Research Paper

Multisensory integration in orienting behavior: Pupil size, microsaccades, and saccades

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ABSTRACT

Signals from different sensory modalities are integrated in the brain to optimize behavior. Although multisensory integration has been demonstrated in saccadic eye movements, its influence on other orienting responses, including pupil size and microsaccades, is still poorly understood. We examined human gaze orienting responses following presentation of visual, auditory, or combined audiovisual stimuli. Transient pupil dilation and microsaccade inhibition were evoked shortly after the appearance of a salient stimulus. Audiovisual stimuli evoked larger pupil dilation, greater microsaccade inhibition, and faster saccade reaction times compared to unimodal conditions. Trials with faster saccadic reaction times were accompanied with greater pupil dilation responses. Similar modulation of pre-stimulus pupil-size-change rate was observed between stimulus-evoked saccadic and pupillary responses. Thus, multisensory integration impacts multiple components of orienting, with coordination between saccade and pupil responses, implicating the superior colliculus in coordinating these responses because of its central role in both orienting behavior and multisensory integration.

1. Introduction

Salient events in the environment initiate orienting responses including gaze shifts and pupil dilation (Boehnke & Munoz, 2008; Sokolov, 1963). Salient stimuli can be of different modalities and therefore activate more than one sense, and to detect and react optimally, the signals induced by different modality stimuli are combined and integrated in the brain (Stein & Meredith, 1993). Orienting behavior is typically enhanced towards presentation of multi-modal stimuli that are aligned in space and time compared to uni-modal stimuli, a phenomenon referred to as multisensory enhancement (e.g., Corneil, Van Wanrooij, Munoz, & Van Opstal, 2002; Stein & Stanford, 2008; Stevenson et al., 2014). While providing great insights into multisensory processing, these investigations have been mostly confined to saccadic eye movements.

Pupil dilation and microsaccade occurrence are additional components of orienting (Corneil & Munoz, 2014; Wang & Munoz, 2015). Transient pupil dilation can be evoked following the appearance of salient stimuli, and is systematically modulated by stimulus saliency, with faster and larger evoked responses for higher stimulus contrast (Wang, Boehnke, Itti, & Munoz, 2014; Wang & Munoz, 2014). Microsaccade generation is also modulated by stimulus presentation (Hafed, 2011; Martinez-Conde, Otero-Millan, & Macknik, 2013), with suppression shortly after stimulus appearance (known as microsaccade

inhibition), followed with an increased rate of microsaccade occurrence (e.g., Engbert & Kliegl, 2003; Hafed & Clark, 2002; Valsecchi & Turatto, 2009).

Components of orienting, if guided by the same underlying neural mechanisms, should be coordinated. The midbrain superior colliculus (SC) receives convergent visual, auditory, and somatosensory inputs, and is considered one of the most important structures for multisensory integration (Stein & Meredith, 1993) and coordination of the orienting response (Boehnke & Munoz, 2008; Corneil & Munoz, 2014). The central role of the SC on pupil dilation and microsaccade generation has recently been revealed through several lines of evidence. Transient pupil dilation can be evoked by weak electrical microstimulation of the SC of behaving monkeys (Wang, Boehnke, White, & Munoz, 2012) and the optic tectum of owls (Netser, Ohayon, & Gutfreund, 2010). Furthermore, the effects of stimulus contrast, modality, and saccade preparation on the pupil response (Wang et al., 2014; Wang, Brien, & Munoz, 2015; Wang & Munoz, 2014) are similar to those observed on activity recorded from single neurons in the SC (Everling, Dorris, Klein, & Munoz, 1999; Marino et al., 2012; Wise & Irvine, 1983). Finally, the SC has been implicated in the generation of microsaccades, showing movement-related neural activity prior to microsaccade onset, with each neuron spatially tuned to a certain microsaccade direction and amplitude similar to tuning observed for macrosaccades (Hafed, Goffart, & Krauzlis, 2009; Hafed & Krauzlis, 2012).

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Here we investigate how multisensory integration impacts pupillary, microsaccadic, and saccadic responses in humans following the presentation of visual, auditory, or combined audiovisual stimuli. We hypothesize that sensory signals induced by stimuli of different modalities are integrated to produce coordinated orienting responses, enabling stronger orienting responses of pupil size, microsaccades, and saccades in the audiovisual condition, compare to the visual or auditory-alone condition. Furthermore, if saccade and pupil responses are mediated by the shared circuits, then evoked saccadic and pupillary responses should be correlated. Namely, trials with faster saccades should be accompanied by faster pupil responses. Moreover, the rate of pupil size change prior to stimulus appearance (baseline epoch) is known to modulate ensuing responses (Reimer et al., 2014). Because of the overlapped neural substrates, the influence of baseline pupil size change rate should be observed not only on saccade reaction times in saccade trials but also on stimulus-evoked pupil responses in fixation trials.

2. Materials and methods

2.1. Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board in accordance with the declaration of Helsinki. Twenty participants ranging between 18 and 35 years of age were recruited for this study. All participants had normal or corrected-to-normal vision, were naïve to the purpose of the experiment, provided informed consent, and were compensated for their participation.

2.2. Recording and apparatus

Eye position and pupil size were measured by a video-based eye tracker (Eyelink-1000 binocular-arm, SR Research, Osgoode, ON, Canada) at a rate of 500 Hz with binocular recording (left pupil was mainly used). Stimulus presentation and data acquisition were controlled by Eyelink Experiment Builder and Eyelink software. Stimuli were presented on a 17-inch LCD monitor at a screen resolution of 1280 × 1024 pixels (60 Hz refresh rate), subtending a viewing angle of 32° x 26°, and distance from the eyes to the monitor was set at 58 cm. Pupil area values recorded from the eye tracker were transformed to actual pupil size in diameter following previously described methods (Steiner & Barry, 2011; Wang et al., 2012; Wang & Munoz, 2014). Pupil size data can be distorted by eye movements because the size of the pupil depends on the angle of the eyeball in a video-based eye tracker. Saccade generation could also confound our test of the role of stimulus contrast on the evoked pupil responses, because any observed differences in pupil response between different conditions could be triggered by saccadic eye movement itself, rather than stimulus contrast per se. To maintain an accurate measure of pupil size before, during, and after visual stimulation and to avoid contamination by saccadic eye movements, participants were required to maintain visual fixation on a point at the center of the screen throughout the trial except for the trials that required saccadic eye movements.

