Involuntary Markers of Saliency and Surprise Revealed by Oculomotor Inhibition in Response to Auditory Sequences

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Abstract

Our eyes move constantly but are often inhibited momentarily in response to external stimuli. The properties of this Oculomotor-Inhibition (OMI) depend on stimulus saliency, anticipation, and attention. Previous studies have shown prolonged saccadic inhibition for auditory oddballs; however, they required active counting of the oddballs. Here we investigated whether the OMI response to auditory deviants can provide a quantitative measure of deviance strength (auditory pitch difference) and studied its dependence on the Inter-Trial Interval (ITI). Participants fixated on a central fixation stimulus and passively listened to repeated short sequences of pure tones that contained a deviant tone either regularly or with 20% probability (the Oddball paradigm). They did not perform any task or requested to attend to a specific stimulus. As in previous studies, the results showed prolonged microsaccade inhibition and increased pupil dilation following the rare deviant tone. Moreover, the inhibition onset latency was shorter in proportion to the pitch deviance (the saliency effect), and the release was significantly longer for rare deviants (the surprise effect) as long as the ITI was short (<2.5s). Longer ITIs induced higher microsaccade and blink rates together with smaller pupil dilation, indicating a reduction of alertness. Taken together, these results suggest that OMI provides involuntary markers of saliency and surprise, which can be obtained without the participant's response.

Introduction

Survival largely depends on one's ability to detect sudden changes in the environment, anticipate upcoming events, and process them optimally. Predictive computations represent one of the fundamental principles of neural processing, and a prediction mismatch may support behavioral complexity and dynamics [1]. Responses to an auditory mismatch can reflect the violations of predictive assessments or adaptation to a repeated stimulus. However, a mismatched response to an omitted predicted signal, for example, is better interpreted as top-down predictive processing rather than simple stimulus adaptation [2,3]. Although many of the studies dealing with auditory deviants used electrophysiology, similar effects can be produced by involuntary eye movement measures [4].

Involuntary eye movements during fixation, including microsaccades, spontaneous eye blinks, and ocular drift, occur continuously; however, the eyes tend to freeze in response to transient stimuli (Oculomotor-Inhibition, OMI) and the latencies of the inhibition onset and release depend on stimulus saliency [5–8], attention [9,10], expectations, or surprise [11]. Microsaccades are rapid, small-amplitude saccades that can be executed voluntarily to desired locations, even from memory [12], but typically they occur involuntarily during fixation, with a rate of about one or two per second [13], and an inhibitory pattern in response to transient stimuli (saccadic inhibition) that has been studied extensively [6,8,10,11,14–18]. For example, the latency of the first microsaccade relative to stimulus onset, following inhibition, termed the microsaccade response time (msRT), was found to be sensitive to the contrast and spatial frequency of the stimulus; a

shorter msRT occurs with more salient stimuli [6]. Microsaccade inhibition results from a peak of activity at the fixation (central) location in the superior colliculus (SC) saccade map [15], which plays a role in attentive and orienting behaviors and is involved in generating microsaccades [16]. The SC activity reflects a map of the relevant behavioral goals and may correspond to sensory input from different modalities rather than only to a visual stimulus [19].

In recent studies, microsaccades have been found to be highly informative about cognitive processes. Whereas saliency driven by stimulus properties such as contrast shortens the inhibition, longer inhibition was found for oddballs in a sequence. This was found for a blue patch among frequent red patches [14]. However, these findings were obtained when participants had to attend to and report the deviant stimulus, possibly reflecting a prolonged inhibition to the attended stimulus rather than a perceptual surprise. In more recent studies from our lab we found preliminary evidence of similar effects obtained in passive viewing without specifically attending to the oddballs. This was demonstrated for visual oddballs such as a high-contrast patch among low-contrast patches [20], with similar results obtained with eye blinks [7] and for temporal oddballs (unpredicted intervals) [21], all showing preliminary evidence of prolonged inhibition for the deviant stimulus. Prolonged OMI for an auditory deviant tone in a sequence has been reported in a few studies before [4,17,22], however, auditory oddball effect without attending specifically to the deviant stimulus and it's dependency on the deviant magnitude was never demonstrated.

The original purpose of this study was to develop involuntary oculomotor measures of different surprise levels similar to those obtained via ERP [23] to test non-communicating individuals; however, the current study focused on healthy participants. We, therefore, focused on two specific research questions: (1) Can OMI be used as an involuntary marker of auditory deviance detection? (2) Can OMI be used as a measure for saliency and surprise effects in auditory sequences? To address these questions, participants were asked to attend a stream of sounds in a predictable (experiment 1) and oddball conditions (experiment 2) while fixating a central visual fixation in a "passive attentive" paradigm [24,25], which didn't involve a task. In this way, the methods we develop in the current study could apply to non-communicating individuals in the future.

Methods

Participants

Fifty-six participants, 29 females and 27 males, were recruited for Experiment 1 and seventeen, 6 females and 11 males for experiment 2, ages 20-40. One participant was removed from the data analysis of the first experiment because of bad recording (gaps or blinking in 97% of the trials). All participants had normal or corrected-to-normal vision and were naïve to the purpose of the study, except for the first author. The experiments were approved by the Bar-Ilan Internal Review Board (IRB) ethics committee. All participants gave written informed consent and all the experiments were conducted according to the IRB guidelines.

Apparatus

Stimuli were displayed at a distance of 0.6m on a 24-in LCD monitor (Eizo Foris fg2421) running at 1920 x 1080 screen resolution and at a 100 Hz refresh rate, using an in-house-developed platform for psychophysical and eye-tracking experiments (PSY) developed by Y.S. Bonneh. All experiments were administered in dim light and the screen background was gray with 50cd/m^2 luminance. We used a remote video-based eye tracking system (Eyelink, SR Research), with a sampling rate of 500 Hz, and recorded from a distance of 50-55cm. All recordings were done binocularly, with analyses done on data from the left eye. A standard 9-point calibration was performed before each session. We chose a 25mm-wide lens in a head-free mode for compatibility with a parallel study with Disorder of Consciousness (DOC) patients, of which we received a Helsinki approval of the Lowenstein hospital in Israel and obtained some preliminary results.

Stimuli and Procedures

Experiment 1: Participants , N=56, passively attended to a series of sounds played through headphones and watched a rapid serial visual presentation (RSVP) of small (~1 degree of visual angle), low-contrast, upside down Hebrew letters, presented at the center of the screen. A task was not used for compatibility with a parallel DOC patients study and the participants were only instructed to fixate on the screen center and to attend a series of sounds played through headphones. Some of our former experiments in the lab suggested that asking the participants to count or attend a specific stimulus prolongs the OMI in response to that stimulus. For this reason, we used a “passive attentive” paradigm (see [24,25] for a similar approach) in which participants were asked to attend to all sounds without using a task to control their attention. That is in contrast to previous oddball studies (see Discussion for further details). One random letter out of 27 options was presented in parallel with each sound in a series. The visual stimuli were not informative regarding the auditory conditions and were used for obtaining a steady fixation without gaze wandering and a regular and strong OMI, whose modulation by the auditory stimuli was the effect we aimed to measure.

