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NEUROSYSTEMS

Modulation of stimulus contrast on the human pupil orienting response

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Abstract

The sudden appearance of a novel stimulus initiates a series of responses to orient the body for appropriate actions, including not only shifts of gaze and attention, but also transient pupil dilation. Modulation of pupil dynamics by stimulus properties is less understood, although its effects on other components of orienting have been extensively explored. Microstimulation of the superior colliculus evoked transient pupil dilation, and the initial component of pupil dilation evoked by microstimulation was similar to that elicited by the presentation of salient sensory stimuli, suggesting a coordinated role of the superior colliculus on this behavior, although evidence in humans is yet to be established. To examine pupil orienting responses in humans, we presented visual stimuli while participants fixated on a central visual spot. Transient pupil dilation in humans was elicited after presentation of a visual stimulus in the periphery. The evoked pupil responses were modulated systematically by stimulus contrast, with faster and larger pupil responses triggered by higher contrast stimuli. The pupil response onset latencies for high contrast stimuli were similar to those produced by the light reflex and significantly faster than the darkness reflex, suggesting that the initial component of pupil dilation is probably mediated by inhibition of the parasympathetic pathway. The contrast modulation was pronounced under different levels of baseline pupil size. Together, our results demonstrate visual contrast modulation on the orienting pupil response in humans.

Introduction

Pupil size is controlled by balanced activity between the parasympathetic and sympathetic pathways. A sudden increase in illumination results in an activation of the parasympathetic system to initiate pupil constriction, whereas a luminance decrease mostly activates the sympathetic system to increase pupil size (Loewenfeld, 1999; Gamlin, 2006). These illumination-dependent modulations are referred to as the light and darkness reflex, respectively. Pupil size is also widely used to index cognitive processing (Beatty, 1982; Nassar *et al.*, 2012; Wierda *et al.*, 2012; Eldar *et al.*, 2013), probably mediated by arousal systems via the locus coeruleus–norepinephrine network (Aston-Jones & Cohen, 2005), and a growing number of studies have incorporated pupil size in clinical investigation (Bremner, 2009; Karatekin *et al.*, 2010; Daluwatte *et al.*, 2013; Frost *et al.*, 2013).

Changes in pupil size have also been associated with the orienting response (Sokolov, 1963; Lynn, 1966), and presentation of a salient stimulus initiates not only saccades and attentional shifts (Carrasco, 2011; Kowler, 2011), but also transient pupil dilation (Qiyuan *et al.*, 1985; Loewenfeld, 1999; Netser *et al.*, 2010; Wang *et al.*, 2014). The superior colliculus (SC), a critical structure in the control of saccadic eye movements and attention (Gandhi & Katnani, 2011; Krauzlis *et al.*, 2013), has been hypothesized to encode stimulus saliency to initiate various components of the orienting response (Fecteau & Munoz, 2006; Boehnke & Munoz, 2008; Knudsen, 2011). Recently, the role of the SC was extended to pupil dynamics because SC microstimulation evoked transient pupil dilation (Netser *et al.*, 2010; Wang *et al.*, 2012). Furthermore, similar modulations of stimulus contrast, as one of the most primitive components of saliency (Itti & Koch, 2001; Borji *et al.*, 2013), on SC activities and pupil size were demonstrated in monkeys, suggesting that the SC could be involved in coordinating stimulus-evoked pupil dilation (Wang *et al.*, 2014).

Although stimulus contrast modulated evoked pupil responses, the effect has yet to be established in humans. Moreover, the individual contribution of sympathetic and parasympathetic pathways to this behavior is less clear. Here, we manipulate local stimulus contrast to examine the contrast effect on human pupil responses. Consistent with previous results in monkeys (Wang *et al.*, 2014), transient pupil dilation can be evoked by visual stimuli and, importantly, the onset and size of evoked pupil responses scale with the level of stimulus contrast, with faster and larger pupil responses observed for higher contrast stimuli. The pupil response onset latency (PROL) evoked by high contrast stimuli is similar to that induced through the light reflex, and is significantly faster than the darkness reflex, suggesting that the initial component of transient pupil dilation is probably mediated by inhibition of the parasympathetic pathway. Furthermore, the effects of stimulus contrast are consistent under different levels of baseline pupil size, manifesting

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the contrast modulation regardless of the level of arousal. Overall, our results demonstrate the modulation of stimulus contrast on transient pupil responses in humans, and argue that the SC may coordinate this behavior.

Materials and methods

Participants

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

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 (the left pupil was mainly used, except for consensual analyses). 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° × 26°, and the distance from the eyes to the monitor was set at 58 cm. We used the following method to transfer output pupil area values recorded from the eye tracker to actual pupil size (Steiner & Barry, 2011; Wang *et al.*, 2012). We made a number of different-sized false pupils and placed them at approximately the same position as the participants' pupil position during data recording. Eyelink pupil values from false pupils were used to transform Eyelink pupil values recorded from real participants to actual pupil diameter simply using a linear interpolation after using a square root of all pupil area data. 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 an influence of the 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.

Visual stimulus task

Participants were seated in a dark room and the experiment consisted of 210 trials lasting approximately 40 min (Fig. 1A). Each trial began with the appearance of a central fixation point (FP) (0.6° diameter; 6 cd/m^2) on a gray background (11 cd/m^2). After 1–1.4 s of central fixation, a peripheral visual stimulus (0.6° diameter) was presented for 100 ms to the left or right of the FP (8° 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 condition, Fig. 1A). Because stimulus-evoked pupil responses were attenuated by the repetition of the same stimulus repeatedly via habituation (Netser *et al.*, 2010; Steiner & Barry, 2011), we included a no-stimulus control (Ctrl condition, Fig. 1A) condition on a subset of trials (30 trials) to reduce the habituation effects. In addition, to compare different orienting behaviors (saccade and pupil response) and to prevent the subject from strategically ignoring the peripheral visual stimulus, on another proportion of trials (90 trials), the FP was removed simultaneously with visual stimulus appearance, and the participant was required to generate a saccade toward the stimulus (Sac condition, Fig. 1A). The intertrial interval was about 3.5 s, during which time a slightly dimmer blank