2.3. Behavioral task (Fig. 1A)

Participants were seated in a dark room (background noise ~40 dB) and the experiment consisted of 210 trials. Each trial began with the appearance of a central fixation point (FP) (0.6° diameter; 6 cd/m^2) and two black open circle placeholders (0.6° diameter; 12° eccentricity to the left and right of FP on the horizontal axis) on a gray background (11 cd/m^2). After 1–1.4 s of central fixation, a peripheral stimulus was presented for 100 ms to the left or right of the FP (~12° eccentricity on the horizontal axis) on a subset of trials (90 trials) and participants were required to maintain steady fixation for an additional 2–2.5 s (Fix
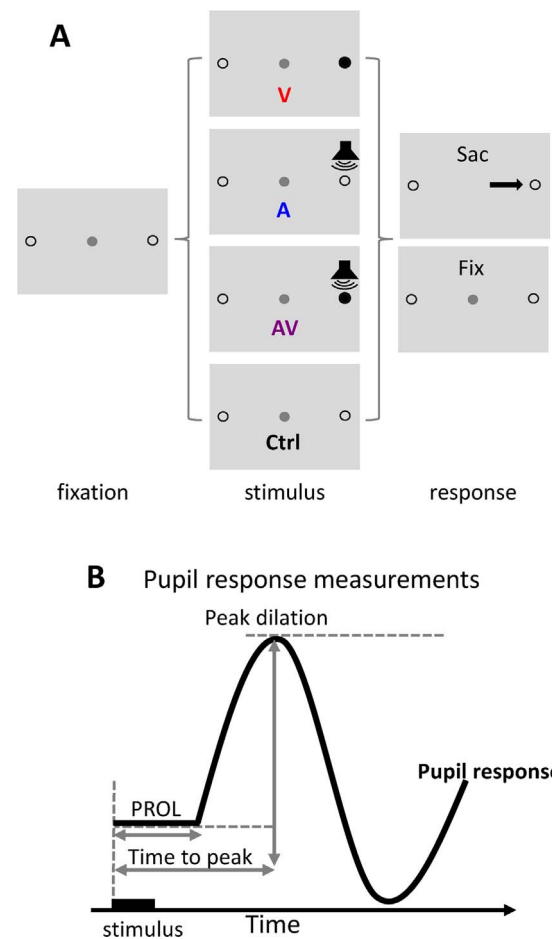

Fig. 1. **A)** Each trial started with a central fixation point on a gray background. After a random delay there was a brief presentation (100 ms) of a visual, auditory, or audiovisual stimulus (Fix) or no stimulus presented (Ctrl) and participants required to maintain central fixation for another 2-2.5 s. In some trials, the presentation of visual stimuli coincided with the disappearance of central fixation, and participants required to move their eyes to the stimulus (Sac). **B)** Measurements of the evoked pupil response. PROL: pupil response onset latency, V: visual, A: auditory, AV: audiovisual, Ctrl: control (no stimulus).

condition, Fig. 1A). Three types of peripheral stimuli were used, namely, visual (black, 0.6° diameter), auditory (60 dB SPL, narrow-band noise ranging from 2000 to 4000 Hz generated by Matlab software), or audiovisual (combined visual and auditory stimuli). There was also a no stimulus control (Ctrl condition, Fig. 1A) condition on a subset of trials (30 trials). In addition, to examine the effects of multisensory integration on saccadic behaviors and to also prevent the participant from strategically ignoring the peripheral stimulus, on another proportion of trials (90 trials), the FP was removed simultaneously with stimulus appearance (100 ms), and the participant was required to generate a saccade toward the stimulus (Sac condition, Fig. 1A), and maintain fixation until the disappearance of placeholders (1000 ms). Stimulus location (left and right), stimulus type (visual, auditory, and audiovisual), and task condition (Fix, Ctrl, and Sac) were randomly interleaved.

The current study used relatively low intensity for auditory stimuli to induce multisensory integration because multisensory integration is stronger using lower stimulus contrast (Fetsch, DeAngelis, & Angelaki, 2013; Populin & Yin, 2002; Stanford, Quessy, & Stein, 2005). Note that the sounds were presented from small speakers attached to the middle position of the left or right side of the monitor, and therefore there was a subtle difference on the horizontal location between visual and auditory stimulus (~3°). To reduce this potential influence, as mentioned, there were two placeholders on the left and right of the FP, and

participants were simply instructed to look at the left or right place-holder according to the stimulus location (left or right). Moreover, multisensory integration is still pronounced in saccade reaction times in despite subtle differences in spatial location of different modality stimulus (Kadunce, Vaughan, Wallace, & Stein, 2001).

2.4. Data analysis

The initial transient component of the evoked pupil response was of primary interest because it was related to the pupil response evoked by SC microstimulation (Wang et al., 2014, 2012). Trials with blinks or an eye position deviation of more than 2° from the central FP during the required period of fixation were excluded from analysis. There were at least 20 remaining trials for each condition. For each trial, original pupil diameter values were subtracted from the baseline pupil diameter value determined by averaging pupil size from 200 ms to stimulus onset (Bala & Takahashi, 2000; Moresi et al., 2008; Wang et al., 2012). Because pupil size was constantly changing even when there was no stimulus presented, to simplify data presentation and quantification, we normalized pupil diameter values by contrasting the visual stimulation versus no-stimulation conditions directly. Specifically, pupil values from each Fix trial were contrasted to the average pupil value from all Ctrl trials.

Fig. 1B shows a schematic of the measurements extracted to capture dynamics of transient pupil responses (Wang et al., 2014). The pupil response onset latency (PROL) was defined as the earliest point in which the stimulus pupil size change rate statistically exceeded the no-stimulus pupil size change rate ($p < 0.05$) and remained so for at least 50 ms. To compute the rate of pupil size change, following a similar procedure (Bergamin & Kardon, 2003; Wang & Munoz, 2014), we first increased the signal-to-noise ratio of pupil size values by filtering high frequency pupil change (change in pupil size exceeded 0.1 mm/ms) and smoothing each data point with averaging ± 25 sampling points. The rate of pupil size change was derived by the pupil size values after application of 15-point second-order polynomial moving Savitzky-Golay filter (Savitzky & Golay, 1964), which gradually reduced high-frequency component noises. The peak dilation was defined as the maximum value observed within 1000 ms after the stimulus onset, and the time to the peak dilation (peak time) was also measured.