The sound series consisted of rapid sequences of 5 identical tones (70 dB SPL, 50 ms each, 50 ms gap) or they contained a deviant tone at the end of the sequence (a deviant 5^{th} tone). A schematic presentation of the paradigm is shown in Figure 1. All together there were five separate conditions, Standard trials with five identical 659 Hz pure tones and Deviant trials that varied in the frequency of the fifth tone with 50 Hz steps (709, 759, 809, and 859 Hz). The total duration for each presentation of the five tones and letters was 450 ms and the interval between presentations (ITI, inter-trial interval) was 550 ms; therefore, the combined stimulus rate was 1 Hz. There was no mixing between trials from different conditions (blocks of 20 trials); however, the blocks were played in random order in three separate short runs. Participants completed a total of 60 trials for each of the five conditions in three runs (20 trials per condition in a run).

Experiment 2: As in experiment 1, Participants, N=17, passively viewed and attended to a series of sounds. To obtain gaze fixation and regular OMI, we used a small low-contrast white circle (0.65^{o} in diameter), flashed 50 ms before the deviant onset, which remained until the end of the sound series. We applied an auditory oddball paradigm with a rare deviant. There were Standard trials with 6 identical 535 Hz pure tones and Oddball trials with a deviant tone (635 Hz) in the third location of the sequence, 200 ms after the stimulus onset. (See the schematic presentation of the paradigm in Figure 2). Stimuli from the Standard and Oddball conditions were played in a mixed order where the number of Oddball trials constituted 20% of all trials. The sound sequence duration was 550 ms, and the interval between the sequences (ITI) varied (0.5, 1, 1.5, 2, and 2.5 sec) in separate runs. Participants completed a total of 200 trials for each of the five different ITIs in two short runs per ITI; each included 100 mixed Standard and Oddball trials. We also ran a reversed oddball experiment, same as experiment 2, which involved seven new participants and ITI of 1.5 seconds. Here the deviant sequence (AAAAB) was played 80% of all trials, and the Standard sequence (AAAAA) was rare, 20% of the trials.

The design of the two experiments was based on the idea of using a strong and predictable visual OMI (characterized by a typical robust “rebound” effect) that is modulated by an auditory stimulus, where this modulation depends on the deviance strength or oddball effect we measure. In Exp2, the deviant tone timing within the sequence was predictable for the reason explained above, but the appearance of the oddball sequence was unpredictable.

Data Analysis

Microsaccade and blink detection

For the microsaccade detection we used the algorithm introduced by Engbert and Kliegl [26], which is based on the eye movement velocity, and has been implemented in our recent study [27]. Raw data were first smoothed using the LOWESS method with a window of 15 ms to optimize microsaccade extraction, especially for noisy recordings [26]. Because microsaccades are ballistic movements as saccades they show a high correlation between the peak velocity and the amplitude. A velocity range of 8 ^{o}/s–150 ^{o}/s, and an amplitude range of 0.08-1^{o} were allowed. We also rejected eye movements with a duration smaller than 9 ms. Eye blinks were detected as in our previous study [7]. We first defined periods with zero pupil size, and then extended by estimating the eyes’ closed and open times, based on the vertical eye movement that typically precedes the blink [27]. The blink rate was calculated per session and condition as the percent of epochs (equal in time for all conditions) containing a blink, averaged within participants, demeaned, and adjusted by adding the grand mean of all conditions and participants. Finally, the mean and standard error were recalculated across participants. In experiment 1 the grand mean was 17.2% of all trials, SD=14.9% and 20.3%, SD=17.9% in experiment 2. Epochs were extracted, triggered by stimulus onset in a range of -0.1 sec to 1.1 sec relative to this trigger with one epoch per experimental trial. Periods of missing data within an epoch, for example as during an eye blink, were discarded from analysis with an additional margin of 50 ms, without discarding the whole epoch. It was verified that the blinks didn’t

affect the results in both experiments. In experiment 1, the blink rate and time didn't differ between conditions, and the time of the blink in experiment 2 was later than the time period used to calculate the microsaccade latencies. The rejection rate varied across recordings and was typically 5–25%.

Microsaccade rate function calculation

The microsaccade rate modulation function was calculated to compute the event-related modulation of eye movements [28] as in [18] and [29]; it was calculated for the raw microsaccade onsets (see Figure 3a for an example of a raster plot of microsaccade occurrences) and it is described here briefly. For each epoch the rate function was computed by convolving a raw rate estimate of one microsaccade per sample duration with a Gaussian window and with a sigma of 50 ms, at the time of microsaccade onset. The rate functions were then averaged across the epochs within participants separately for each condition and demeaned by subtracting the participants' mean and adjusted by adding the total average for all conditions and the participants. Finally, the mean and standard error were recalculated across participants. In some cases (specified in each condition), we used baseline correction of the average rate modulation within participant and condition, by subtracting the rate value at time zero (stimulus onset).

Statistical assessment

To assess the significance of the microsaccade rate results, we used a Monte-Carlo cluster-based nonparametric permutation test (as in [17], see also [30]) to determine the difference between conditions. We first looked for a significant continuous cluster between the two conditions by performing paired t-tests at each time point. Then we randomized the condition labels of the participant's means at each time point and recalculated the group averages to create 1,000 permutations tests, then repeated the first step. We then computed the p value as the fraction of permutations in which the original test statistic was exceeded by the permuted data.

Microsaccade RT and pupil peak calculation

The Microsaccade Reaction Time (msRT) was calculated for each epoch relative to the stimulus onset in predefined time windows. The choice of the range was made to accommodate the variability between participants while focusing on the region of interest derived from the rate modulation functions (a region that shows a difference across conditions). To estimate the onset of the microsaccade inhibition, msRT-last was computed as the latency of the last microsaccade in the selected window. In experiment 1 an early window was chosen that starts a few hundred ms before the deviant stimulus onset because the microsaccade probability tends to decrease before this onset if the stimulus timing is predictable [11]. In experiment 2 msRT-first was computed to estimate the onset of the release from the microsaccade inhibition (since the oddball prolongs the OMI) as the latency of the first microsaccade in a late window as was done in our previous study [6]. Epochs without microsaccades within the selected windows were excluded from the average, typically around 30-50%. The microsaccade RTs were averaged across the epochs of each condition within participants and demeaned by subtracting the participants' mean, then averaged across participants, and finally, the total average for all conditions and participants was added

(Cousineau & Morey's method [31], see also Bonneh et al. [6]). This normalization procedure affected only the error bars and did not alter the averages. In computing error bars for the RT values averaged across subjects, we applied the Cousineau method (multiplied by Morey's correction factor (√ (n/ (n−1))), which controls the between-subject variance and allows a better representation of within-subject effects (Cousineau & Morey's method [31], see also Bonneh et al. [6]). The pupil peak was detected for every epoch in the time window of 0-1 sec relative to the stimulus onset for all conditions. It was converted to the percent change in pupil area from the average of a 100 ms period pre-stimulus onset.