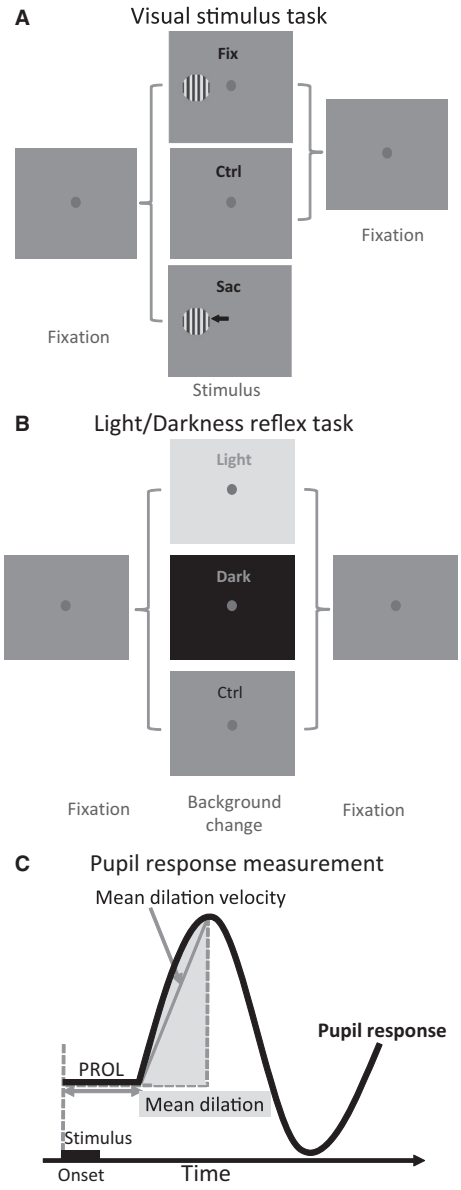

FIG. 1. (A) Each trial started with a central FP (6 cd/m^2) on a gray background (11 cd/m^2). After a random delay there was a brief presentation (100 ms) of a visual stimulus (Fix) or no stimulus presented (Ctrl) and participants were required to maintain central fixation for another 2–2.5 s. In some trials, the presentation of visual stimuli coincided with the disappearance of central fixation, and participants were required to move their eyes to the stimulus (Sac). Note that the displayed squarewave grating circle here is only for illustration of the paradigm. (B) Each trial started with a central FP (6 cd/m^2) on a gray background (11 cd/m^2). After a random delay the background luminance became brighter (Light: 21 cd/m^2) or dimmer (Dark: 1 cd/m^2), and participants were required to maintain central fixation for another 2–2.5 s. (C) Measurements of the evoked pupil response. Ctrl, control condition; Fix, fixation condition; PROL, pupil response onset latency; Sac, saccade condition.

screen (8 cd/m^2) was presented to inform participants of this interval.

Pupil size is sensitive to the level of illumination, with a constriction following increases in illumination and dilation following decreases in illumination (Loewenfeld, 1999). Therefore, changes in pupil size can be driven by a sudden change of overall illumination due to the brief presentation of luminant stimuli. To eliminate these effects, the peripheral stimulus was a circular squarewave grating with a clear contour (16 cycles/deg, two luminance levels), which resulted in a stimulus with the same average luminance as background (11 cd/m^2). Contrast is defined as $(Lum_{high}-Lum_{low})/(Lum_{high}+Lum_{low})$, and three levels of stimulus contrast were used (0.98, 0.74, and 0.49), which were referred to as the high, mid, low contrast, respectively. Although peripheral contrast sensitivity is low for such high spatial frequency (Peli *et al.*, 1991), the stimulus was visible to participants because they made correct saccades toward the stimulus on most of the saccade trials (average error rate for the low contrast condition was 3.1%, ranging between 0 and 13%). Stimulus location (left and right), stimulus contrast (high, mid, and low), and task condition (Fix, Ctrl, and Sac) were randomly interleaved.

Light/dark reflex task

Seven participants (age range from 18 to 35 years; four of them from the previous experiment) were recruited for the light/dark reflex task (Fig. 1B). Each trial began with the appearance of a central FP (0.5° diameter; 6 cd/m^2) on a gray background (11 cd/m^2). After 1–1.2 s, background luminance either increased (21 cd/m^2), decreased (1 cd/m^2), or stayed the same (11 cd/m^2), and the participants were required to maintain steady fixation for an additional 2 s. Background luminance conditions were randomly interleaved, and each condition had 25 trials.

Data analysis

The initial transient component of the evoked pupil response was of primary interest (Fig. 1C) because it was related to the pupil response evoked by SC microstimulation (Wang *et al.*, 2012, 2014). 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 100 ms before to 100 ms after (PROL was always > 100 ms) stimulus/background presentation (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 vs. no-stimulation conditions directly. Specifically, pupil values from each Fix trial were contrasted to the average pupil value from all Ctrl trials.

If pupil size associates with orienting, the presentation of a salient stimulus should evoke pupil dilation, and pupil dilation should scale with the level of stimulus contrast because it is one of the most primitive saliency components (Itti & Koch, 2001; Borji *et al.*, 2013), with faster and larger evoked responses observed for more salient stimuli. Figure 1C shows a schematic of the measurements extracted to capture dynamics of transient pupil dilation (Wang *et al.*, 2014). The PROL was defined as the time at which velocity exceeded half of its greatest absolute velocity value with the same direction in acceleration (dilation or constriction), and these remained so for at least 100 ms. To determine the onset of the pupil response, following a similar procedure (Bergamin & Kardon, 2003), we first increased the signal-to-noise ratio of pupil size tracing 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 velocity and acceleration tracings were derived by the pupil size tracing after application of a 20-point second-order polynomial moving Savitzky–Golay filter (Savitzky & Golay, 1964), which gradually reduced high-frequency component noise. The mean dilation was defined as the average of the pupil size from PROL to the time when the pupil reached the largest dilation within 1000 ms after the stimulus onset. The mean dilation velocity was computed using the same time window for the mean pupil dilation (positive and negative values indicate the dilating and constricting process, respectively).

To examine the modulation of stimulus contrast by the level of arousal, we separated trials with larger and smaller pupil size according to the baseline pupil size (averaged from the epoch of the final 500 ms prior to stimulus appearance) on Sac and Fix trials separately (2 × 3 ANOVA: large/small baseline × high/mid/low contrast), because the baseline pupil size (prior to an event) is often used to indicate different levels of arousal (Gilzenrat *et al.*, 2010; Nassar *et al.*, 2012). It is argued that there is an inverted U relationship between arousal level and behavioral performance (Aston-Jones & Cohen, 2005), i.e. performance worsens when the level of arousal is too high or too low. Gilzenrat *et al.* (2010) separated two arousal conditions using 25th percentile or lower baseline diameter and 75th percentile or higher baseline diameter because human participants, dissimilar to monkeys, showed little variation or periodicity in performance during the task (the level of arousal should be relatively within the modest range). We followed a similar procedure because our participants did not show periodicity in performance, and used a median split to increase the number of trials on each baseline condition to strengthen statistical power.

On Sac trials, the saccade reaction time 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 the saccadic target and failure to make a saccade to the correct location (within 1.5° radius around the target) were marked as errors on the saccade condition (Sac); these occurred rarely (0, 0, and 3% for high, mid, low conditions, respectively) and were removed from analysis. On Fix trials, the saccadic error was labeled if a saccade was made toward the stimulus within 500 ms after the appearance of visual stimulus, and these trials were removed from pupil analysis. A repeated-measures ANOVA was performed for statistical analysis, and a Bonferroni-corrected *t*-test was used for the planned comparisons, except where indicated.

