64.43	61.85	60.39	69.13
S71	83.22	42.17	48.99	18.12
S73	22.15	37.35	21.48	29.53

Table 1. Percentage of analysis time window where p-values of the regression fits were less than 0.05. Significance for greater than 10% of the analysis window was used to determine the presence of an EMREO for that ear (onset-aligned analysis window: -5 to 70ms relative to saccade onset; offset-aligned analysis window: -25 to 50ms relative to saccade offset; see Methods).

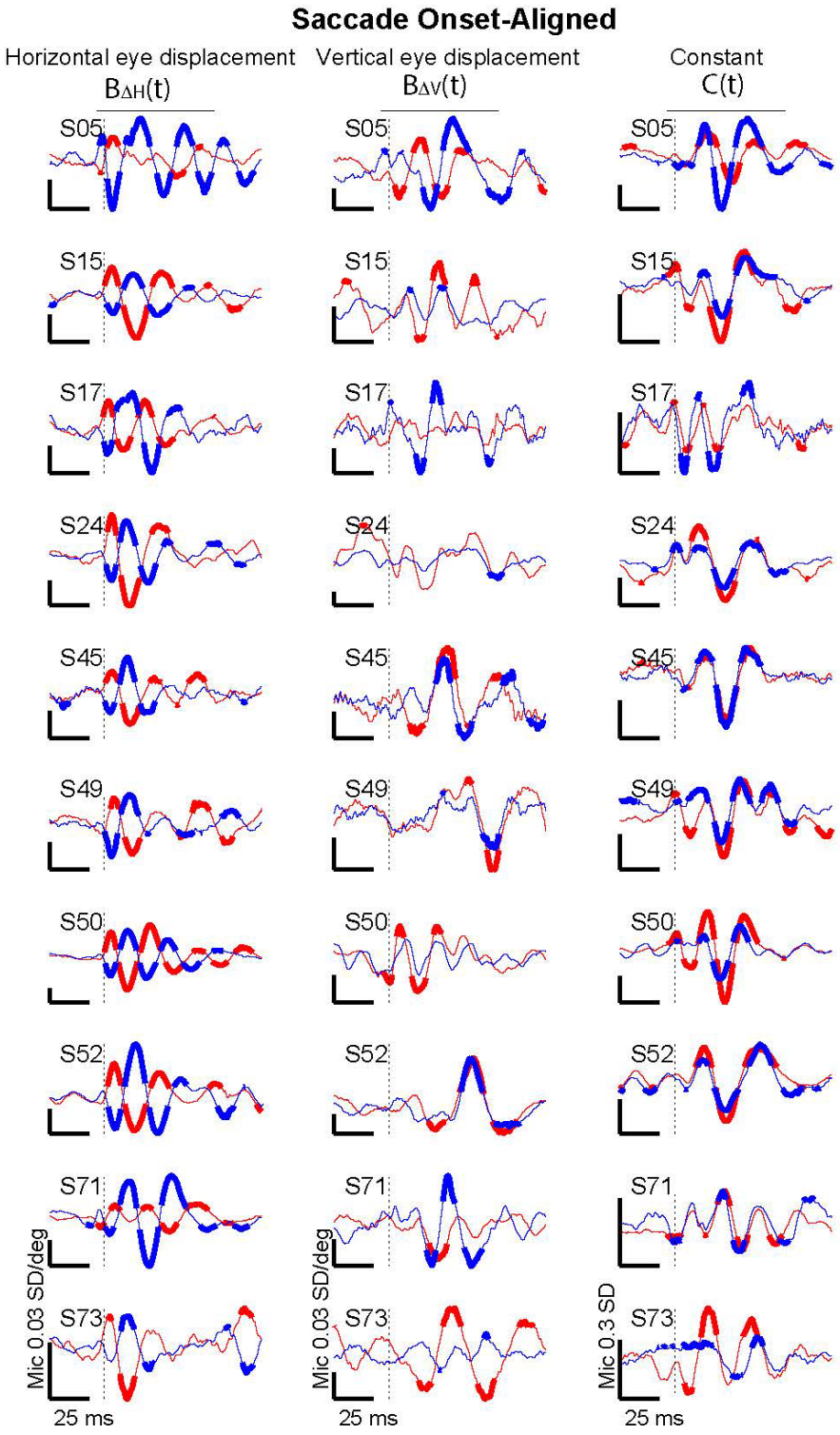

Figure 2. Coefficients of linear regression fits for individual subjects, aligned to saccade onset. Blue traces are left ear data and red traces are right ear data. Thick line segments indicate epochs of time in which the corresponding regression coefficient differed from zero (p<0.05). The time window for analysis of aggregate statistical significance as provided in Table 1 is marked by the horizontal black bar at the top of each column (-5 to 70ms with respect to saccade onset). Y-axis units are standard deviations per degree (horizontal and vertical eye displacement columns) or simply standard deviations ("constant" column) and vary across panels as indicated by the calibration bars.

Horizontal and vertical coefficients of regression fits across time

Each coefficient of the regression equation can be plotted over time. Figure 2 shows the slope coefficients for horizontal eye displacement (left column), vertical eye displacement (middle column) and the time-varying constant (right column), aligned to saccade onset. In the left column, all subjects show an oscillatory pattern in relation to the horizontal displacement of the eyes with the peaks of the oscillations significantly different from zero for all subjects (thick lines, $p<0.05$). Note the phase of the oscillations is opposite for the two ears, thus encoding horizontal saccade direction relative to the recorded ear.

Compared to the horizontal component, the time where vertical eye displacement (middle column) differs significantly from zero is much shorter and the latencies of the significant regions are not the same across subjects. However, all but one subject (S24) has a waveform peak within the EMREO analysis time window that is significantly different from zero.

For the time-varying constant component (right column), several subjects show tri-phasic waveforms (S05, S24, S45, S49, S50, S52 and S73 right ear), while S15, S17 and S71 show multiple positive and negative peaks that are significantly different from zero. This portion of the regression fits can be thought of as the basic EMREO waveform upon which dependency on horizontal and vertical eye displacement is superimposed.