Statistical assessment

Statistical analysis of variance (ANOVA) and multiple comparisons post-hoc tests were performed using Matlab 2018b, (One-way in Experiment 1 and Two-way in Experiment 2, the Tukey method). We first verified that the msRT or the pupil peak distributions of different conditions come from normal distributions with equal variance. For the msRT statistics in experiment 2, after acquiring the significance, we ran two-tailed paired t-tests and applied the Bonferroni correction method for multiple comparisons.

Results

In experiment 1we investigated whether the OMI depends on the magnitude of an auditory pitch deviance. We hypothesized two possible outcomes; 1) a prolonged OMI after the deviant tone as in previous oddball studies; or 2) early-onset of OMI even before the deviant tone due to anticipation. To test this, we extracted epochs triggered by stimulus onset in a range of -0.1 sec to 1.1 sec relative to this trigger. We first calculated the microsaccade rate modulation averaged across participants (N=55), and baseline corrected to the value at stimulus onset time (see Methods). We then compared the five conditions: a Standard stimulus with five equal tones (659 Hz) and four Deviant stimulus conditions with a deviant tone in the fifth location and with different magnitudes (frequency differences) relative to the Standard (659+50/100/150/200 Hz). Figure 3b shows a typical microsaccade inhibition and release in response to the combined visual and auditory, bimodal stimulus onset (letters and the sound sequence) and a second inhibition in response to the stimulus offset, which describes the different conditions because it starts around the time of the deviant tone. The onset of this second inhibition is measured by the last microsaccade in a window of 100 ms and 600 ms after stimulus onset and is termed "msRT-last" (see Figure 3c). This time window was selected by visually inspecting the microsaccade rate function and finding a region of interest that shows a difference across conditions. We found that a larger deviant produced a faster onset of inhibition ($F(4,270)=3.07$, $p<=0.017$), which confirms our second initial prediction. The msRT-first (release from inhibition) with a time range of 500-1000 ms to account for a possible surprise effect didn't reach significance ($F(4,270)=0.27$, $p=0.9$) and contradicted our first expected outcome. The individual scatter-plot in Figure 3c (2) shows that most participants had longer microsaccade latencies in the Standard condition compared with 809 Hz (+150 Hz) Deviant condition, which was found to be significantly different in the posthoc tests (Figure 3d). Figure 3e shows a difference of 809 and 859 Hz (+200 Hz) Deviant conditions from the Standard, with a histogram comparison and effect size estimation using Cohen's d. Paired t and ranking tests show a significant

difference (Figures 3e-1, 3e-3) and medium effect sizes were calculated in (Figures 3e-2, 3e-4). Areas under the curve (AUC) of the ROC results are also shown.

In experiment 2 we tested whether the time interval between the auditory sequences affects the OMI. We estimated a decline in the Oddball effect with longer temporal separation since the sensory memory of the preceding item decays, and the Oddball is defined by its relationship to the preceding items. The results are shown in Figures 4 and 5. Microsaccade rate modulations for an illustration of the Oddball effect averaged across participants with all ITIs combined ($p <= 0.002$, Monte-Carlo, permutation test, see Methods) are shown in Figure 4a. As in experiment 1, the rate shows a typical response for stimulus onset and offset, but here, the first inhibition provides more information about the difference between the Standard and Oddball conditions, determined by the earlier onset of the deviant tone. Here, the visual stimulus was timed 50 ms before the oddball to obtain a strong OMI at the oddball time (see Methods). To quantify the OMI after stimulus onset for the different conditions, we computed “msRT-first”, which is calculated for the latency of the first microsaccade released from the inhibition in a window of 200-700 ms after stimulus onset. This time window was selected by visually inspecting the microsaccade rate function and estimating a time region that shows a difference across conditions (see Methods for further details). Thirteen out of 17 participants had a longer msRT in the Oddball condition (Figure 4b. Trials from all ITIs were combined). The msRT results were analyzed using Two-way ANOVA (Figure 4c). Oddball msRTs were significantly longer ($F(1,160)=4.83$, $p<=0.029$), but no interaction was found with the ITI factor. We used Bonferroni corrected, 2-tailed paired t-tests to assess the significance for multiple comparisons of the Standard and Oddball conditions in each ITI separately. Figure 4d shows the Standard and Oddball conditions in all five different ITIs (0.5-2.5sec). The results show a significant difference between the Standard and Oddball msRTs in ITIs shorter than 2.5 sec. We tested the reverse combination of Standard and Oddball and didn’t observe an Oddball effect for the rare Standard trials interleaved with frequent Deviant trials (Figure 4e), although it involved only 7 participants. Pupil measurements showed an Oddball effect (Figure 4f) as well as ITI effect (Figure 5e). Significance was assessed using the pupil peak (% change in pupil area), detected for every epoch in a time window of 0-1 sec relative to stimulus onset, for all conditions (see Methods). A Two-way Anova showed significant effects; $F(4,160)=3.91$, $p<0.005$ for the Oddball factor and $F(1,160)=11$, $p<0.0012$ for the ITI factor. The results for the inter-trial interval effect are shown in Figure 5, showing higher microsaccade rates for longer ITIs. We then calculated the “microsaccade hit rate” (denoted here as “mshit”) corresponding to the percentage of trials with at least one microsaccade occurring within a time window of 200-700 ms after stimulus onset. We found that (1) Oddball trials had significantly higher microsaccade hit rates at that window for all ITIs (Figure 5b, c. $F(1,160)=8.34$, $p<=0.004$); and (2) longer ITIs also produced a significant increase in the rates (Figure 5b, d. $F(4,160)=2.62$, $p<=0.037$). A significant increase in Blink rates ($F(4,80)=9.36$, $p<0.00005$), was also observed with longer ITIs (Figure 5f). It was calculated at a 0-1 sec time range for all conditions (see Methods).

Discussion

In the current study we conducted two experiments with auditory pitch deviance and measured the OMI response. We found that when the deviant was frequent and therefore predictable, microsaccade inhibition onset was faster as a function of the deviant size (higher pitch) and when it was rare, the inhibition was prolonged. This was achieved without the participant's response. Next, we will discuss the different aspects of these findings and their interpretation.