Results

Saccadic responses were modulated by visual contrast

Consistent with the literature (Ludwig *et al.*, 2004; Marino & Munoz, 2009; Kowler, 2011), stimulus contrast modulated saccade behaviors, with faster saccade reaction times observed for higher contrast stimuli on Sac trials (Fig. 2A; $F_{2,22} = 29.47$, $P < 0.001$; Bonferroni-adjusted comparisons between high and low contrast, and mid and low contrast were significant, all $P < 0.01$). On Fix trials, where participants were required to maintain fixation, more erroneous saccades occurred when the visual stimulus was higher contrast (Fig. 2B; $F_{2,22} = 6.07$, $P = 0.012$; high and low: $P = 0.045$; mid and low: $P = 0.08$). The differences between high

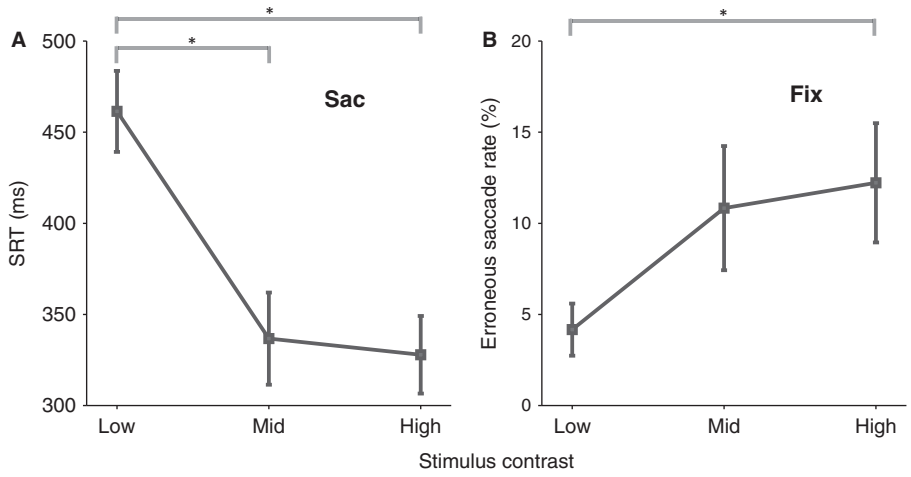

FIG. 2. Effect of stimulus contrast modulation on saccadic behaviors. (A) Saccade reaction times (SRTs) at different stimulus contrast conditions on saccade trials. (B) Erroneous saccade rates at different stimulus contrast conditions on fixation trials. The error bars represent ± SE across participants. *Differences are statistically significant.

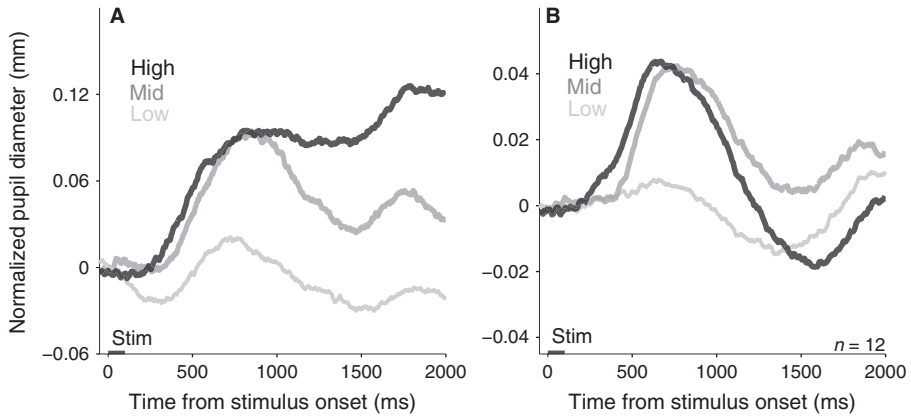

FIG. 3. Transient pupil dilation evoked by visual stimuli. Normalized pupil response following the presentation of visual stimuli with three levels of visual contrast on (A) a single participant and (B) all participants. The black bar on the X-axis indicates the time line of stimulus presentation. The black, dark gray, and light gray lines indicate the high, mid, and low visual contrast stimulus conditions, respectively. *n*, number of participants.

and mid contrast conditions were not significant, however, which could be the result of insufficient contrast differences between high and mid contrast stimuli to reveal a difference due to the use of high spatial frequency stimuli.

Visual stimuli evoked transient pupil dilation that scaled with visual contrast

Figure 3A shows the normalized pupil diameter measured from one participant, demonstrating that the presentation of visual stimuli evoked transient pupil dilation, and the evoked pupil dilation was modulated by stimulus contrast. The population results in Fig. 3B revealed the same pattern, i.e. transient pupil dilation was evoked after the presentation of a visual stimulus, followed by constriction before pupil size returned to the control condition (no stimulus). More importantly, evoked pupil responses scaled with the level of stimulus contrast, with faster and larger evoked pupil responses observed for higher contrast stimuli.

The latency of pupil modulation scaled negatively with visual contrast (Fig. 4A), the PROL being 577, 400, and 329 ms for low, mid, and high contrast condition, respectively ($F_{2,22}$ = 7.45, P = 0.014; high and low: P = 0.017). The mean pupil dilation was 0.009, 0.026, and 0.032 mm (Fig. 4B, $F_{2,22}$ = 4.76, P = 0.042; high and low: P = 0.038) and mean dilation velocity was 0.058, 0.099 and 0.105 mm/s (Fig. 4C, $F_{2,22}$ = 7.72, P = 0.008; high and low: P = 0.033; mid and low: P = 0.045) for low, mid, and high contrast condition, respectively. Although some measurements of pupil responses appeared to saturate in the high contrast condition, as did saccade reaction times and erroneous saccade rates (Fig. 2A and B), a clear pattern was observed, i.e. stimulus contrast systematically modulated the evoked pupil response (Fig. 4A–C). Larger pupil dilation was observed in the high compared with the low contrast condition for the majority (10/12) of participants (Fig. 4D, one-sample *t*-test: t_{11} = 2.97, P = 0.013).

Pupil response was coordinated in laterality and ocularity

Given that the pupil response was more pronounced for higher levels of visual contrast, responses from the high contrast condition were selected for subsequent analyses. Consistent with previous monkey results (Wang *et al.*, 2014), the pupil response evoked by the presentation of visual stimuli was confirmed to be consensual