To examine the correlation between pupil and saccade responses, we analyzed pupil dynamics in the Sac condition. The rate of pupil size change was used because this measure was more sensitive to moment-to-moment pupillary changes, therefore allowing us to examine this correlation prior to saccade eye movements. To calculate trial-by-trial correlation between SRT and pupil size dynamics, we used the average pupil size change rate value in a sliding 20 ms window starting from 100 ms before stimulus onset and correlated it with corresponding SRT in each participant. To eliminate any artifacts of pupil measures related to changes in eye position, we only included trials in which the eyes remained centrally fixated (removed trials where saccades has initiated). Two time windows were selected arbitrarily: a baseline epoch (50 ms to the stimulation onset) was selected to capture the influence of baseline (pre-stimulus) brain states, a stimulus epoch (160–200 ms after the stimulation onset) was selected to examine the coordination between saccade and pupil responses because it was close to the time of fastest stimulus-evoked pupil responses.

Microsaccades were detected using our previous algorithm (Brien, Corneil, Fecteau, Bell, & Munoz, 2009) that is similar to the algorithm developed by others (Martinez-Conde, Macknik, & Hubel, 2000). Briefly, the eye position data were differentiated to produce instantaneous horizontal and vertical velocities. The eye velocity threshold of microsaccades had to exceed 8°/sec and the instantaneous eye direction could not change more than 15°. The minimum duration of microsaccades that exceeded the velocity threshold was set to 5 sample points (10 ms). Microsaccade rate was first calculated on an individual subject (averaged all trials in each condition), then rates for

the corresponding conditions were averaged across participants (N = 20). Following previous research (e.g., Engbert and Kliegl, 2003; Laubrock, Engbert, & Kliegl, 2005; Valsecchi & Turatto, 2009), the histogram of microsaccades was scaled to a rate-per-second measure (computed within a moving window of 100 ms). Microsaccade direction analysis was not conducted due to insufficient number of microsaccades from each participant at the selected epochs.

On Sac trials, saccade reaction time (SRT) was defined as the time from the target appearance to the first saccade away from fixation that exceeded 30°/s. Failure to initiate a saccade within 1000 ms after the appearance of saccadic target, or failure to make a saccade to the correct location (within 1.5 deg radius around the target) were marked as errors for the saccade condition (Sac). These occurred infrequently (2.0, 9.3, and 1.2% for visual, auditory, audiovisual conditions, respectively) and were removed from analysis. On Fix trials, the trial was scored as an error if a saccade was made toward the stimulus within 500 ms after stimulus appearance, and these trials were removed from pupil analysis. A one-sided t test was used (except where indicated) to examine the multisensory integration hypothesis, that is, responses should be stronger in the audiovisual condition, compared to the visual- or auditory-alone conditions.

3. Results

3.1. Audiovisual enhancement of saccadic responses

On Sac trials, participants were required to make a saccade toward the stimulus location, and they generated faster SRTs on correct audiovisual trials (mean SRT: 356 ms), compared to correct visual (405 ms) or auditory (477 ms) trials (Fig. 2A; AV versus V: $t(19) = 4.51, p < 0.01$; AV versus A: $t(19) = 6.14, p < 0.01$). These results were consistent with several previous studies, showing enhanced responses in the multimodal condition when multisensory stimuli were aligned in space and time, compared to the unimodal conditions (Angelaki, Gu, & DeAngelis, 2009; Corneil et al., 2002; Fetsch et al., 2013; Goldring, Dorris, Corneil, Ballantyne, & Munoz, 1996). On Fix trials, participants were required to maintain central fixation. More erroneous saccades, triggered toward the stimulus, occurred in the audiovisual condition (13.7%), compared to the visual (6.1%) or
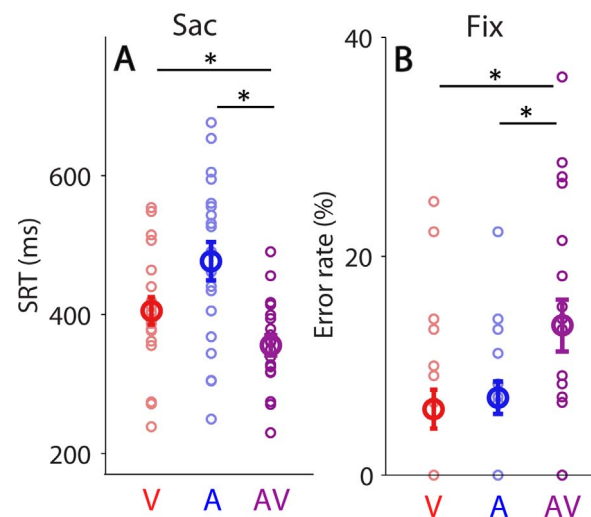
Fig. 2. Effect of multisensory integration on saccadic behaviors. **A)** Saccade reaction times at different stimulus conditions on saccade trials (20 participants). **B)** Erroneous saccade rates at different stimulus conditions on fixation trials (20 participants). The bold-circle represents the mean value across participants. The error-bar represents ± standard error across participants. The colored small-circle represents mean value for each participant. * indicates differences are statistically significant. SRT: saccade reaction times, Sac: saccade condition, Fix: fixation condition. V: visual, A: auditory, AV: audiovisual.
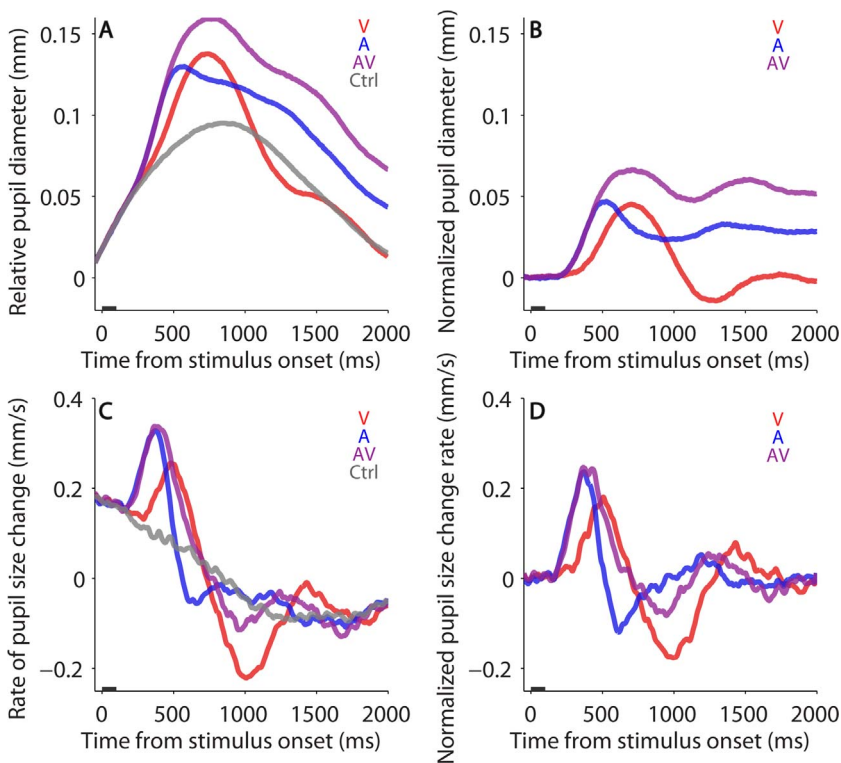
Fig. 3. Pupil dynamics following different stimulus presentation in Fix trials. **A, B)** Relative **(A)** and normalized (stimulus minus control condition) **(B)** pupil responses following the presentation of visual, auditory, or audiovisual stimuli (20 participants). **C, D)** Rate of pupil size change **(C)** and normalized rate of pupil size change (stimulus minus control condition) **(D)** following the presentation of visual, auditory, or audiovisual stimuli (20 participants). The gray bar on X-axis indicates the time line of stimulus presentation. V: visual, A: auditory, AV: audiovisual, Ctrl: control (no stimulus), Fix: fixation.