Auditory deviance and OMI: salience vs. surprise

Given that an auditory oddball was found to increase the period of saccadic inhibition, i.e., postpone its release, at least when a task was involved [4,17], one would expect that this inhibition will be prolonged with a larger deviance. On the other hand, since the OMI is known to be faster and shorter with the saliency of the stimuli, e.g., for higher visual contrast [6], one would expect faster and shorter inhibition with a larger deviance that appears perceptually more salient.

In experiment 1, the stimulus was a repeated short sequence of 5 identical tones, or it contained a fifth deviant tone. The deviant was fixed within a condition and varied between conditions; thus, the deviant was frequent and entirely predictable. We found that the OMI was sensitive to auditory pitch deviance and was affected by its magnitude. In response to larger deviance, the OMI was faster (started earlier) as evident by the difference in the rate modulation function (Figure 3b) and by the earlier inhibition onset around the time of the deviant tone presentation (Figure 3c). Because the deviant was predictable, the results resemble those of the OMI in response to visual contrast stimuli [6] that show a faster inhibition onset for higher contrast. Here, the effect of the deviant tone did not stem from an unpredictable change or surprise, but instead from its contrast with the 4 preceding Standard tones, hence, the similarity to the effect of visual contrast. We, therefore, can conclude that the OMI measured in this experiment reflects the perceived stimulus saliency. Widman et al. found prolonged OMI for pitch as well as location oddball [17]. We show here for the first time that OMI depends on the pitch deviance magnitude, which can be interpreted here as a marker of saliency.

The results of this experiment could be explained by referring to two early processes of change detection in the auditory modality, originating from the auditory cortex and biasing attention away from the common stimulus. Stimulus Specific Adaptation (SSA) and Mismatch Negativity (MMN) are not entirely dissociated, and some studies suggested that SSA provides a neuronal correlate of MMN [32,33]. Stimulus Specific Adaptation (SSA) reflects the habituation to a recurring stimulus, spanning several time scales ranging from milliseconds to tens of seconds [34]. The evoked potential (ERP) Mismatch Negativity (MMN) reflects the brain's response to a sudden change in stimulus, peaking at about 150 ms [35–37]. Based on these known processes, we considered the following explanation of our results: Early inhibition onset indicates preparation and is associated with temporal anticipation due to the paradigm's design. A higher sensory saliency of the deviant sequence is caused by habituation of the repetitive reference tone (SSA) and a fresh response to the deviant tone (depending on its deviance [38]), resulting in faster inhibition

onsets. In addition, the mismatched deviant tone signals a prediction error relative to the size of the difference, leading to a better adjustment of a temporal model [39].

In experiment 2 we used an oddball paradigm, where an infrequent sequence of tones was presented randomly among 6 repeated identical tone sequences at a ratio of 20/80. The results showed that a rare auditory pattern induced a significant surprise response, with a prolonged OMI as in previous oddball studies[4,17,22]. With a long inter-trial interval (ITI) of two and a half seconds, this effect became non-significant (p=0.05, 2-tailed paired t-test) (Figure 4d). This might be associated with a reduction in alertness due to the slow pace of the experiment, together with the lack of any attentive task, as discussed in the next paragraph. We also observed a surprising increase in microsaccades in the Oddball condition (see Figure 5b and 5c). A very recent animal study in monkeys reported an exploratory oculomotor search response following surprise signals by neurons in the supplementary eye field (SEF) [40]. It has also been suggested that some microsaccades in humans are exploratory [41]; suggesting that surprise might trigger exploration. The results indicate a surprise response reflected by prolonged inhibition triggered by a violation of temporal expectations [11]; however, it could also be associated with early change detection processes combined with the predictive top-down re-direction of attention. The oddball paradigm has been traditionally used in ERP studies for both MMN and P300. The latest ERP component is associated with attention shifts; P3a is a subcomponent of the P300 complex, reflecting the top-down response to violations of expectations and decision making [42]. It occurs as early as 250 ms, at least 100 ms later than MMN, bottom-up recruitment of attention, peaking around 150 ms. Although we believe that top-down and bottom-up attention re-orientation mechanisms account for the prolonged inhibition, as microsaccade direction and its inhibition was found to be related to spatial attention [26,43–45], other studies suggest earlier categorization of sound. Widman et al. reported an early oculomotor marker of an auditory oddball found at 80-100 ms after the deviant onset derived from the microsaccade rate difference between targets and non-targets [17]; this is earlier than suggested by ERP studies. Animal studies provide evidence for early and low-level mechanisms that could be related to the effects we have found. There is evidence for the categorization of sound in the rat inferior colliculus (IC) [47], and for inhibitory inputs from the external nucleus of the IC to the SC that can affect eye movements [46].

The effect of Inter Trial Intervals on the oculomotor response

We observed a significant increase in the microsaccade and blink rates as a function of ITI (Figure 5). This could be explained by reduced alertness due to a lower stimulus rate, resulting in reduced inhibition in the longer ITIs. Such explanation is supported by the results of the pupil response (Figure 5e). Alertness induced more pupil dilation [48,49] in response to the Oddball [50]. Figure 4f illustrates the pupil response to Standard and Oddball sequences showing an oddball effect as previously found by Quirins et al. [25]. The pupil first dilated and then constricted after stimulus presentation, but the amount of constriction was correlated with the ITI (Figure 5e); pupil constriction might have been reduced by the readiness demanded by the upcoming stimulus. The pupil response and blink rates were calculated within a similar time range for all ITIs. The link between alertness and microsaccade inhibition was demonstrated, for example, in the

finding of reduced inhibition in ADHD in a continuous performance task, which was recovered by administering a stimulating medication[10]. It was also reported that higher attentional loads, as in the shorter ITIs with increased alertness, are associated with a lower microsaccade rate [51]. An alternative explanation may be related to the microsaccade preparation time; there is less time to prepare in the shorter intervals, resulting in fewer microsaccades.

Comparison with previous Oddball studies

Previous OMI studies of auditory oddballs [4] involved a task that could have influenced the results by generating an attention effect. For example, our preliminary results from a serial dependency study, in which participants were asked to count a colored patch from a group of red and green patches, showed a significantly longer OMI for the attended stimuli [20]. A task such as counting the oddballs [4] involves additional processing time to hold the current number of oddballs within working memory (WM) [52] and to make a decision involving target discrimination. Thus, it could have prolonged the saccadic inhibition for targets regardless of whether or not these targets were oddballs. In our study, the participants were asked to attend to all sounds without any request to pay specific attention to the oddballs in a passive attentive way. Unlike previous ERP studies that investigated the mismatch negativity (MMN) we didn't aim to bias attention away from the auditory stimuli by engaging the participants with a visual task. We instructed them to pay attention to the sounds (see the Methods for the specific instruction), but there was no control over their attention. We show here, for the first time, the OMI effects for auditory oddballs in a passive attentive paradigm (see [23–25] for a similar passive-attentive paradigm). However, these OMI effects appear smaller than those obtained with attended stimuli [4] or in response to visual stimuli as a function of contrast [6].