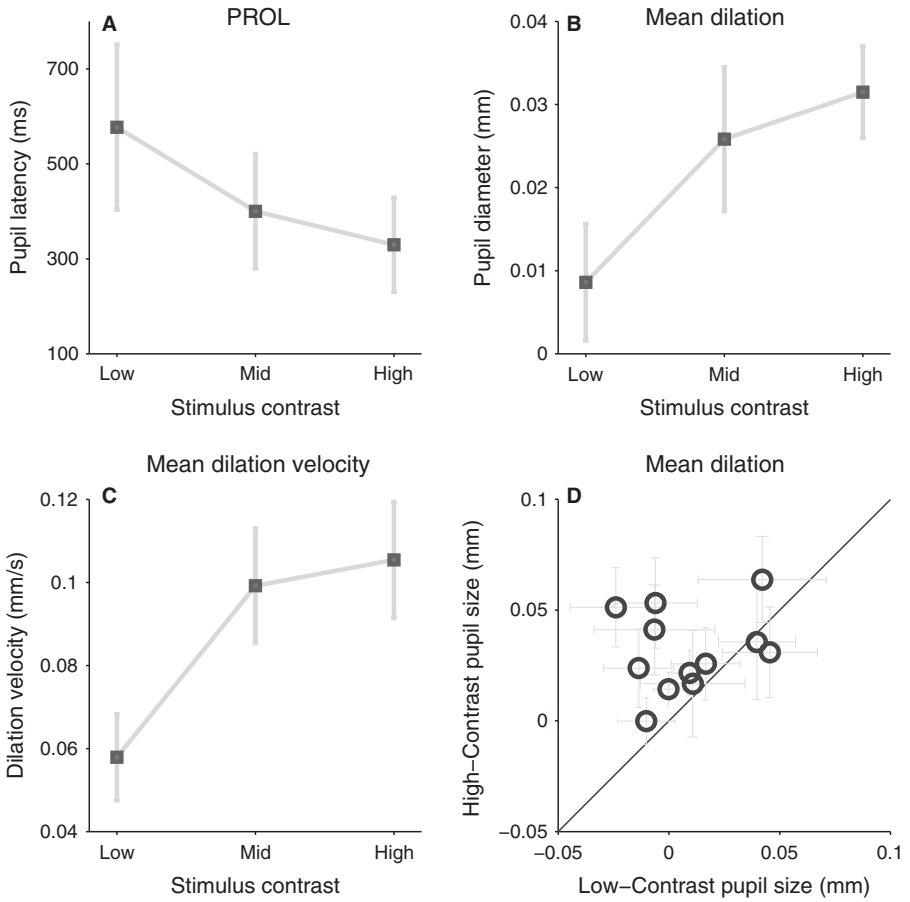

FIG. 4. Effect of stimulus contrast modulation on transiently evoked pupil responses. Modulation of stimulus contrast on (A) the pupil response onset latency (PROL), (B) the mean size of pupil dilation, and (C) the mean velocity of pupil dilation. (D) Pupil size between high and low contrast conditions for each individual participant (n = 12) (mean size of pupil dilation). In A–C, the error bars represent ± SE across participants. In D, the error bars represent ± SE within participants.

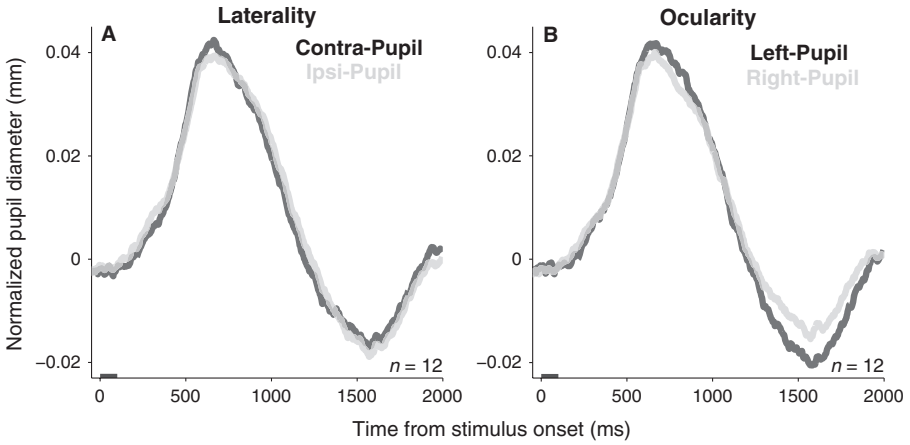

FIG. 5. Coordinated pupil response evoked by visual stimuli. Summary of pupil effects for high contrast stimuli on (A) the contralateral or ipsilateral pupil of the stimulus visual field and (B) the left or right pupil. The black bar on the X-axis indicates the time line of stimulus presentation. In A, the dark gray and light gray lines indicate the contralateral and ipsilateral pupil of the stimulus visual field, respectively. In B, the dark gray and light gray lines indicate left and right pupils, respectively. Contra-Pupil, contralateral pupil of the stimulus visual field; Ipsi-Pupil, ipsilateral pupil of the stimulus visual field; n, number of participants.

(Fig. 5A and B). There were approximately the same responses between the contralateral and ipsilateral pupil with respect to the visual field stimulated (Fig. 5A, $P > 0.8$ across all times). The evoked pupil responses between the left and right pupil were indifferent (Fig. 5B, $P > 0.5$ across all times).

Comparison of the pupil response evoked by visual stimuli and background luminance change

Although pupil size is determined by an interaction between the parasympathetic and sympathetic pathways, it has been suggested

that the light reflex is primarily driven by activation of the parasympathetic system, whereas the darkness reflex is mostly modulated by activation from the sympathetic pathway (Nisida *et al.*, 1960; Bitsios *et al.*, 1996; Loewenfeld, 1999; Clarke *et al.*, 2003). The pupil response to the light and darkness reflex was thus used to estimate the response characteristic of the two systems under the current experimental situation. A sudden increase of background luminance (from 11 to 21 cd/m^2) resulted in pupil constriction (Fig. 6B, gray line) that began 268 ms after the background luminance change (Fig. 6C) [a 0.61 mm constriction in pupil diameter (Fig. 6D), and a 1.06 mm/s mean constriction velocity (Fig. 6E)]. In contrast, a decrease in background luminance (from 11 to 1 cd/m^2) caused pupil dilation (Fig. 6B, black line) that began only 467 ms after the luminance change (Fig. 6C) [a 0.27 mm dilation of pupil diameter within 1 s after its onset (Fig. 6D), and a 0.46 mm/s mean dilation velocity (Fig. 6E)].

Pupil dilation evoked by presentation of visual stimuli must presumably be mediated by activity from the parasympathetic and/or sympathetic pathways. The PROL produced by the high contrast visual stimuli was similar to that related to the light reflex (independent samples *t*-test: $t_{17} = 1.3$, $P = 0.19$), and it was much faster (< 135 ms; independent samples *t*-test: $t_{17} = 2.81$, $P = 0.012$) than the PROL produced by the darkness reflex (Fig. 6C). Although PROL values may change with different stimulus parameters (i.e. changes in background luminance or stimulus size), the PROL for the darkness reflex should still be slower than that for high contrast visual stimuli, because the background was changed to almost complete black in this experiment. This suggests that the initial component of stimulus-evoked transient pupil dilation was probably mediated by inhibition of the parasympathetic pathway, rather than excitation of the sympathetic pathway. Moreover, although the size of pupil dilation evoked by salient visual stimuli in humans was much smaller than that induced by the background luminance change, this change in size was similar to that in monkeys evoked by salient stimuli (Wang *et al.*, 2014) or by SC microstimulation (Wang *et al.*, 2012).

Contrast modulation under different levels of baseline pupil size

Pupil size is also linked to the level of arousal, presumably mediated by the locus coeruleus–norepinephrine system (Aston-Jones & Cohen, 2005), and the modulation of stimulus contrast could be influenced by different levels of arousal. We separated trials with larger and smaller pupil size (median split) according to the baseline pupil size, which represents different levels of arousal (see Materials