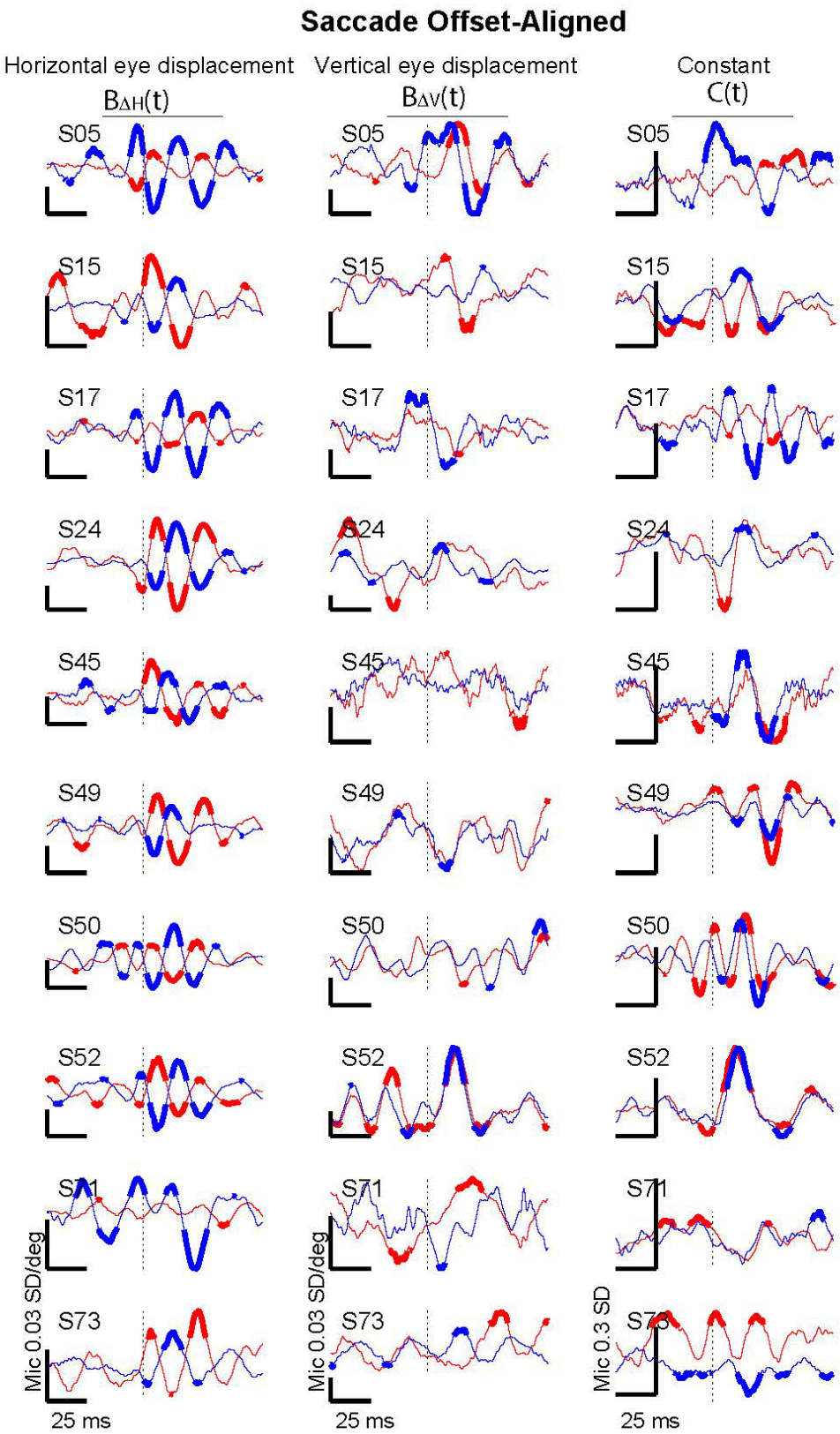

Figure 3: Coefficients of linear regression fits to saccade-offset-aligned responses. Conventions same as Figure 2. The time window for evaluation of aggregate statistical significance of regression coefficients (Table 1) was defined as -25 to 50ms with respect to saccade offset as denoted by a black bar at the top of each column. Thick lines indicate when the waveform differs significantly from zero ($p<0.05$).

Figure 3 shows the same data as Figure 2, but aligned to saccade offset. As before, the oscillatory pattern in the horizontal displacement component (left column) is seen following saccade offset and the peaks of the oscillations are significantly different from zero (thick lines, $p<0.05$) for all subjects and all ears. The vertical eye displacement component (middle column) reveals even greater variability across subjects compared to corresponding vertical onset-aligned responses, with significant waveform peaks present in only two subjects during the EMREO time window (S05, S52). The time-varying constant (right column) is also less predictable across subjects when aligned to saccade offset than when aligned to saccade onset.

Overall, for both onset- and offset-aligned responses, the duration of statistical significance is generally greater in relation to horizontal eye displacement compared to the other two regression coefficients. In other words, the confidence intervals for the coefficient concerning horizontal eye displacement differ from zero for a greater fraction of the time during the evaluated time windows (-5 to 70ms with respect to saccade onset and -25 to 50ms with respect to saccade offset) in relation to vertical displacement and the time-varying constant.

EMREO waveforms by target location

A deeper dive into the EMREO waveforms for each target location confirms the general patterns observed via regression. Since EMREOs are detected in all ears tested, and since the temporal patterns are largely similar across ears within individual subjects, we combined right and left ear microphone data as a function of target location with respect to the recorded ear. Therefore, rightward/leftward targets for left ear recordings were combined with corresponding leftward/rightward targets for right ear recordings, maintaining the contralateral/ipsilateral distinctions.