Our study implements an auditory oddball paradigm similar to that of Bekinschtein et al. [23], which measured the ERP markers of violations of auditory regularities, either "local" in time, within a single trial (similar to our exp1), or "global" across trials of several seconds (similar to our exp2). Their Local-Global paradigm suggests the existence of a hierarchical organization consisting of at least two levels of perceptual prediction mechanisms: (1) an early mechanism, reflected in the MMN signal, which is effective only in a limited time window for changes that are "local" in time [53], and (2) a later, more distributed predictive mechanism, reflected by P3b (a second subcomponent of P300) response to more "global" violations of expectations [2]. They report a global effect as a marker of awareness for a rare auditory pattern with an ITI of ~1.5 seconds, measured by P3b when participants were asked to count the oddballs. In contrast, when participants were engaged in mind-wandering or in an active visual target detection of letters, the P3b magnitude for the surprise sounds decreased dramatically [23]. Thus, it follows that in this study the P3b signal could have resulted from counting rather than as a marker of predictive violation because P3b is also related to context updating and is associated with memory operations [54] as holding the number of oddball occurrences in working memory. When we compared our results to this ERP study [23], we found both similarities and differences. Unlike Bekinschtein et al., we did not find an OMI effect for the reversed combination of a global Standard (AAAAB) and a global Deviant (AAAAA),

which implies a strong contribution of early mechanisms to the oddball OMI effect (see Figure 4e). Our participants reported being aware of the oddballs when asked after the experiment; however, their level of engagement and its contribution to the OMI are unknown. It is therefore impossible to distinguish between the contribution of an automatic change detection process and a higher-level predictive mechanism.

Summary And Conclusions

In measuring oculomotor inhibition (OMI) for microsaccades in response to auditory deviant tones, we found shorter inhibition onset in proportion to the pitch deviance (the saliency effect), and longer inhibition release latency for rare deviants (the surprise effect) as long as the inter-trail interval was shorter than 2.5 sec. Longer ITIs induced higher microsaccade and blink rates together with smaller pupil dilation, indicating a reduction of alertness. We also found an increased pupil dilation for the rare deviant tone as previously reported. These results were obtained with a passive attentive paradigm and without an active task to direct attention to or away from the deviant sound sequences. Thus, the use of involuntary ocular measures for assessing saliency and surprise could serve as a valuable tool in cognitive assessment and rehabilitation, especially for unresponsive individuals.

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Declarations

Author Contributions

OK and YSB designed the experiments. OK collected the data. OK and YSB developed the software used for running the experiments and the data analysis. OK analyzed the data and wrote the manuscript, YSB reviewed it.

Competing Interests: The authors declare no competing interests.

Data Availability: The experimental datasets generated during the current study will be available from the corresponding author upon reasonable request.

Figures

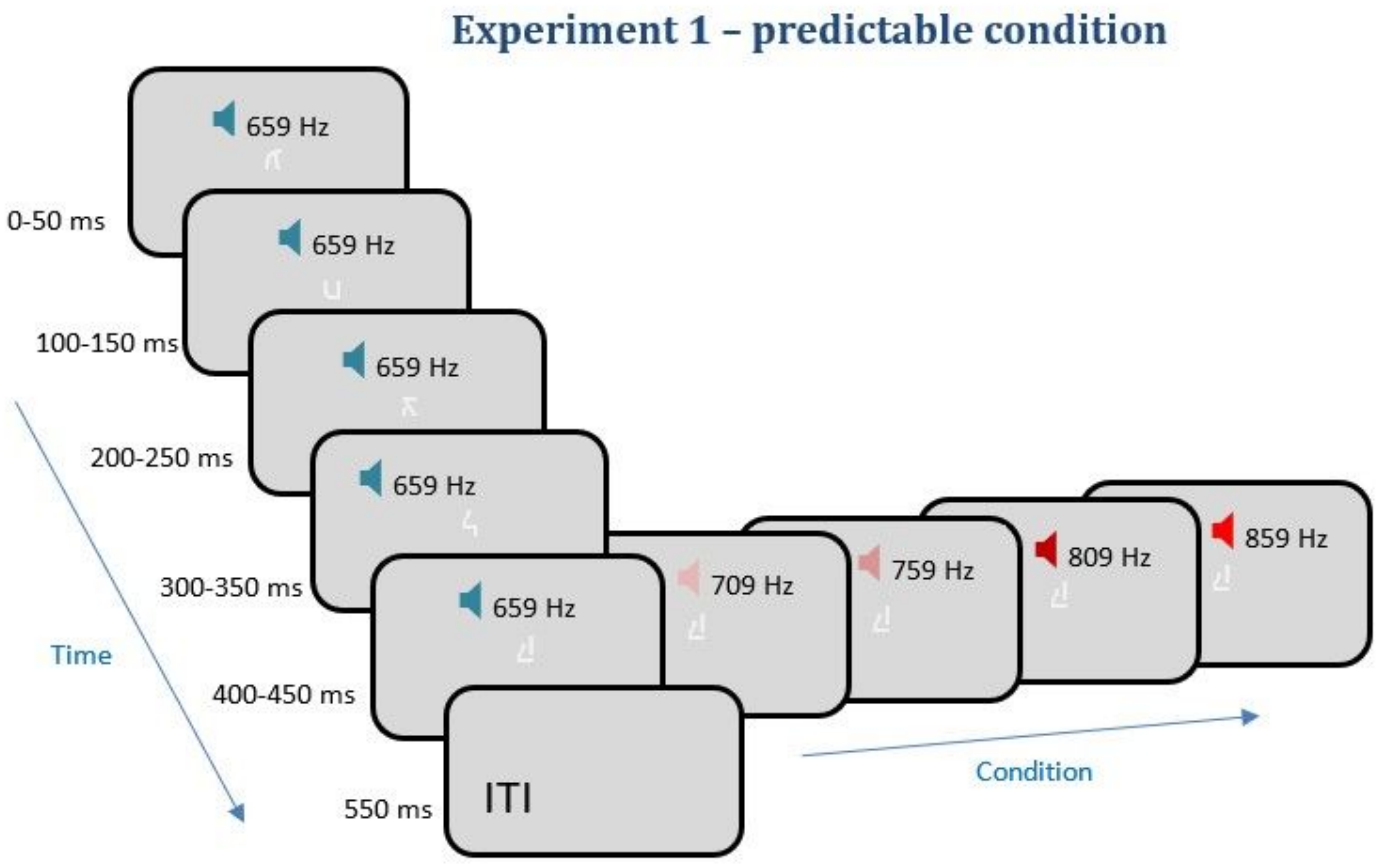

Figure 1

Schematic illustration of the trial sequence of experiment 1. There were auditory and visual stimuli of five conditions with a fifth tone frequency difference. Trials from the different conditions were played in separate blocks and there was no mixing between conditions.