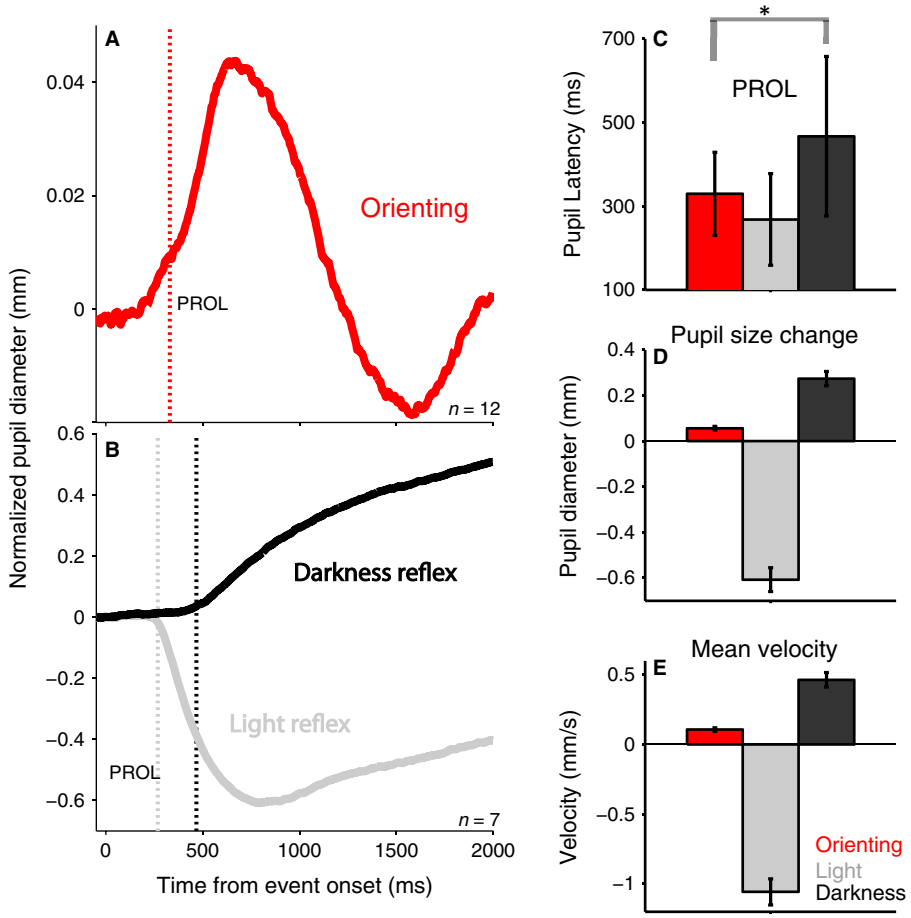

FIG. 6. Comparison of the pupil response evoked by salient visual stimuli or background luminance changes. (A) Pupil response following the presentation of salient visual stimuli (high contrast). (B) Pupil response following the change of background luminance (light reflex: increase 10 cd/m^2; darkness reflex: decrease 10 cd/m^2). Comparison of different evoked pupil responses on (C) the PROL, (D) the change in pupil size and (E) the mean velocity of pupil size change. In A and B, the red, gray, and black lines indicate the evoked pupil response related to orienting and the light and darkness reflex, respectively. The dashed lines indicate the PROL. In C–E, the red, gray, and black bars indicate the evoked pupil response related to orienting and the light and darkness reflex, respectively. The error bars represent ± SE. *Differences are statistically significant. *n*, number of participants; PROL, pupil response onset latency.

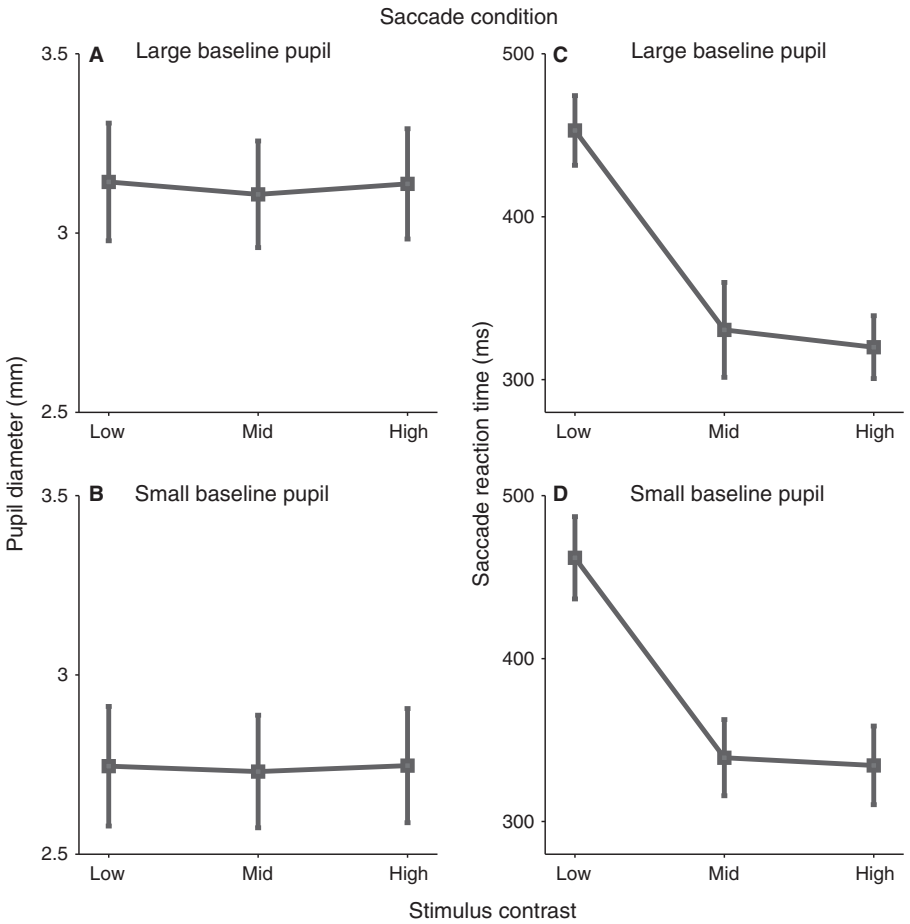

FIG. 7. Stimulus contrast modulation on saccade reaction time under different levels of baseline pupil size. Baseline pupil size on high, mid, and low conditions with (A) larger and (B) smaller baseline pupil condition. Stimulus contrast modulation on SRTs with (C) larger and (D) smaller baseline pupil size. The error bars represent ± SE across participants (n = 12).

and methods). We further hypothesized that the contrast modulation should be pronounced regardless of baseline pupil size because it is mediated by a different neural substrate, namely through the SC (Wang *et al.*, 2012, 2014).

On Sac trails, for the larger baseline pupil condition, the diameters were 3.14, 3.11, and 3.14 mm for low, mid, and high contrast condition, respectively (Fig. 7A), and pupil sizes for the smaller baseline condition were 2.75, 2.73, and 2.75 mm for low, mid, and high condition, respectively (Fig. 7B). These differences in baseline pupil diameter were highly significant ($F_{1,11}$ = 155.54, P < 0.001). However, the effects of baseline pupil size on stimulus contrast modulation were not pronounced on Sac trials. Saccade reaction times were 453, 331, and 320 ms for low, mid, and high condition, respectively in the larger baseline pupil condition (Fig. 7C), and were 462, 339, and 334 ms for low, mid, and high condition, respectively, in the smaller baseline pupil condition (Fig. 7D). The main effect of stimulus contrast was significant ($F_{2,22}$ = 28.56, P < 0.001), indicating that the modulation of stimulus contrast was pronounced regardless of the baseline pupil size. Neither interaction nor the main effect of baseline pupil size were significant (interaction: $F_{2,22}$ = 0.57, P = 0.95; pupil size: $F_{1,11}$ = 3.32, P = 0.1).