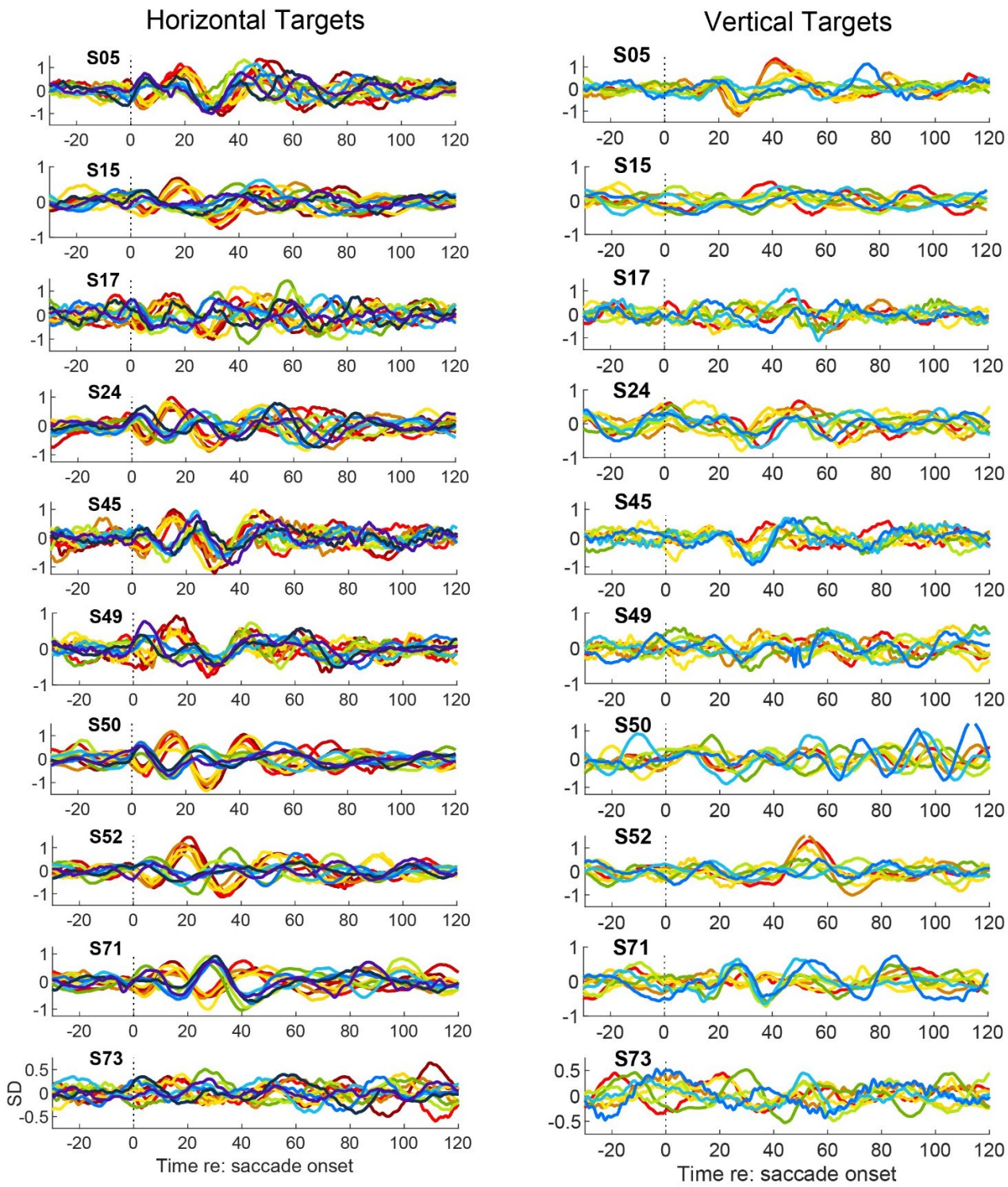

Figure 4. EMREOs recorded during saccades to horizontal targets show more consistent patterns within and across subjects compared to responses during saccades to vertical targets. Raw microphone data, z-scored and aligned to saccade onset, are shown for all subjects (y-axis units = standard deviation relative to baseline variation). Each waveform trace is a subject's averaged microphone response to a single target (both ears combined; see Figure 1 for color code). Red-orange-yellow traces are responses during saccades to contralateral targets and indigo-blue-green traces are to ipsilateral targets. For horizontal targets, in the first 30ms after saccade onset, every subject has the expected phase inversion with change in saccade direction and amplitude; latency and phase direction of peaks are aligned. In the 40 to 90ms time window,

which coincides with saccade offsets, there are peaks with latency shifts that appear to align to saccade duration. For vertical targets, no consistent pattern in waveform amplitude or latency can be discerned across subjects.

Figure 4 shows each subject's microphone responses to both horizontal (1st column) and vertical (2nd column) saccade targets, aligned to saccade onset, and color-coded according to the scheme illustrated in Figure 1. As seen with the regression fits, all subjects show oscillations that invert phase with change in horizontal saccade direction (red-orange-yellow traces are from saccades to contralateral targets; indigo-blue-green traces are to ipsilateral targets). For all horizontal target locations, the oscillations begin close to saccade onset and have a similar waveform pattern both within and across subjects for approximately 30ms. There is a small peak/trough at ~5ms after onset, followed by larger peaks/troughs at ~15 and ~30ms. The amplitude, latency and phase direction of the waveform peaks are in sync across all subjects. Although the oscillations continue beyond 30ms, the pattern becomes less predictable across subjects. The consistent phase reversals for contralateral/ipsilateral targets do not persist for most subjects and waveform amplitude is reduced until returning to pre-saccade baseline levels around 100ms after saccade onset. (The waveform variations by target location observed in the time window between 40 to 90ms after saccade onset will be discussed later, in Figure 8).

As observed with the regression fits, the oscillation patterns to purely vertical saccades are much less predictable across subjects. The latency of the largest peak in the oscillation to vertical saccades is variable across subjects. There is no consistent pattern of phase inversion with changes in saccade direction (up vs. down). In addition, latencies of the maximum peak responses do not show a predictable pattern across subjects. Overall, there is greater variability in response latencies and amplitudes during vertical saccades compared to responses during horizontal saccades.