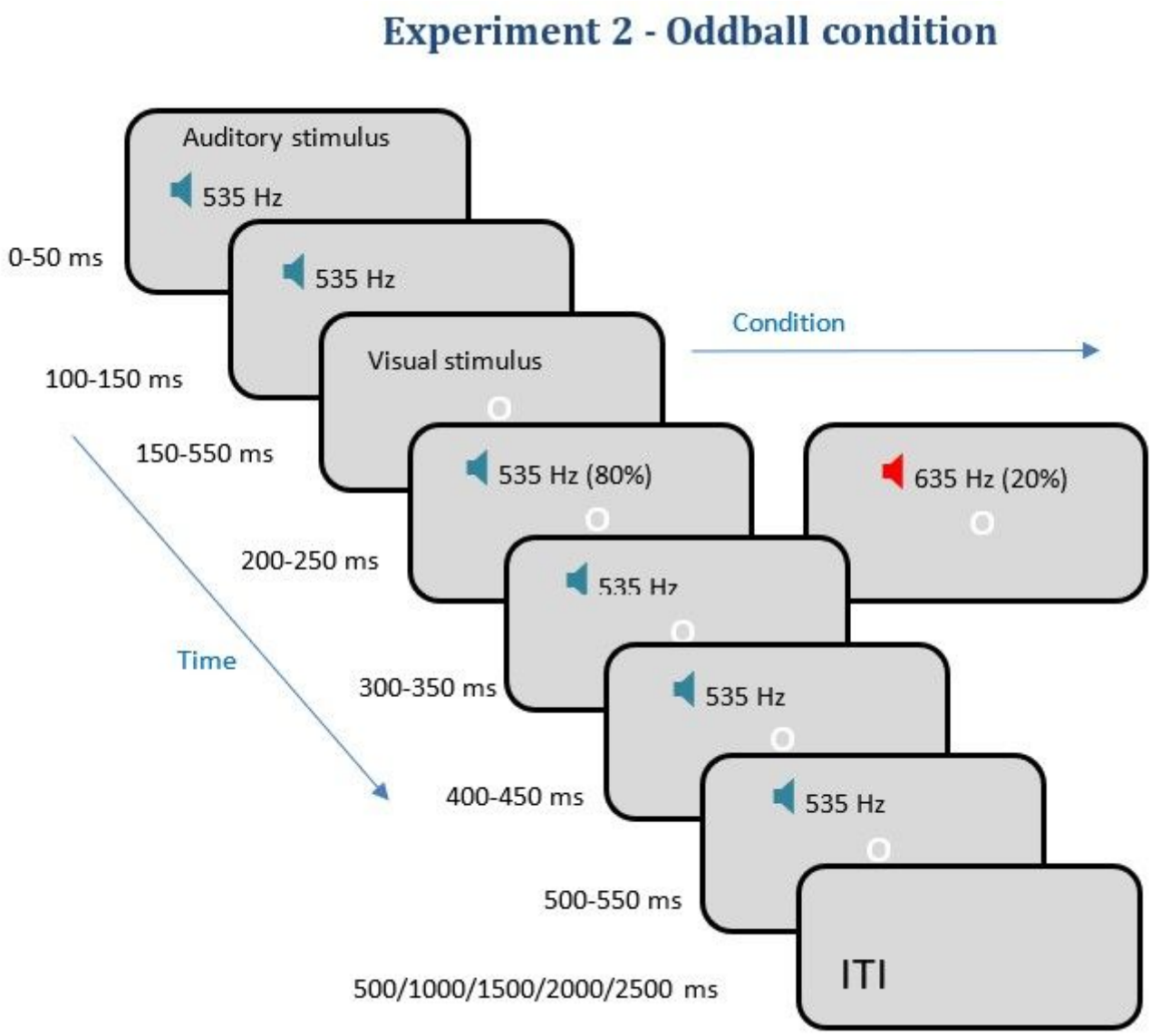

Figure 2

Schematic illustration of the trial sequence of experiment 2. Oddball trials with a deviant tone were interleaved within the Standard trials with a ratio of 20/80.