auditory (7.1%) condition (Fig. 2B; AV versus V: $t(19) = 3.9$, $p < 0.01$; AV versus A: $t(19) = 2.98, p < 0.01$), suggesting that it was more difficult to maintain central fixation in the audiovisual condition, compared to the unimodal conditions.

3.2. Audiovisual enhancement of pupil responses

Transient pupil dilation was evoked shortly after the presentation of salient visual or auditory stimuli compared to the no-stimulus condition (Fig. 3A: the subject-based averaged pupil response from correct Fix trials). This transient dilation was followed by constriction, which was consistent with our previous studies in humans (Wang & Munoz, 2014) and monkeys (Wang et al., 2014). Larger pupil dilation was evoked by the combined audiovisual stimuli (Fig. 3A). Pupil size in the no-stimulus condition was subtracted from pupil size of the stimulus condition to illustrate the pupil response specifically related to stimulus presentation (Fig. 3B; see Materials and Methods for details). As illustrated in Fig. 3C and D, the rate of pupil size change revealed the same pattern: the rate of pupil size change abruptly increased shortly after stimulus presentation.

To further examine multisensory integration in pupil responses, we calculated the pupil response onset latency (PROL; timing measurement) and pupil peak dilation (magnitude measurement). As illustrated in Fig. 4A, the PROL was 420, 296, and 309 ms for the visual, auditory, and audiovisual conditions, respectively. The PROL was shorter in the audiovisual compared to the visual condition (Fig. 4B, $t(19) = 7.32$, $p < 0.01$). However, there was no significant difference in PROL between the audiovisual and auditory condition (Fig. 4C, $t(19) = 0.84$, $p > 0.21$).

Peak dilation was 0.065, 0.081, 0.099 mm for the visual, auditory, and audiovisual conditions, respectively (Fig. 4D). As shown in Fig. 4E, dilation size was significantly larger in the audiovisual compared to visual condition ($t(19) = 3.27$, $p < 0.01$). Peak dilation was also larger in the audiovisual condition compared to the auditory condition (Fig. 4F; $t(19) = 1.75$, $p < 0.05$). Together, the results demonstrated multisensory enhancement on most parameters measured in the pupil orienting response.

3.3. Audiovisual enhancement of microsaccade responses

Microsaccades were identified (the epoch of 500 ms before to 1000 ms after stimulus onset in the Fix condition in Fig. 5A) that followed the relationship between saccade amplitude and peak velocity observed in the previous studies (for reviews: Hafed, 2011; Martinez-Conde, Macknik, & Hubel, 2004; Martinez-Conde et al., 2013). Fig. 5B illustrates microsaccade rate dynamics after stimulus appearance, showing microsaccade inhibition shortly after stimulus onset (Fig. 5C, stimulus versus control: 100–200 ms after stimulus appearance, $t(19) = 1.46, p = 0.058$), followed by microsaccade enhancement (Fig. 5C, stimulus versus control: 350–500 ms after stimulus appearance, $t(19) = 2.68, p < 0.05$). Fig. 5D illustrates normalized microsaccade rate (stimulus conditions subtracted from the control condition), highlighting microsaccade inhibition (Epoch I) and enhancement (Epoch II) that are consistent with previous studies (for reviews: Hafed, 2011; Martinez-Conde et al., 2004, 2013). Microsaccade inhibition in epoch I was greater in the audiovisual condition compared to the visual or auditory condition (Fig. 5E, V vs AV: $t(19) = 1.9$; A vs AV: $t(19) = 1.8$, all $ps < 0.05$). There was no multisensory enhancement observed in the later epoch (Fig. 5F, V vs AV: $t(19) = 0.29, p > 0.3$; A vs AV: $t(19) = 0.66, p > 0.7$).