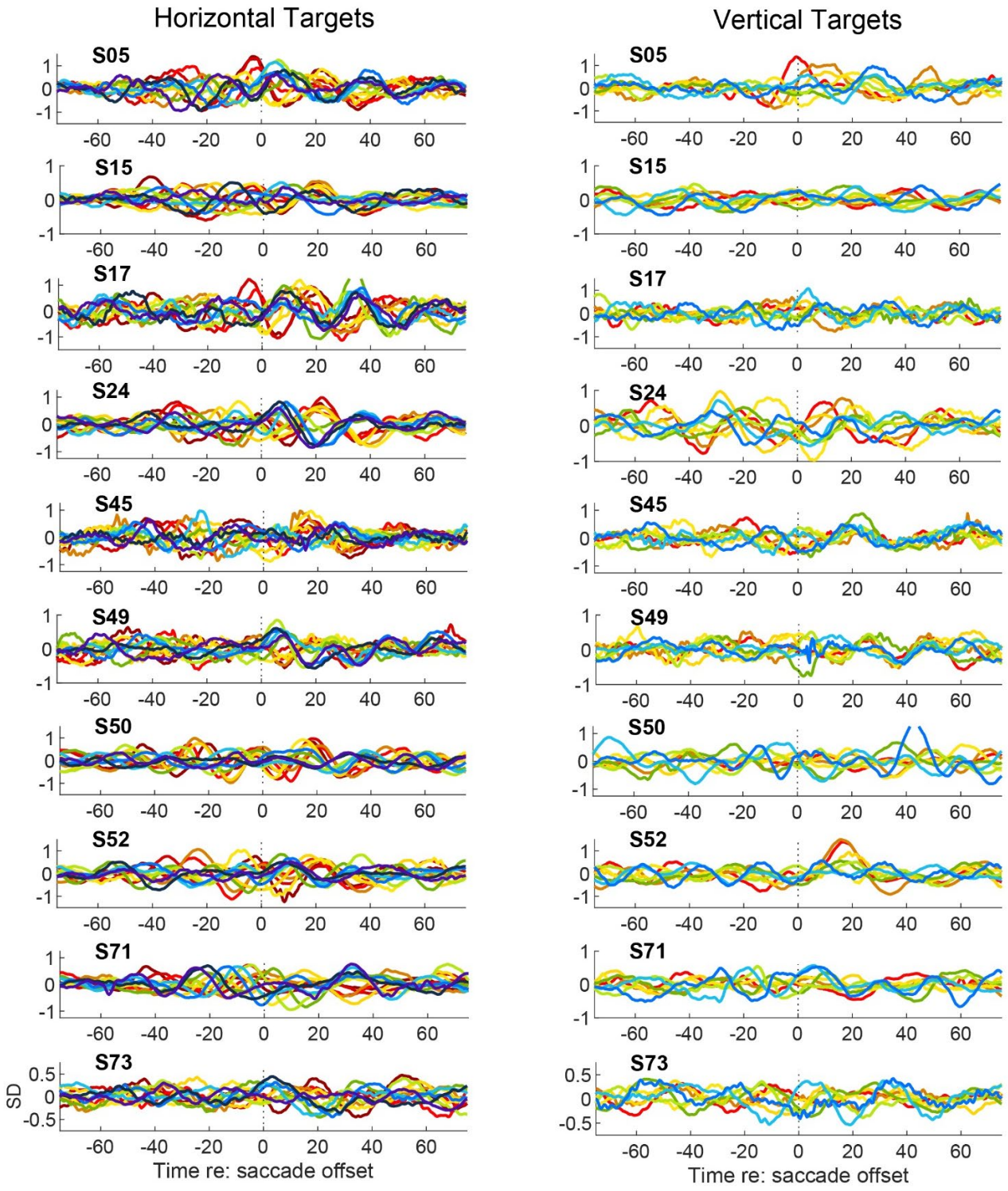

Figure 5: Similar to Figure 4 but aligned to saccade offset. Offset responses to horizontal saccade targets reveal patterns similar to those seen in onset responses but are not as well organized. A phase inversion of the response with change in saccade direction is seen in all subjects. The waveforms align with the first peak/trough around 5ms and the second peak trough around 20ms after saccade offset. The responses return to pre-saccade baseline levels by approximately 60ms in all subjects. Vertical offset responses are quite variable across subjects and similarities in response patterns across subjects do not easily emerge.

The EMREO waveforms following saccade offset show similar properties as seen in the saccade onset-aligned data (Figure 5). As with onset-aligned responses, EMREOs are especially evident for saccades in the horizontal dimension (left column). A phase-reversed pattern for contra- vs. ipsiversive saccades is evident in all subjects, although the time course and latency of the peaks varied across subjects. EMREOs lasted for at least 40ms after horizontal saccade offset in all subjects, and are present to approximately 60ms after saccade offset in several subjects (e.g. S05, S17, and S73). As with saccade onset-aligned data, inter-subject variability in saccade offset-aligned responses is greater for vertically directed saccades than for horizontally directed saccades. Generally, the waveforms appear less stereotyped across vertical target locations both within and across subjects, just as they do for saccade onset-aligned waveforms.

EMREOs for contralaterally-directed saccades are larger and less variable than ipsilateral ones

Although EMREOs that occur during horizontal saccades are less variable than those during vertical saccades, the EMREOs associated with saccades within the horizontal dimension were not fully symmetric across the contralateral vs. ipsilateral directions. Two types of differences were found. First, the amplitude of the EMREO waveform was slightly larger for contralaterally-directed vs. ipsilaterally-directed saccades. This can be seen in Figures 4 and 5, where the red-orange-yellow traces exhibit larger oscillations than the indigo-blue-green traces for individual subjects. Figure 6 breaks this out in another way, also showing EMREOs from individual subjects, but grouped by contralateral vs. ipsilateral saccade direction (upper vs. lower rows in panels a and b) to target locations (columns). Each trace is the average microphone signal from an individual subject based on a single target location.