On Fix trails, pupil size was larger in the larger baseline pupil condition ($F_{1,11}$ = 149.75, P < 0.001). Specifically, pupil diameters were 3.17, 3.17, and 3.15 mm in the larger condition for low, mid, and high condition, respectively (Fig. 8A), and were 2.77, 2.79, and 2.8 mm in the smaller baseline pupil condition for low, mid, and high condition, respectively (Fig. 8B). Moreover, transient pupil dilation was evoked under different levels of baseline pupil size (larger baseline pupil, Fig. 8C; smaller baseline pupil, Fig. 8D). Because the observed values in the low contrast condition failed to fit the PROL criterion, in order to compare the pupil size across all conditions we selected the average pupil size in the epoch (500–550 ms after stimulus onset) when pupil size regularly reached half of the value of the largest magnitude response, except in the low contrast condition with the larger pupil baseline. Consistent with results from the Sac trails, the effects of baseline pupil size on stimulus contrast modulation were not pronounced. Pupil diameters were 0.003, 0.025, and 0.027 mm for low, mid, and high condition, respectively in the larger baseline pupil condition (Fig. 8E), and were 0.007, 0.014, and 0.027 mm for low, mid, and high condition, respectively in the smaller baseline pupil condition (Fig. 8F). Although the main effect of stimulus contrast was significant ($F_{2,22}$ = 6.25, P = 0.01), neither interaction nor the main effect of baseline pupil size were significant (interaction: $F_{2,22}$ = 0.28, P = 0.76; pupil size: $F_{1,11}$ = 0.16, P = 0.7), indicating that the modulation of stimulus contrast was pronounced regardless of the baseline pupil size.

Discussion

Presentation of a salient stimulus initiates a series of coordinated responses that orient the body, including not only shifts of gaze and attention, but also transient pupil dilation. Although pupil size has

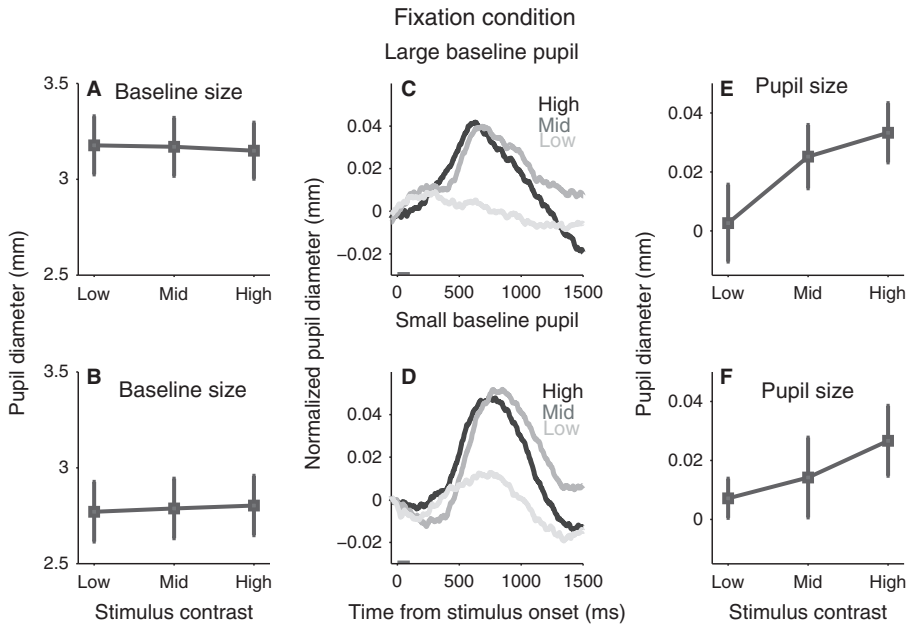

FIG. 8. Transient pupil dilation evoked under different levels of baseline pupil size. Baseline pupil size on high, mid, and low conditions with (A) larger and (B) smaller baseline pupil condition. Normalized pupil response following the presentation of visual stimuli (High, Mid, and Low condition) with (C) larger and (D) smaller baseline pupil. Stimulus contrast modulation on pupil size (500–550 ms after stimulus onset) under (E) larger and (F) smaller baseline pupil size condition. In A, B, E, and F, the error bars represent ± SE across participants (n = 12). In C and D, the gray bar on the X-axis indicates the time line of stimulus presentation. The black, dark gray, and light gray lines indicate the high, mid, and low visual contrast stimulus conditions, respectively.

long been linked to orienting (Sokolov, 1963; Lynn, 1966), the effects of stimulus contrast on the pupil response are less known. Our results showed that transient pupil dilation in humans was evoked following the presentation of visual stimuli. Importantly, the modulation of stimulus contrast was manifested not only in saccade behaviors, but also in evoked pupil dilation, with faster and larger evoked pupil responses elicited by higher contrast stimuli. The results also showed that the PROL associated with orienting and the light reflex were relatively close, and statistically earlier than the darkness reflex PROL, implying that the sympathetic system was less likely to coordinate the immediate response of transient pupil dilation because dilation via the sympathetic activation was ~135 ms later than the stimulus-evoked dilation. We propose that inhibition of parasympathetic pathways initiates the immediate dilation of the evoked response, and activation of sympathetic pathways slowly facilitates the increase in pupil size. Moreover, the effects of stimulus contrast were consistent under different levels of baseline pupil size, suggesting that the contrast modulation is possibly dissociable from arousal effects.

Pupil orienting response and its relationship with arousal

Saccadic eye movements and attention shifts, as components of the orienting response, are evoked by the appearance of a novel stimulus and are modulated by stimulus contrast (Carrasco, 2011; Kowler, 2011), as one of the most primitive saliency components, widely implemented in a number of computational models (Itti & Koch, 2001; Borji *et al.*, 2013). This effect on pupil dynamics has yet to be established systematically, although a number of studies have observed that human pupil size increased transiently after presentation of visual or auditory stimuli in various paradigms (Stelmack & Siddle, 1982; Qiyuan *et al.*, 1985; Loewenfeld, 1999; Reinhard *et al.*, 2007; Gilzenrat *et al.*, 2010; Steiner & Barry, 2011). In monkeys, transient pupil dilation was evoked by presentation of salient visual or auditory stimuli, and the evoked response scaled with stimulus contrast, with faster and larger responses observed for higher contrast stimuli (Wang *et al.*, 2014). Moreover, the initial pupil dilation induced by SC microstimulation in monkeys was similar to that produced by the presentation of salient stimuli (Wang *et al.*, 2012). Here, transient pupil dilation was evoked by presenting visual stimuli, and similar effects of contrast modulation were shown in humans. Although the full dynamics of the evoked pupil responses were different, the initial component of transient pupil dilation was consistent, whether evoked by different types of stimulation (SC microstimulation or sensory stimulus) or across different species (monkeys and humans), suggesting a particular role of initial pupil dilation for orienting. Although the pupil response in monkeys was faster than that in humans (PROL: monkeys, approximately 222 ms; humans, approximately 329 ms; time to peak: monkeys, approximately 350 ms; humans, approximately 650 ms), these species differences were consistent with the literature on the express saccade (Fischer & Weber, 1993), showing faster express saccade latencies in monkeys than in humans (monkeys, ~70 ms; humans, approximately 100 ms). Some possibilities have been proposed to account for this numerical difference (Fischer & Ramsperger, 1984), including effects of excessive over-training (Munoz *et al.*, 2005).