3.4. Coordination between pupil and saccade responses

Although pupil measurements are less accurate when eye position is off-centered or during eye movements, similarities in pupil responses were still observed between Fix (Fig. 6A and B) and Sac (Fig. 6C and D) trials. Transient pupil dilation in Fix and Sac trials had similar onset latencies: that is, pupil size in the stimulus condition started to differentiate from the control condition ~240 ms after stimulus onset in Fig. 6A and B (the rate of pupil size change in Fig. 6C and D, differentiated ~160 ms after stimulus onset). Moreover, pupil responses were faster in audiovisual and auditory conditions compared to the visual condition in both Fix and Sac trials despite artifacts in pupil measurement from eye position and movements on Sac trials. Because the rate of pupil size change indicates moment-to-moment changes, we
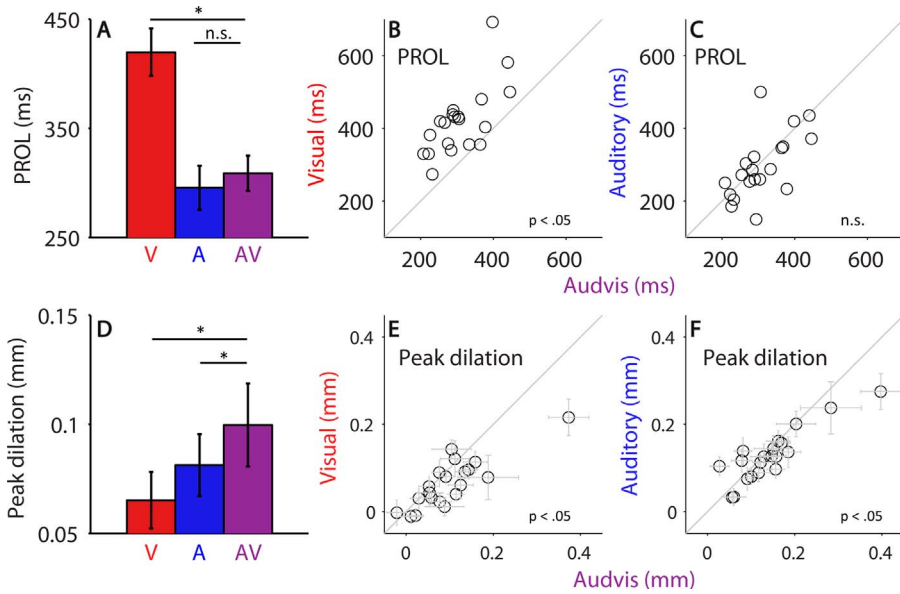
Fig. 4. Effect of multisensory integration on the pupil response. **A, D)** Modulation of stimulus condition (20 participants) on the pupil response onset latency (PROL) **(A)** and peak pupil dilation **(D)**. **B, E)** PROL **(B)** and peak dilation **(E)** between audiovisual and visual conditions for each individual participant. **C, F)** PROL **(C)** and peak dilation **(F)** between audiovisual and auditory conditions for each individual participant. In **A, D**, the error-bar represents ± standard error across participants. In **E, F**, the error-bar represent ± standard error within participants. * indicates differences are statistically significant, n.s.: not statistically significant, V: visual, A: auditory, AV: audiovisual, Audvis: audiovisual, PROL: pupil response onset latency, Peak: peak pupil dilation.
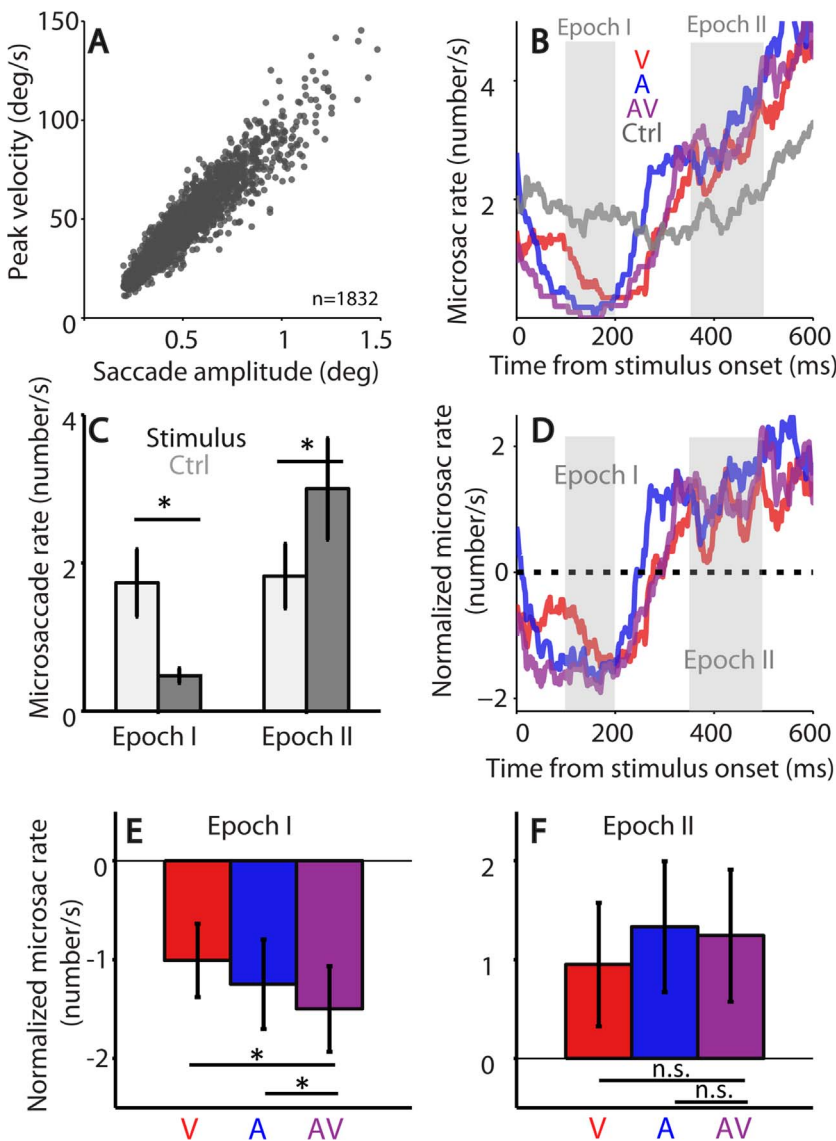

Fig. 5. Effect of multisensory integration on microsaccade occurrence. **A)** Relationship between microsaccade amplitude and peak velocity (n: number of microsaccades identified from 500 ms before to 1000 ms after stimulus onset). **B)** Microsaccade occurrence rate following the presentation of visual, auditory, audiovisual stimuli (20 participants). **C)** Microsaccade occurrence rate between stimulus and control (no stimulus) conditions during microsaccade inhibition (I: 100–200 ms) and enhancement epochs (II: 350–500 ms). **D)** Normalized microsaccade rate (stimulus minus control condition) following the presentation of visual, auditory, audiovisual stimuli. **E, F)** Modulation of stimulus condition on microsaccade occurrence rate on epoch I **(E)** and epoch II **(F)**. In **B, D**, the grey area represents the selected epochs for microsaccade analyses. In **C, E, F**, the error-bar represents ± standard error across participants, * indicates differences are statistically significant, n.s.: not statistically significant, V: visual, A: auditory, AV: audiovisual, Ctrl: control (no stimulus).
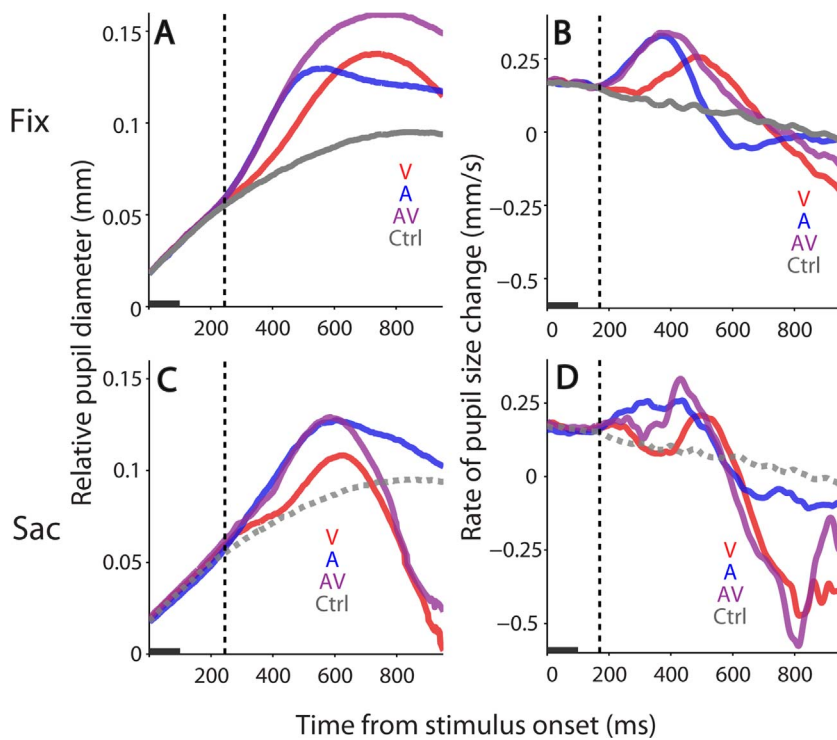
Fig. 6. Pupil dynamics following different stimulus presentations between Fix and Sac conditions. **A, B)** Pupil responses **(A)** and rates of pupil size change **(B)** following the presentation of visual, auditory, or audiovisual stimuli in Fix trials (20 participants). **C, D)** Pupil responses **(C)** and rates of pupil size change **(D)** following the presentation of visual, auditory, or audiovisual stimuli in Sac trials (20 participants). The gray bar on X-axis indicates the time line of stimulus presentation. The dark dotted vertical line indicates the estimated time that pupil size in the stimulus conditions differentiated from the control condition. V: visual, A: auditory, AV: audiovisual, Ctrl: control (no stimulus).