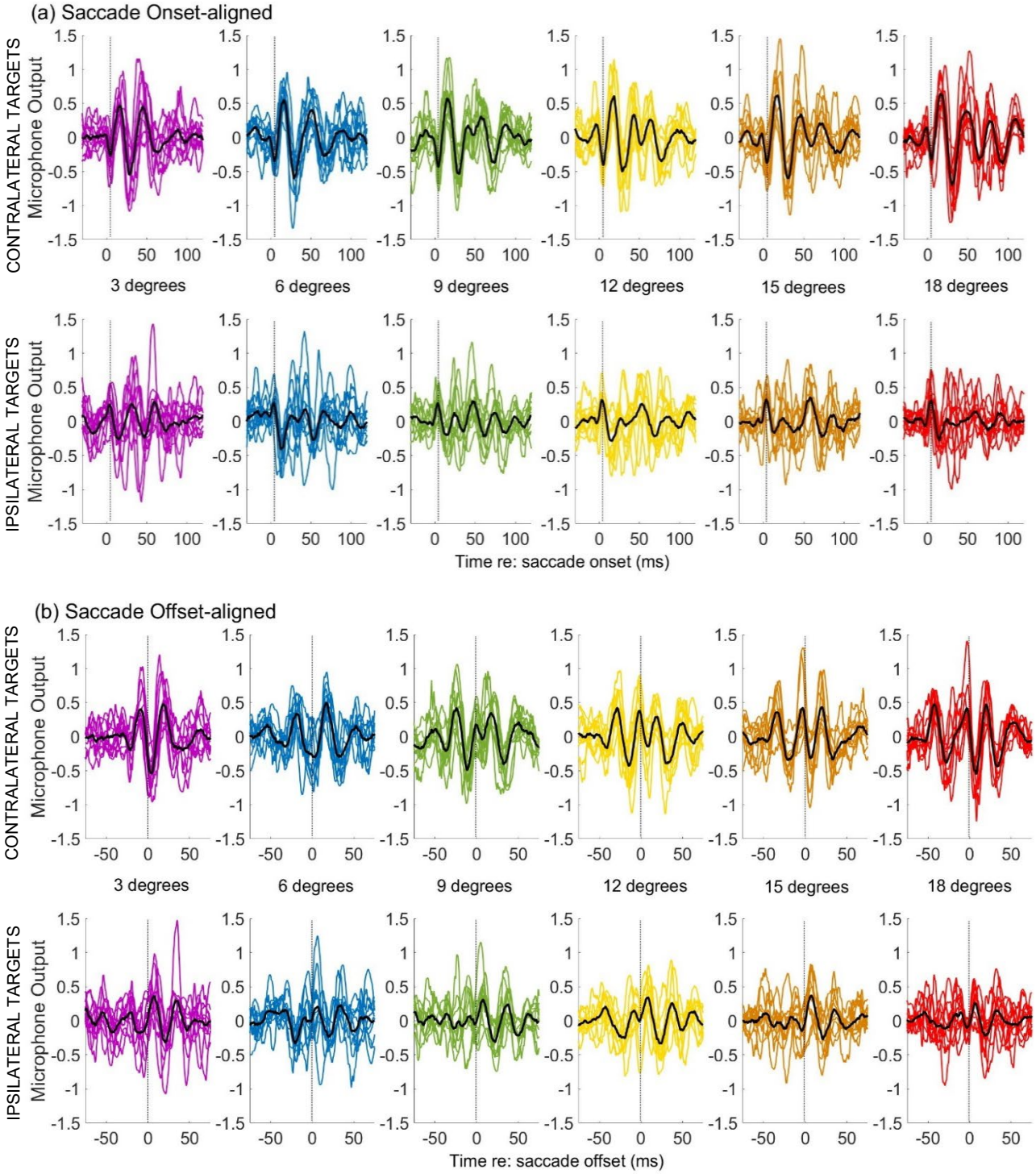

Figure 6. Peak/trough amplitudes and latencies are more consistent across subjects during saccades to contralateral than ipsilateral targets. Each trace is an individual subject's averaged microphone response to a specific target location, aligned to saccade onset (a) and offset (b). All responses are plotted on the same scale. On visual inspection of EMREOs plotted by target location, it is evident that responses are more similar across all subjects for contralateral targets (1st row of panels a and b) than for ipsilateral targets (2nd row of panels a and b). Overall, amplitudes of ipsilateral responses appear slightly smaller in individual subjects compared to contralateral responses. The amplitudes and latencies of ipsilateral responses are more variable across subjects compared to contralateral responses, suggesting that variability across subjects is a bigger underlying factor determining smaller EMREO amplitudes to ipsilateral visual targets.

Second, there was greater variability in the EMREOs associated with the ipsilateral targets. This variability is evident in both amplitude and latency. Not only were the EMREOs associated with saccades to ipsilateral targets smaller on average than those involving contralateral targets, but there was also greater inter-subject variation in EMREO amplitude, whereas the EMREOs associated with contralateral saccades were quite consistent across subjects. Furthermore, the latencies of the peaks/troughs are more precisely aligned across subjects' responses to contralateral targets than is the case for ipsilateral targets. These differences in the magnitude and variability of EMREO amplitude and latency were seen for both saccade onset-aligned and saccade offset-aligned EMREOs (Figure 6). Overall, the amplitudes and latencies of ipsilateral responses are more variable across subjects compared to contralateral responses, suggesting that variability across subjects is a bigger underlying factor determining what otherwise appears to be smaller EMREO amplitudes to ipsilateral visual targets previously seen in group-averaged population data (Lovich et al 2022).

Relationship between EMREOs and horizontal saccade length/duration

The alignment of EMREOs on both saccade onset and saccade offset implies a relationship to saccade duration. Saccade duration is known to co-vary with amplitude: to move the eyes to a new position as fast as possible, the brain causes the extraocular muscles to initially apply nearly the same amount of force per unit time for all saccades regardless of their amplitude, and simply stops the movement sooner for shorter vs. longer amplitude saccades. Does the EMREO show a corresponding pattern? To investigate this question, we focused on the EMREOs to contralateral targets given that they exhibited the largest amplitudes, making the identification of peak latencies most reliable. Figure 7A shows the grand-average microphone responses (mean waveform of all subjects' averaged waveforms) to each contralateral horizontal target, aligned to saccade onset. The latencies of the

waveform peaks and troughs align across all target locations during the first 30ms after saccade onset (which is during the saccade for all but the shortest amplitude saccades). The peak amplitudes do increase with increasing saccade amplitude during this period, but the effect is relatively modest. After this initially temporally aligned peak, there is a systematic delay in the latencies of subsequent peaks with increasing saccade amplitude, i.e., in the 40 to 90ms time window following saccade onset. In short, saccade amplitude is encoded in two ways, first via the amplitudes of the initial short latency peaks/troughs within 30ms after saccade onset, and then via a series of temporally delayed peaks/troughs that appear to be related to the duration of the saccades. Overall, this combination of relatively modest differences in amplitude paired with substantial differences in latency/duration are strongly reminiscent of the known temporal/amplitude patterns of force generation of oculomotor saccade commands (Bahill et al., 1975; Baloh et al., 1975; Van Opstal and Van Gisbergen, 1987).

This pattern is confirmed when viewing the same grand-average waveforms aligned on saccade offset (Figure 7B). In the 50ms time window prior to saccade offset, there is a systematic shift in the latencies of the peaks/troughs that roughly corresponds with saccade onsets for each target location. Following saccade offset, the peak latencies re-align. However, the systematic increase in peak amplitude with increase in saccade magnitude that was seen during the saccade is less evident and the waveform returns to baseline levels by 60ms after saccade offset.