Pupil size is also related to the level of arousal, and the locus coeruleus–norepinephrine system is regularly implicated as a key part of the neural substrate mediating this effect (Aston-Jones & Cohen, 2005). This raises an interesting question about whether the contrast modulation that we report here is influenced by the level of arousal. The arousal-biased competition hypothesis has suggested that arousal increases the modulation (or bias), i.e. the contrast modulation should be more pronounced in a higher level of arousal (Mather & Sutherland, 2011). In contrast, according to Aston-Jones & Cohen (2005), a higher level of arousal, revealed by larger pupil baseline diameter, should be associated with decreases in task utility and thus generally diminish the task-required behavioral performance (Gilzenrat *et al.*,

2010). In support of none of these hypotheses, our results showed similar modulation of stimulus contrast on pupil dilation under different levels of baseline pupil size, implying that contrast modulation could be dissociated from the general arousal effect. Note that Gilzenrat *et al.* (2010) divided baseline pupil size conditions with 25th percentile below and 75th percentile above baseline pupil diameter to demonstrate the arousal effect. Although the differences in pupil size between two baseline conditions were highly significant in our study, it is still possible that there were insufficient size differences between the two baseline conditions to reveal a significant interaction.

Possible anatomical pathways underlying the evoked pupil response

Pupil size is controlled by combined activity between parasympathetic and sympathetic pathways, and the individual contribution of parasympathetic and sympathetic pathways to this response is still unknown. The PROLs associated with orienting and the light reflex were similar to one another, and shorter (approximately 135 ms) than those related to the darkness reflex, implying that the sympathetic pathway was less likely to coordinate the initial transient pupil dilation. The parasympathetic system could possibly mediate this transient response via inhibition of the parasympathetic constriction pathway. It is possible that the inhibition of the parasympathetic pathway initiates immediate dilation, and then the activation of the sympathetic pathway facilitates the rise in pupil size, an idea that is consistent with previous suggestions (Loewenfeld, 1999). Pupil dilation, referred to as the pupillary reflex dilation, was impaired by blocking either the parasympathetic-inhibitory or sympathetic-active component. Early pupil experiments used a motion picture technique to measure pupil size with a film at 10 Hz (Loewenfeld, 1999), and it was thus difficult to examine how individual pathways uniquely contribute to evoked pupil responses. Note that it is still possible that the initial component of transient pupil dilation is mediated by activating the sympathetic pathway because distinctive neural pathways may be involved following the appearance of salient stimuli, and this mechanism may be faster than the illumination-dependent system, making the activation on the sympathetic pathway still a plausible hypothesis. Future physiological research is required to answer the question.

As the evoked pupil response reflects the combined activity of both pathways, the response should theoretically depend on background luminance (Steinhauer & Hakerem, 1992). The gray background used here probably induced constant parasympathetic activation, and therefore the parasympathetic inhibition elicited by presentation of salient stimuli was pronounced and probably mediated the initial component of transient dilation. In contrast, if using a dark background, because the parasympathetic activation is greatly reduced, the evoked pupil response should be driven mostly by activation on the sympathetic system, not by inhibition on the parasympathetic system; thus the PROL should be larger in this situation and numerically similar to that induced by the darkness reflex. Such predictions should be tested in future experiments.

The role of the superior colliculus in mediating the pupil orienting response

The SC, a midbrain structure, is known for its central role in the control of saccadic eye movements and attention (Gandhi & Katnani, 2011; Krauzlis *et al.*, 2013). The superficial layers receive visual inputs, including the retina and primary visual cortex, whereas the intermediate layers of the SC (SCi) receive inputs from the superficial SC, multisensory, basal ganglia, and frontal–parietal areas, and project directly to the brainstem and spinal cord to execute the orienting response (White & Munoz, 2011). The SCi encodes stimulus salience and relevance to coordinate all components of orienting (Sparks, 1986; Fecteau & Munoz, 2006; Knudsen, 2007; Boehnke & Munoz, 2008; Mysore & Knudsen, 2013). In line with this, SCi microstimulation not only biases spatial attention (Kustov & Robinson, 1996; Cavanaugh & Wurtz, 2004; Muller *et al.*, 2005) and induces saccades (Robinson, 1972), but also evokes transient pupil dilation (Netser *et al.*, 2010; Wang *et al.*, 2012).

Recently, we suggested that the SCi might coordinate the orienting of pupil dilation because the modulation of stimulus contrast was similar between SCi neural responses and transient pupil responses, with faster and larger SCi and pupil responses observed for higher contrast stimuli (Wise & Irvine, 1983; Marino *et al.*, 2012; Wang *et al.*, 2014). Moreover, stimulus modality modulated SCi activity and transient pupil responses in a similar fashion, with shorter response latencies produced with auditory compared with visual stimuli (Bell *et al.*, 2004; Wang *et al.*, 2014). Importantly, the PROL evoked by SCi microstimulation was about 50 ms shorter than when using visual stimulation (same time as required for visual signals traveling from the retina to the SCi) (Marino *et al.*, 2012). Transient pupil dilation in humans was consistently evoked following the presentation of visual stimuli and modulated by stimulus contrast, thus suggesting that the SCi may also coordinate the orienting pupil response in humans. We propose that SCi sensory responses produced by presentation of salient stimuli are systematically carried through to not only initiate a saccade but also evoke pupil dilation. Therefore, experimental manipulations that would modulate SCi responses should also influence the pupil response. The link between the SC and pupil size can potentially provide a neural substrate for coordinating pupil size and cognitive processing because the SC not only plays an important role in attentional processing (Zenon & Krauzlis, 2012; Krauzlis *et al.*, 2013), but also encodes stimulus priority and saliency (Fecteau & Munoz, 2006; Boehnke & Munoz, 2008).

The SCi has anatomical connections to pupil pathways to dilate the pupil. It can inhibit parasympathetic pathways via indirect inhibitory projections to the Edinger–Westphal (EW) nucleus (Edwards & Henkel, 1978; Harting *et al.*, 1980; Grantyn & Grantyn, 1982) or activate sympathetic pathways via projections to the mesencephalic cuneiform nucleus (Harting, 1977; Huerta & Harting, 1984; May, 2006), which in turn influence the sympathetic projections (Verberne, 1995). Because initial dilation probably relies on inhibition of the parasympathetic pathway, it is possible that indirect projections from the SCi to the EW nucleus represent the neural substrate underlying an initial rise of the evoked pupil response.

Summary

Pupil size changes rapidly in response to local sensory events in the environment in addition to the well-documented global illumination-dependent modulation. The ability to recognize a salient stimulus (i.e. higher contrast) in the environment is impaired among patients with neurological disorders (Winton-Brown *et al.*, 2014). The orienting-related pupil response demonstrated here thus has the potential to be developed as a biomarker for clinical investigation. Because stimulus contrast is considered to be one of the primitive saliency components (Itti & Koch, 2001), it is possible that the identified modulation of pupil size is associated with the stimulus saliency effect. However, the saliency computation is defined by the

conspicuous nature of the stimulus relative to other available stimuli in the environment (spatial relationship), or the conspicuous nature of the stimulus relative to a series of presented stimuli at different points in time (temporal relationship), thus involving the competition of all available stimuli spatially and temporally (Itti & Koch, 2000; Dutta & Gutfreund, 2014). Our results only show contrast modulation, and future research is required to examine modulation by other aspects of saliency in order to fully understand the effects of stimulus saliency on pupil size.

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Abbreviations

Ctrl, no-stimulus control condition; Fix, fixation condition; FP, fixation point; PROL, pupil response onset latency; Sac, saccade condition; SC, superior colliculus; SCi, intermediate layers of the superior colliculus.