used this measurement to index momentary pupil responses.

Fig. 7A shows temporal dynamics of correlation coefficients between SRT and the rate of pupil size change (see Materials and Methods for the method excluding artifacts of pupil measures related to eye motion). There was a negative correlation between SRT and pupil size change rate in all conditions, suggesting trials with faster SRTs having stronger dilation responses. Fig. 7C summarizes the distribution of correlation coefficients for all subjects in the epoch of 160–200 ms after stimulus presentation, demonstrating a negative correlation (median correlation coefficient: V: -0.14, $t(19) = 3.0$, $p < 0.01$; A: -0.12, $t(19) = 2.1$, $p = 0.05$; AV: -0.10, $t(19) = 2.2$, $p < 0.05$, two-tailed parried t test of R values against zeros). Interestingly, the negative correlation between the rate of pupil size change and SRT was present even before the stimulus appearance in the visual and audiovisual conditions (Fig. 7B: epoch from 50 ms to stimulus onset: median correlation coefficient: V: -0.16, $t(19) = 4.1$, $p < 0.01$; A: 0.00, $t(19) = 0.05$, $p > 0.9$; AV: -0.11, $t(19) = 3.4$, $p < 0.01$). Although there was no correlations between SRT and the rate of pupil size change in the baseline (or pre-stimulus) epoch in the auditory condition, this may be attributed to the mechanisms involved particularly in auditory-triggered saccades (Bell, Fecteau, & Munoz, 2004; Corneil et al., 2002; Frens & Van Opstal, 1995; Gabriel, Munoz, & Boehnke, 2010).

In Fix conditions, trials were separated according to the rate of pupil

size change (larger or smaller- median split) during the baseline pupil epoch (averaged from 50 ms before to the stimulus appearance). Fig. 8A and B illustrate pupil dynamics with larger or smaller baseline rates of pupil size change, respectively. Dynamics of pupil size change rate were different between the two baseline pupil size change rate conditions in the control (no-stimulus) condition (gray lines in Fig. 8A and 8B). To normalize the data, we contrasted pupil responses between stimulus and no-stimulus condition in each baseline pupil size change rate condition separately. Consistent with previous baseline modulations on SRTs in Sac trials, the results demonstrated stronger pupil responses to the stimulus when baseline pupil size change rate was larger, compared to when it was smaller in the visual (Fig. 8C), auditory (Fig. 8D), and audiovisual conditions (Fig. 8E, cyan bar on the x-axis indicates the time line at which differences were statistically significant, $p < 0.05$).

4. Discussion

Presentation of a salient stimulus initiates a series of coordinated movements, including saccade, pupil, and microsaccade responses, to orient the body for appropriate action (Lynn, 1966; Sokolov, 1963). Here, we demonstrated that multisensory integration influenced these responses. Importantly, larger pupil dilation and stronger microsaccade inhibition, as well as faster SRTs, were observed when an auditory and
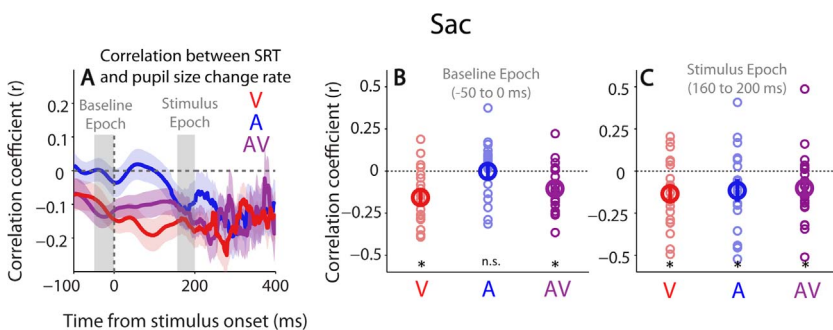