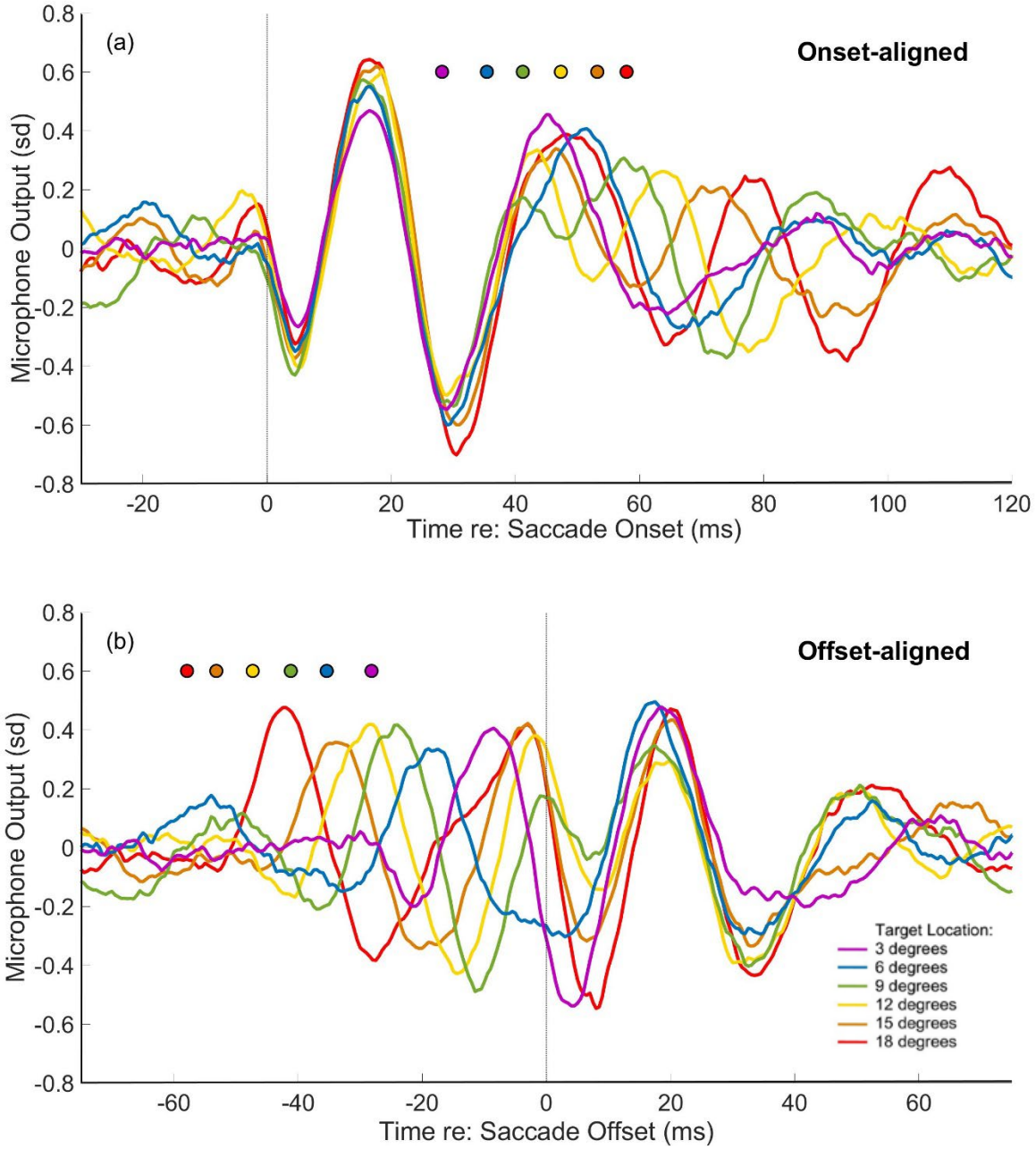

Figure 7. Relationship between timing of EMREO peaks and saccade onset/offset. (a) Grand-averaged waveforms (n=10) to contralateral horizontal visual targets aligned to saccade onset. The latency of the first peak (i.e. in the 0-to-40ms time window) is consistent across different target locations (different saccade durations), but later peaks (i.e. 40 to 90ms after onset) are delayed by amounts that depend on target location (different colors) and corresponding saccade duration (colored circles above the waveforms). (b) Same data as in panel (a) but aligned on saccade offset. The first positive-going peak after offset occurs at approximately 20ms for all target locations.