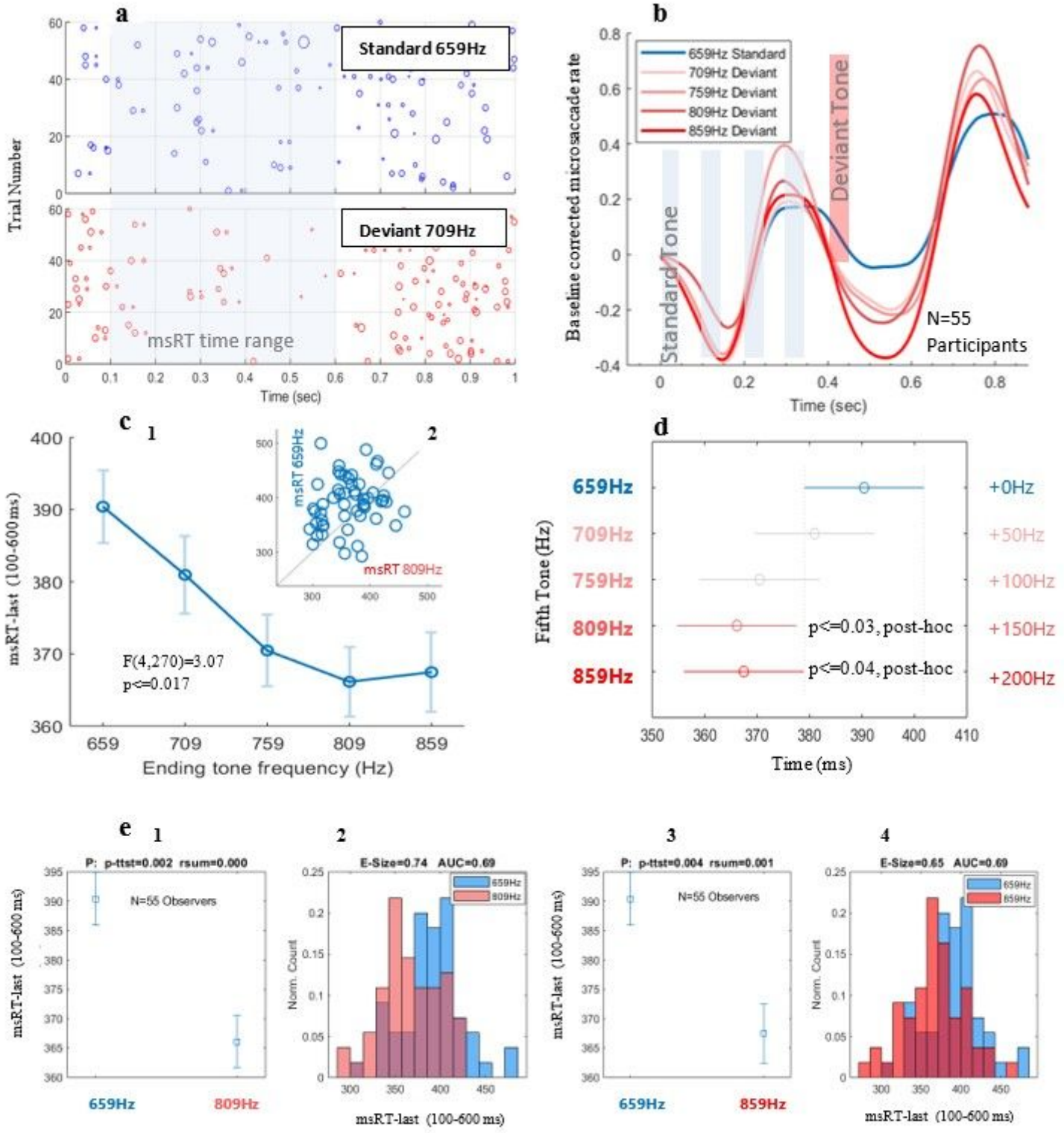

Figure 3

Results showing the deviance strength effect (experiment 1). (a) Microsaccade raster plot example, with 60 epochs per condition from a single participant. Each row represents one epoch and each dot a microsaccade with the dot size proportional to the saccade's size. (b) Microsaccade rate modulation functions for all conditions, averaged across participants and baseline corrected. (c) 1. Second inhibition onset estimated via msRT-last in the window [100-600 ms] marked by the light blue block in (a). The

msRT values were calculated per participant, demeaned, and then averaged across participants (n=55), with error bars denoting 1SE across participants. 2. Scatter plot showing participants' msRTs for the Standard condition (659 Hz) vs. the Deviant condition (809 Hz); note that most participants had a longer msRT for the Standard (positioned above the symmetry line). (d) To determine whether msRTs in the Standard condition (blue) differ from the Deviant (red), one-way ANOVA ($F(4,270)=3.07$, $p<=0.017$) and posthoc tests were performed. Two Deviant means (809,859 Hz) significantly differ from the Standard's mean; note that the bars do not overlap. Lower and upper limits of 95% confidence intervals are represented by the shortest and largest distance between the endpoints of the red and blue bars. (e) Standard and Deviant means as well as the Standard histogram comparisons (659 Hz) and the Deviant ones (809 Hz, 1, 2 and 859 Hz, 3, 4). Note that the p values here are shown without multiple comparison correction.

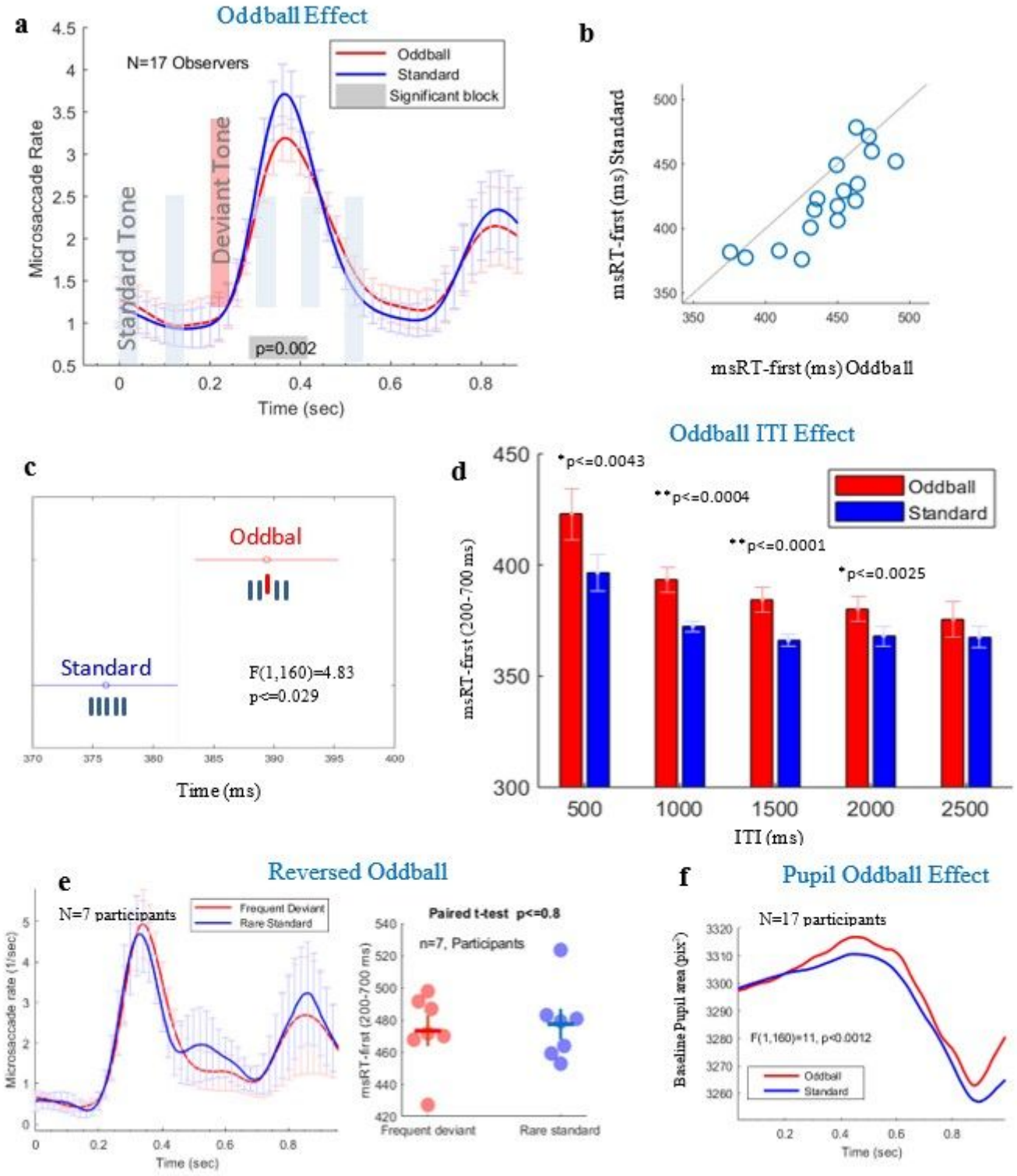

Figure 4

Results for the auditory oddball effect in different inter-trial intervals, ITIs (experiment 2). (a) Microsaccade rate modulation for the rare Oddball (red), compared with the Standard (blue), all ITIs combined, averaged across participants (N=17). A time segment with a statistically significant difference (in gray) was found between 300 and 420 ms after stimulus onset (p=0.002, Monte-Carlo, non-parametric permutation test). The faded bars illustrate the sound sequence timing. (b) A diagonal scatter plot of