Fig. 7. Relationship between saccade and pupil responses in Sac trials. **A)** Correlation coefficients between SRT and the rate of pupil size change dynamics following the presentation of visual, auditory, or audiovisual stimuli (20 participants). **B, C)** Distribution of correlation coefficients for the relationship between SRT and rate of pupil size change in the epoch of 160–200 ms **(B)** and -50–0 ms **(C)** for all participants in the visual, auditory, and audiovisual condition. In **A**, the black vertical and horizontal dotted lines indicate the time of stimulus onset and a zero value of correlation coefficient, respectively. The shaded colored region surrounding the correlation coefficient value represents ± standard error range (across participants) for different conditions. In **B,C**, the vertical colored bold-circle represents the mean value of correlation coefficient across all participants for each condition, and the error-bar represents ± standard error across participants for each condition. The colored small-circle represents correlation coefficient for each participant. The horizontal dotted line represents a zero value of correlation coefficient ($r = 0$). * indicates differences are statistically significant, n.s.: not statistically significant, V: visual, A: auditory, AV: audiovisual.
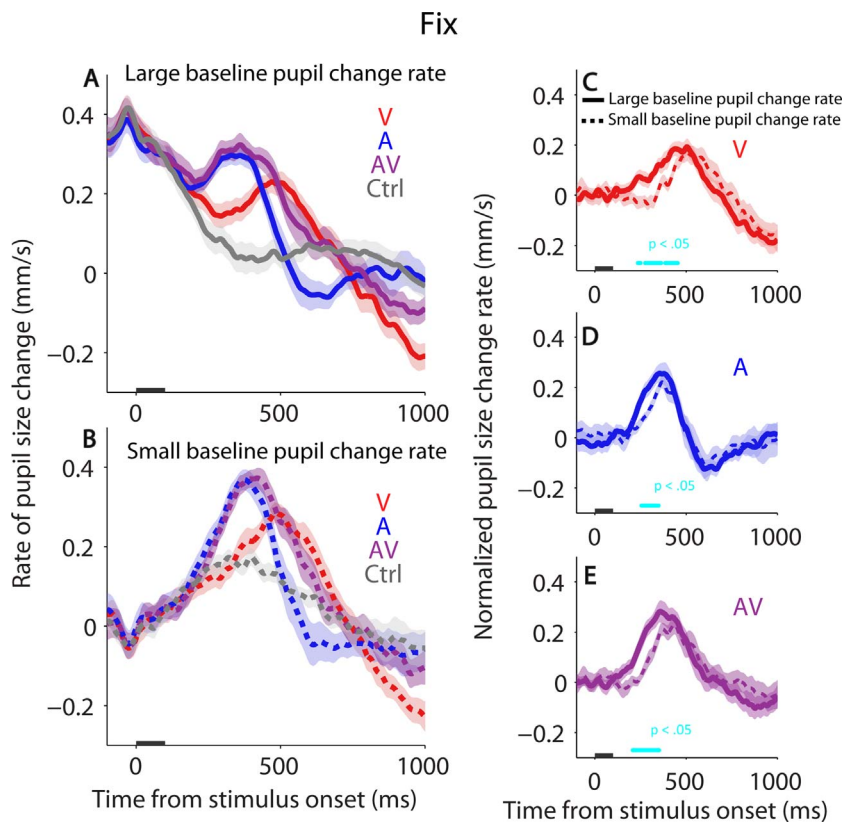
Fig. 8. Baseline pupil-size-change rate modulation on the pupil response in Fix trials. A, B) Baseline pupil effects on visual, auditory, audiovisual, and control conditions (20 participants) with (A) larger and (B) smaller baseline pupil size change rate (50 ms to stimulus onset). C, D, E) Normalized pupil size change rate (stimulus minus no-stimulus condition) between larger and smaller baseline pupil size change rate following the presentation of (C) visual, (D) auditory, and (E) audiovisual stimuli. The gray bar on X-axis indicates the time line of stimulus presentation. The shaded colored regions surrounding the pupil velocity value represent ± standard error range (across participants) for different conditions. In C-E, the cyan bar on the x-axis indicates the time line at which differences between larger and smaller baseline pupil velocity conditions were statistically significant ($p < 0.05$). V: visual, A: auditory, AV: audiovisual, Ctrl: control (no stimulus).

visual stimulus was aligned in space and time, compared to when the visual or auditory stimulus was presented alone. Moreover, saccade and pupil responses were correlated: trials with faster SRTs were accompanied with greater pupil dilation responses. Trials with larger baseline pupil size change rate were accompanied with faster SRTs on Sac trials and stronger pupil dilation on Fix trials. Together, multisensory integration was manifested on saccade, pupil, and microsaccade responses, and the coordination between saccade and pupil responses was present across stimulus conditions. Because the superior colliculus is importantly involved in both multisensory integration and the initiation of the orienting response (Boehnke & Munoz, 2008; Corneil & Munoz, 2014; Stein & Meredith, 1993), our results implicate the SC in co-ordinating such behavior.

4.1. Effects of audiovisual presentation on pupil size and microsaccade as components of orienting

Because pupil and microsaccadic responses are also components of orienting (Corneil & Munoz, 2014), multisensory integration should not only impact saccades (Stein & Meredith, 1993) but also pupil and microsaccade responses. Although pupil responses induced by the presentation of combined visual and auditory stimuli were previously examined in monkeys, stimulus locations from different modality stimuli were not spatially aligned, and monkeys were not required to respond to the auditory stimulus (Wang et al., 2014). Given the importance of stimulus location in multisensory integration (Meredith & Stein, 1996), it is crucial to examine multisensory integration effects when an auditory and visual stimulus are combined in space and time. In the current study, audiovisual stimuli were aligned spatially and temporally and were task-relevant to participants. We found faster SRTs in the audiovisual condition, compared to the visual or auditory condition (Fig. 2). Importantly, pupil responses evoked by stimulus appearance were larger in magnitude in the audiovisual condition compared to both the visual and the auditory condition (Figs. 3 and 4 D–E). The pupil response onset latency in the audiovisual condition was similar to that in

the auditory condition, but faster than that in the visual condition (Fig. 4A–C), together demonstrating effects of multisensory integration in pupil size. Our results are also consistent with a recent study showing larger pupil dilation following foveal presentation of audiovisual stimuli than the linear summation that was obtained in each unimodal condition in a manual detection task (Rigato, Rieger, & Romei, 2016). It is interesting to note that the presentation of a visual stimulus in the fovea often results in pupil constriction (Barbur, 2004; Rigato et al., 2016), but a sudden appearance of a salient stimulus in the periphery (or beyond) regularly evokes pupil dilation. A key difference between these two situations is that presenting a salient stimulus in the periphery initiates various orienting responses such as spatial attention, saccades, and pupil dilation to orient the body for the salient stimulus. However, attentional resources are already confined to the fovea prior to any stimulus presented at the fovea. Future research is required to investigate the differences between presenting a stimulus at the fovea and at other eccentric locations.

Microsaccade generation was greatly suppressed after stimulus presentation regardless of stimulus modality (Fig. 5B). These results are consistent with findings in the literature (e.g., Engbert & Kliegl, 2003; Hafed & Clark, 2002; Hafed & Ignashchenkova, 2013; Laubrock et al., 2005; Valsecchi & Turatto, 2007, 2009; Valsecchi, Betta, & Turatto, 2007; Rolfs, Kliegl, & Engbert, 2008). Moreover, stronger microsaccade inhibition was observed in the audiovisual condition, compared to the visual- or auditory-alone condition (Fig. 5E), although the influence of cross-modal stimuli on microsaccade direction was not examined due to insufficient number of microsaccades observed in each participant. Overall, our results demonstrated similar modulation of pupil size and microsaccade generation by multisensory integration. Such comparable modulation via multisensory integration has previously been suggested by another study using a visual search task (Privitera, Carney, Klein, & Aguilar, 2014), although the accuracy of the pupil measurement in that study may be hampered by free movements of the eyes.