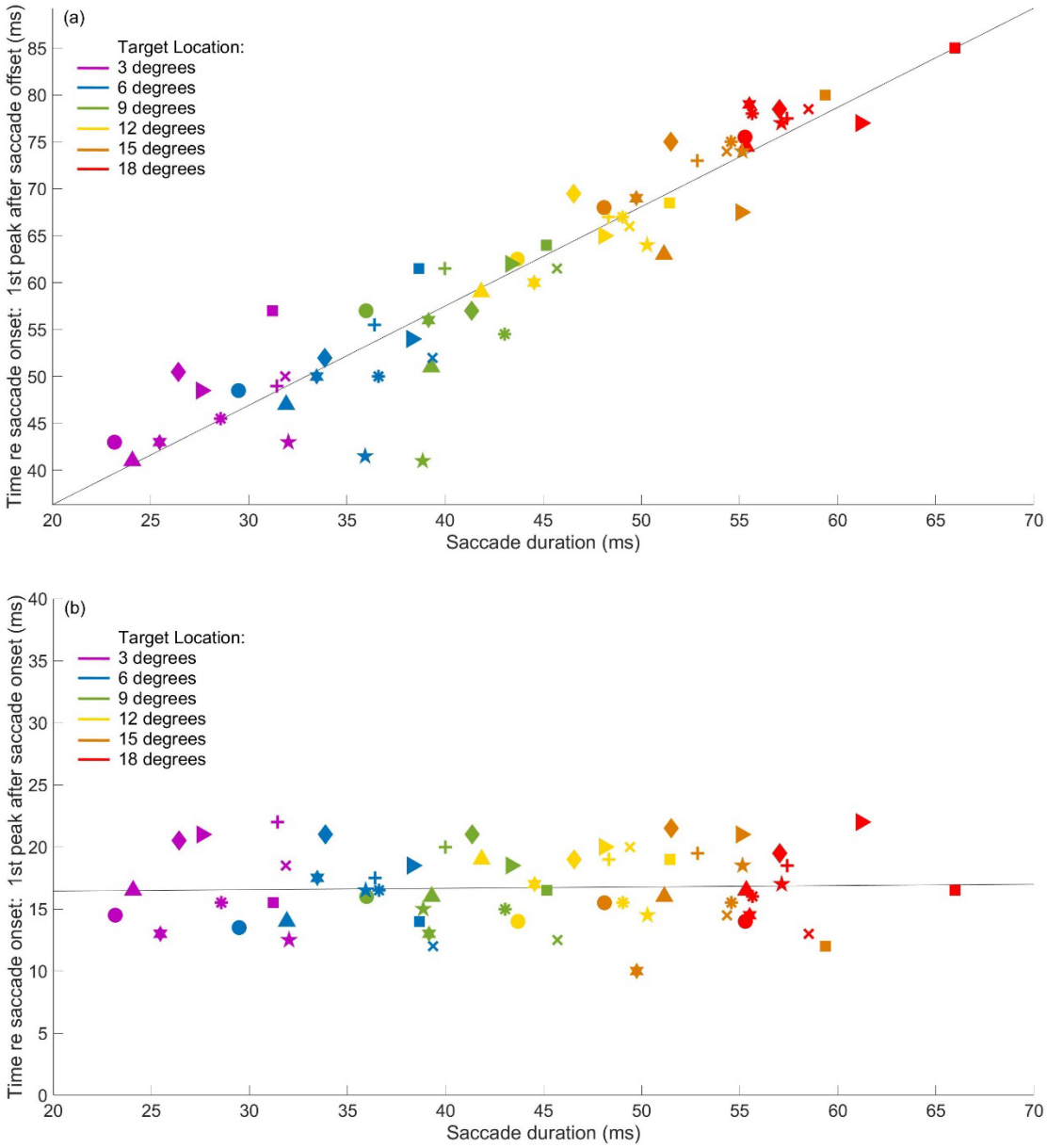

Figure 8. (a) Individual variation in saccade duration is associated with individual variation in EMREO peak timing for the later part of the EMREO waveform. The first peak after saccade offset was identified and its latency with respect to saccade onset was computed (y-axis) and expressed as a function of saccade duration (x-axis). Target locations are coded by color and each subject is identified with a unique symbol. By definition, the latency of this peak will scale with saccade duration, but the relationship could have been different for different subjects. Instead, we see that the relationship between saccade duration and the latencies of peaks clusters well around a single regression line for all subjects. (b) Similar to panel (a) but plots the latency of the first peak after saccade onset as a function of saccade duration. As before, saccades to each target location cluster together (by color) but the latency of this peak is unrelated to saccade duration.

Individual variation in EMREO peak latencies and saccade length/duration

Might the variation in EMREOs across subjects be related to individual variation in saccade duration? While saccades are highly stereotyped eye movements, exhibiting characteristic velocity/duration/amplitude relationships within individuals, there can be variation across individuals. To consider this question, we identified the first positive EMREO waveform peak after saccade offset for each subject and target, averaged across trials. As shown in Figure 8a, there is a linear relationship between the latency of this peak relative to saccade onset (y-axis) and saccade duration (x-axis). The overall pattern is consistent with the pattern illustrated via population grand-average in Figure 7, but here we can also see that the data points for individual subjects cluster along the same regression line for the whole population. Note the clustering by color, indicating that saccade duration is determined by target location. Different subjects' data points are shown via different symbols. Although there is overlap in saccade duration for adjacent targets, the pattern for each subject is rather consistent. For example, the subject denoted with an equilateral triangle has relatively short saccade durations for each target and has the shortest peak latency for each target location. Similarly, the subject denoted with a square has relatively long saccade durations and the longest latencies for target locations.

In contrast, examining the relationship between saccade duration and the first peak of the EMREO after saccade onset for each subject and target, averaged across trials, indicates there is no apparent relationship between saccade duration and peak latency for this EMREO time window (Figure 8b). Again, the clustering by color indicates saccade duration is determined by target location. However, the peak latency does not change with changes in saccade duration. There is little evidence that peak *timing* during this temporal epoch covaries with target location: there is no obvious systematic color pattern along the x-axis for either the peaks or the troughs.

Candidate metrics for future comparisons of EMREOs between normal and clinical populations: considerations for comparing across study designs and with limited data collection

One of the overarching motivations of this study is to identify the aspects of the EMREO that show the most stability across individuals with normal hearing, in anticipation of future comparisons to individuals with hearing loss. Studies in such clinical populations may be constrained in terms of data collection, requiring shorter testing sessions than are commonly used in research settings. What aspects of the experimental design can be sacrificed with minimal impact on the metrics being assessed? If necessary, testing could be limited to two horizontal targets, one on each side, such that there are contralaterally directed saccades for each ear. As shown in Figure 7a, the first 0-35ms of the saccade-onset EMREO waveform varies with saccade amplitude but the amount of this variation is comparatively small. Figure 9 captures this in another way. Here, we plot the peak-trough amplitude during the first 0-35ms after saccade onset, averaged across subjects and plotted in different colors for the different target locations. Similar to previously published findings (Gruters et al., 2018), there is a small but reliable decrease in peak-trough amplitude with decreasing saccade amplitude. However, the impact of the change in saccade amplitude is negligible when averaging across all targets (gray bar, small standard error bars). This suggests that comparisons across studies that have used different horizontal target locations should be possible. Future work in clinical populations could rely on fewer targets, increasing statistical power for analysis at the single target level without increasing testing time.

The bottom line of this and the preceding figures is that several metrics may prove useful for future clinical comparisons. Potential anomalies in EMREO “size” are likely to be best assessed using saccades to contralateral targets, via the maximum peak-trough amplitude observed within 0-30ms of saccade onset. Potential anomalies in EMREO timing

are likely to be best assessed by evaluating (a) the timing of the first peak within 0-30ms after saccade onset, and/or (b) the relationship between saccade duration and the later parts of the EMREO waveform after saccade offset.