individual participants' msRT (first), for the Oddball (X-axes) vs the Standard (Y-axes) conditions, with all ITIs combined. Note the consistently faster (below the diagonal) msRT for the Standard. (c) Two-way ANOVA results for the Oddball vs. Standard in all the ITIs combined. Lower and upper limits of 95% confidence intervals are represented by the shortest and largest distance between the endpoints of the red and blue bars. (d) The group average msRT (first) for the Standard and Oddball conditions for different ITIs (0.5-2.5 sec). Error bars denote 1SE across participants. Multiple comparisons were run using 2-tailed paired t-tests (Bonferroni correction was applied). A significant difference in msRT was found for the rare oddball effect in the short ITIs (ITI<2.5 sec). In all conditions, the msRT was calculated in a time window of 200-700 ms post-stimulus onset. (e) Results of seven participants for the reversed combination of Deviant and Standard tones. Microsaccade rate modulation for the frequent Deviant (AAAAB) in red and the rare Standard (AAAAA) in blue (left). Mean msRT (first) for the frequent Deviant and the rare Standard compared via paired t-test with no significant difference (right). (f) Pupil area (camera pixels2) for the Oddball in red compared with the Standard in blue baseline corrected to the time of the stimulus onset ($F(1,160)=11$, $p<0.0012$, Two-way Anova).

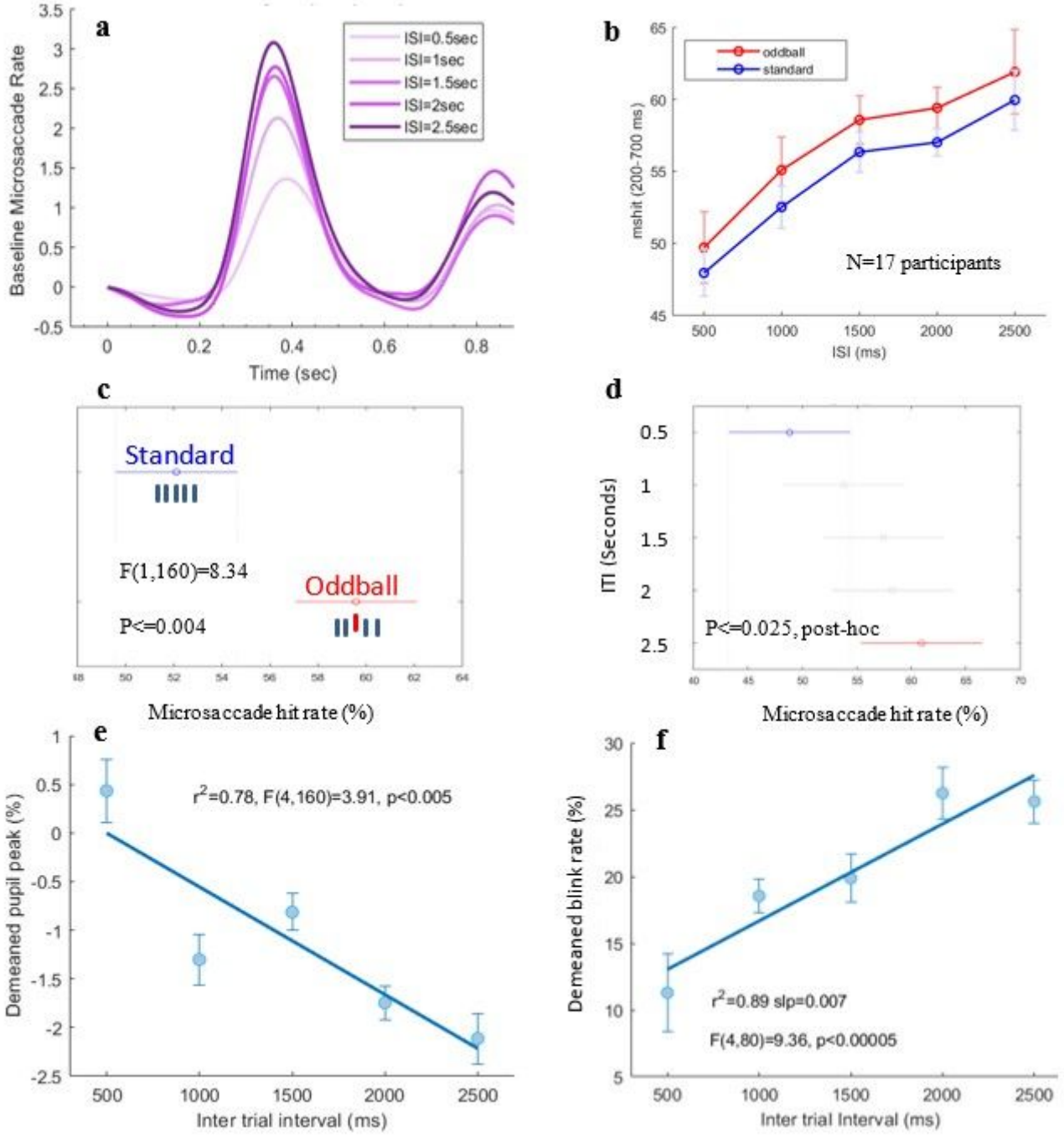

Figure 5

The effect of the inter-trial interval (ITI). (a) Microsaccade rate modulation for different ITIs, Standard and Oddball combined. (b) Percentage of trials with microsaccade (mshit) at a window of 200-700 ms after stimulus onset for all conditions. (c) Two-way ANOVA and posthoc test results for the Oddball vs. Standard in all the ITIs (0.5, 1, 1.5, 2, and 2.5 sec) combined ($F(1,160)=8.34$, $p<=0.004$)). (d) Two-way ANOVA ($F(4,160)=2.62$, $p<=0.037$) and posthoc tests results yielding a significant difference between ITI=0.5 sec and ITI=2.5 sec conditions. (e) Pupil area peak (% change) measurements, demeaned and readjusted with the grand average (see Methods), as a function of the inter-trial interval, showing a

negative correlation ($F(4,160)=3.91$, $p<0.005$). (f) Blink rate (%), demeaned and readjusted with the grand average, showing a positive correlation with ITI ($F(4,80)=9.36$, $p<0.00005$).