4.2. Correlation between saccade and pupil responses and its potential function

The orienting response evoked by salient stimuli is thought to heighten perception and prepare the body for immediate action (Lynn, 1966). To optimize these adjustments of the organism to its environment, different components of the orienting response such as saccades and pupil size should be coordinated. Our results support this hypothesis: 1) trials with faster SRTs were accompanied with greater pupil dilation responses (Fig. 7A and C); 2) the comparable modulation of baseline (pre-stimulus) pupil size change rate between saccadic and pupillary responses was also present. Trials with larger baseline pupil velocities accompanied faster SRTs on Sac trials (Fig. 7B), and stronger evoked pupillary responses on Fix trials (Fig. 8), although SRT effects on Sac trials were not present in the auditory condition. Together, these results suggest that saccade and pupil responses were indeed coordinated.

The observed baseline pupil modulation could be mediated via the level of internal brain states such as arousal (Aston-Jones & Cohen, 2005). The absence of the baseline modulation in the auditory condition on Sac trials could be attributed to different saccade threshold mechanisms involved in auditory-triggered saccades, compared to visual-evoked saccades (Bell et al., 2004; Corneil et al., 2002; Frens & Van Opstal, 1995; Gabriel et al., 2010), or it could suggest that the arousal modulation on auditory saccadic responses is not effective without additional visual signals. Future research is required to address these questions. There are some potential advantages of this coordination on the orienting responses of pupil size and saccade. The pupil dilates prior to saccade initiation, and this increase in pupil size could increase visual sensitivity to optimize perceptual processes immediately after redirecting of the eyes. Note that although this orienting pupil dilation is thought to slightly increase visual sensitivity without diminishing visual acuity, there is still no direct evidence to support this hypothesis. Future research is required to systematically examine the functional role of pupil dilation in visual or more general sensory processing. Nevertheless, the concerted coordination also suggests the shared neural mechanism involved in the initiation of saccade and pupil responses. What brain areas could coordinate saccade and pupil responses? The most obvious candidate is the superior colliculus.

4.3. Role of the superior colliculus in multisensory integration and coordinating the orienting response

The midbrain SC is organized into functionally and anatomically differentiated layers (for a recent review White & Munoz, 2011). The superficial layers (SCs) receive inputs from early visual areas exclusively, including the retina and the primary visual cortex, whereas the intermediate layers (SCi) receive inputs from the SCs as well as from multisensory and frontal-parietal areas, and projects directly to the premotor circuit in the brainstem to initiate the orienting response, including shifts of gaze and attention, pupil dilation, and microsaccade responses (Boehnke & Munoz, 2008; Corneil & Munoz, 2014; Fecteau & Munoz, 2006; Knudsen, 2007; Mysore & Knudsen, 2013; Sparks, 1986). Because the SCi receives visual, auditory, and somatosensory inputs, and many neurons in the SCi respond to stimuli from multiple modalities, it has been hypothesized that the SCi is critical for multisensory integration (Stein & Meredith, 1993). Seminal studies have shown larger responses of SCi multisensory neurons after presenting multi-modal stimuli aligned in space and time, compared to presentation of uni-modal stimuli (Meredith & Stein, 1986; Stein & Stanford, 2008).

The link between the SCi and pupil control has recently been tested directly (Wang & Munoz, 2015). Weak microstimulation of the SCi in monkeys evokes transient pupil dilation (Netser et al., 2010; Wang et al., 2012), and this pupil dilation is similar to that induced by salient stimuli (Wang et al., 2014; Wang & Munoz, 2014). Higher contrast visual stimuli evoke larger and faster pupil dilations (Wang et al., 2014; Wang & Munoz, 2014) as well as sensory responses in the SCi (Marino et al., 2012). Response latencies for auditory stimuli are faster than visual stimuli in both pupil responses (Wang et al., 2014; same findings here in Fig. 4A) and SCi activity (Bell et al., 2004; Wise & Irvine, 1983). Finally, both SCi activity (Everling et al., 1999) and pupil responses (Wang, McInnis, Brien, Pari, & Munoz, 2016; Wang et al., 2015) are modulated by saccade preparation. These results collectively suggest the involvement of the SCi in the control of pupil responses.

The SCi is also causally involved in the control of microsaccade generation as well as larger saccade generation (for a recent review Hafed, 2011). Neurons in the rostral SC are linked to the generation of microsaccades, showing movement-related activities prior to microsaccade onset, with each neuron is spatially tuned to a particular microsaccade direction and amplitude, these characteristics are similar to those observed in larger saccades (Hafed et al., 2009; Hafed & Krauzlis, 2012). Thus, since the SCi is importantly involved in the control of both pupil and microsaccade responses, it is likely a key structure underlying observed multisensory integration in the current study.

Results of multisensory enhancement in magnitude, but not in timing of evoked pupil responses (auditory vs audiovisual), are also consistent with our hypothesis. Because of the temporal asynchrony in the arrival time between auditory and visual responses in the SCi (faster in auditory, e.g., Bell, Corneil, Munoz, & Meredith, 2003; Bell et al., 2004; Jay & Sparks, 1987; Stein & Stanford, 2008), the pupil response induced by audiovisual stimuli should be enhanced in magnitude (overlapping in response timing), but not in latency (non-overlapping in arrival timing). In summary, we argue that the SCi integrates both auditory and visual signals from sensory pathways, and sends the integrated command to both saccade and pupil premotor circuits to initiate coordinated orienting responses of saccade, microsaccade, and pupil size.

4.4. Conclusion

The SC, a hub of sensory and motor processing, integrates sensory-related and goal-directed signals to form a priority map to coordinate the orienting response that includes shifts of gaze and attention, pupil and microsacde responses (Corneil & Munoz, 2014; Fecteau & Munoz, 2006; Gandhi & Katnani, 2011; Krauzlis, Lovejoy, & Zenon, 2013; Wang & Munoz, 2015). Dissimilar to most research that focuses on single orienting response, here, we demonstrated multisensory integration influenced three components of orienting, with the coordination between saccade and pupil responses, and argue an important role of the SC on such behavior. Further investigation of the various orienting components is thus critical to understand how they are coordinated to optimize performance.

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