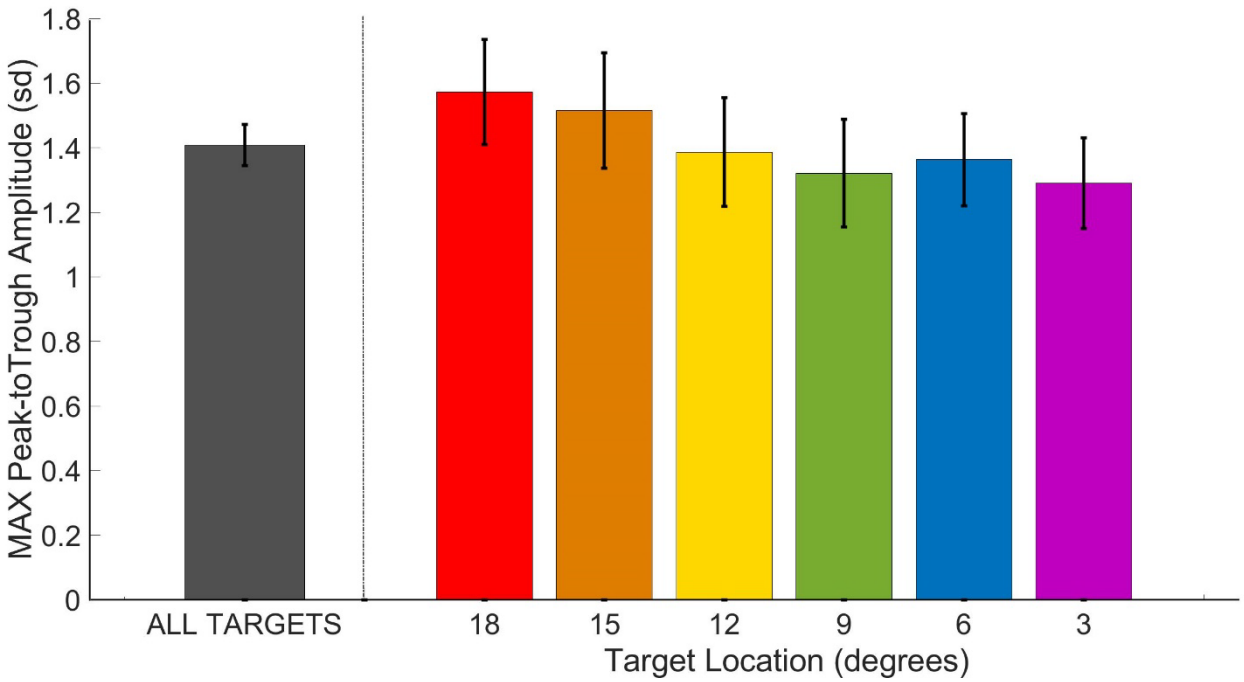

Figure 9.Average peak-trough amplitude scales with target location (colored bars; peaks and troughs obtained within 0-35ms window after saccade onset for contralateral saccades; see also the population grand-average waveforms from Figure 7a). However, the range is narrow, such that pooling across locations loses little information: the gray bar for the 22 normal hearing subjects (44 ears) tested represents the population mean and standard error of the peak-to-trough amplitude. In short, the peak-trough amplitude 0-35ms after onset of a contraversive saccade provides a good metric for EMREO amplitude , regardless of target location, providing a means for comparison across studies using different target locations and permitting use of a single contralateral target location if testing time/trial counts is a limiting factor in future studies.

Discussion

Our primary goal was to identify the similarities and differences in EMREOs observed in participants with *normal* auditory function. Recognizing both the common and unique response properties sets the stage for understanding the purpose EMREOs serve in normal

hearing, as well as for exploring what anatomical mechanisms are responsible for generating these surprising signals in the ear. Ultimately, determining the EMREOs' underlying anatomical mechanism(s) and their relationship to particular attributes of the EMREO signal may permit use of EMREOs as biomarkers to facilitate diagnosis of different types of auditory dysfunction. This latter goal is in the distant future; characterization of the normative population is a preliminary, but essential, step.

The first goal was to ascertain whether the EMREO is present in all normal hearing individuals. We observed EMREOs in all normal hearing subjects who successfully completed various visual saccade tasks (~40), and in all 10 of the subjects who participated in the particular saccade tasks explored here. This indicates that EMREOs are consistently present in the normal hearing population, which in turn suggests that EMREOs reflect a normal part of hearing.

We then considered which aspects of the EMREO show more vs. less variability, either within or across subjects. Our reasoning is that EMREO components that are similar across subjects may provide clues to either the perceptual purpose that EMREOs contribute to, the underlying mechanism that causes them, or both. We found that responses to horizontal targets were more consistent across subjects than responses to vertical targets. This is potentially consistent with a role in spatial localization of sounds in an eye-centered reference frame. It is known that localization of sounds can be slightly more accurate in the horizontal than the vertical dimension (Tabry et al., 2013; Jay and Sparks, 1990; Makous and Middlebrooks, 1990), so to see a comparable difference in the horizontal vs. vertical dimensions in the EMREO provides a striking parallel. Relatedly, another recent study from our group has demonstrated that reconstruction of target location from EMREOs is more accurate in the horizontal dimension than the vertical one (Lovich et al., 2022).

More puzzling is our finding that EMREO responses to contralateral targets are more consistent across subjects than those to ipsilateral targets. The interpretation of this finding is presently unknown. It seems unlikely to relate to any particular perceptual attribute of hearing, as what is ipsilateral to one ear is simultaneously contralateral to the other, so any negative perceptual consequences associated with this variability in signal should in theory balance out, at least for individuals with normal hearing in both ears. We therefore suspect that this asymmetry might ultimately prove to be connected to some aspect of the underlying mechanisms that generate EMREOs. It will therefore be of interest to evaluate whether this aspect of the EMREO phenomenon differs in clinical populations that have dysfunction involving either middle ear muscles or cochlear outer hair cells.

Our current findings confirm and extend our previous report that EMREOs are time-locked to both saccade onset and saccade offset (Gruters et al., 2018). We focused on the responses to contralateral targets as involving the most reproducible/least variable EMREOs, and identified a clear pattern associated with saccade length/saccade duration/target location. This indicates a close connection between EMREOs and the control of saccades by the brain. Saccades are high speed eye movements, accomplished by “flooring the gas pedal”. To move the eyes different distances, the brain adjusts how long it floors the gas pedal. The relationship between EMREOs and saccade length and duration provides a parallel to the format of saccade commands, lending circumstantial support to the likelihood that some form of corollary discharge signal related to the saccade is issued by the brain and sent to the ear.

A major goal for future work is to compare subjects with different types of auditory dysfunction to population data from normal hearing subjects. Studying patients with dysfunction involving any of the three types of actuators in the ear, i.e. the two middle ear muscles and the outer hair cells, will shed light on the contributions of these motor elements to the generation of the EMREO. Different patterns of anomalies in the EMREO may occur in patients with different types of dysfunction. Studies in such clinical populations can be

facilitated by focusing on analysis of the EMREO components that exhibit the most consistency in subjects with normal hearing.

Our overarching theory is that EMREOs are generated as a byproduct of processes involved in connecting the auditory scene to the visual scene across eye movements. Under this view, the underlying mechanisms associated with EMREOs may contribute to our experience of a perceptually stable world in which sights and sounds can be effortlessly linked to one another. The normative dataset presented here can provide a point of comparison not only for further study concerning those underlying mechanisms, but can also lead the way in investigations of what happens to our perception of an integrated visual-auditory scene when EMREOs deviate from the normal pattern.

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