References

Aston-Jones, G. & Cohen, J.D. (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, **28**, 403–450.

Bala, A.D. & Takahashi, T.T. (2000) Pupillary dilation response as an indicator of auditory discrimination in the barn owl. *J. Comp. Physiol. A.*, **186**, 425–434.

Beatty, J. (1982) Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychol. Bull.*, **91**, 276–292.

Bell, A.H., Fecteau, J.H. & Munoz, D.P. (2004) Using auditory and visual stimuli to investigate the behavioral and neuronal consequences of reflexive covert orienting. *J. Neurophysiol.*, **91**, 2172–2184.

Bergamin, O. & Kardon, R.H. (2003) Latency of the pupil light reflex: sample rate, stimulus intensity, and variation in normal subjects. *Invest. Ophth. Vis. Sci.*, **44**, 1546–1554.

Bitsios, P., Prettyman, R. & Szabadi, E. (1996) Changes in autonomic function with age: a study of pupillary kinetics in healthy young and old people. *Age Ageing*, **25**, 432–438.

Boehnke, S.E. & Munoz, D.P. (2008) On the importance of the transient visual response in the superior colliculus. *Curr. Opin. Neurobiol.*, **18**, 544–551.

Borji, A., Sihite, D.N. & Itti, L. (2013) Quantitative analysis of human-model agreement in visual saliency modeling: a comparative study. *IEEE T. Image Process.*, **22**, 55–69.

Bremner, F. (2009) Pupil evaluation as a test for autonomic disorders. *Clin. Auton. Res.*, **19**, 88–101.

Carrasco, M. (2011) Visual attention: the past 25 years. *Vision Res.*, **51**, 1484–1525.

Cavanaugh, J. & Wurtz, R.H. (2004) Subcortical modulation of attention counters change blindness. *J. Neurosci.*, **24**, 11236–11243.

Clarke, R.J., Zhang, H. & Gamlin, P.D. (2003) Characteristics of the pupillary light reflex in the alert rhesus monkey. *J. Neurophysiol.*, **89**, 3179–3189.

Daluwatte, C., Miles, J.H., Christ, S.E., Beversdorf, D.Q., Takahashi, T.N. & Yao, G. (2013) Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. *J. Autism Dev. Disord.*, **43**, 1910–1925.

Dutta, A. & Gutfreund, Y. (2014) Saliency mapping in the optic tectum and its relationship to habituation. *Front. Integr. Neurosci.*, **8**, 1.

Edwards, S.B. & Henkel, C.K. (1978) Superior colliculus connections with the extraocular motor nuclei in the cat. *J. Comp. Neurol.*, **179**, 451–467.

Eldar, E., Cohen, J.D. & Niv, Y. (2013) The effects of neural gain on attention and learning. *Nat. Neurosci.*, **16**, 1146–1153.

Fecteau, J.H. & Munoz, D.P. (2006) Salience, relevance, and firing: a priority map for target selection. *Trends Cogn. Sci.*, **10**, 382–390.

Fischer, B. & Ramsperger, E. (1984) Human express saccades: extremely short reaction times of goal directed eye movements. *Exp. Brain Res.*, **57**, 191–195.

Fischer, B. & Weber, H. (1993) Express saccades and visual attention. *Behav. Brain Sci.*, **16**, 553–567.

Frost, S., Kanagasingam, Y., Sohrabi, H., Bourgeat, P., Villemagne, V., Rowe, C.C., Macaulay, S.L., Szoeke, C., Ellis, K.A., Ames, D., Masters, C.L., Rainey-Smith, S., Martins, R.N. & Aibl Research, G. (2013) Pupil response biomarkers for early detection and monitoring of alzheimer's disease. *Curr. Alzheimer Res.*, **10**, 931–939.

Gamlin, P.D. (2006) The pretectum: connections and oculomotor-related roles. *Prog. Brain Res.*, **151**, 379–405.

Gandhi, N.J. & Katnani, H.A. (2011) Motor functions of the superior colliculus. *Annu. Rev. Neurosci.*, **34**, 205–231.

Gilzenrat, M.S., Nieuwenhuis, S., Jepma, M. & Cohen, J.D. (2010) Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cogn. Affect. Behav. Ne.*, **10**, 252–269.

Grantyn, A. & Grantyn, R. (1982) Axonal patterns and sites of termination of cat superior colliculus neurons projecting in the tecto-bulbo-spinal tract. *Exp. Brain Res.*, **46**, 243–256.

Harting, J.K. (1977) Descending pathways from the superior collicullus: an autoradiographic analysis in the rhesus monkey (macaca mulatta). *J. Comp. Neurol.*, **173**, 583–612.

Harting, J.K., Huerta, M.F., Frankfurter, A.J., Strominger, N.L. & Royce, G.J. (1980) Ascending pathways from the monkey superior colliculus: an autoradiographic analysis. *J. Comp. Neurol.*, **192**, 853–882.

Huerta, M. & Harting, J. (1984) Connectional organization of the superior colliculus. *Trends Neurosci.*, **7**, 286–289.

Itti, L. & Koch, C. (2000) A saliency-based search mechanism for overt and covert shifts of visual attention. *Vision Res.*, **40**, 1489–1506.

Itti, L. & Koch, C. (2001) Computational modelling of visual attention. *Nat. Rev. Neurosci.*, **2**, 194–203.

Karatekin, C., Bingham, C. & White, T. (2010) Oculomotor and pupillometric indices of pro- and antisaccade performance in youth-onset psychosis and attention deficit/hyperactivity disorder. *Schizophrenia Bull.*, **36**, 1167–1186.

Knudsen, E.I. (2007) Fundamental components of attention. *Annu. Rev. Neurosci.*, **30**, 57–78.

Knudsen, E.I. (2011) Control from below: the role of a midbrain network in spatial attention. *Eur. J. Neurosci.*, **33**, 1961–1972.

Kowler, E. (2011) Eye movements: the past 25 years. *Vision Res.*, **51**, 1457–1483.

Krauzlis, R.J., Lovejoy, L.P. & Zenon, A. (2013) Superior colliculus and visual spatial attention. *Annu. Rev. Neurosci.*, **36**, 165–182.

Kustov, A.A. & Robinson, D.L. (1996) Shared neural control of attentional shifts and eye movements. *Nature*, **384**, 74–77.

Loewenfeld, I.E. (1999) *The Pupil: Anatomy, Physiology, and Clinical Applications*. Butterworth-Heinemann, Boston.

Ludwig, C.J., Gilchrist, I.D. & McSorley, E. (2004) The influence of spatial frequency and contrast on saccade latencies. *Vision Res.*, **44**, 2597–2604.

Lynn, R. (1966) *Attention, Arousal and the Orientation Reaction*. Pergamon Press, Oxford.

Marino, R.A. & Munoz, D.P. (2009) The effects of bottom-up target luminance and top-down spatial target predictability on saccadic reaction times. *Exp. Brain Res.*, **197**, 321–335.

Marino, R.A., Levy, R., Boehnke, S., White, B.J., Itti, L. & Munoz, D.P. (2012) Linking visual response properties in the superior colliculus to saccade behavior. *Eur. J. Neurosci.*, **35**, 1738–1752.

Mather, M. & Sutherland, M.R. (2011) Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.*, **6**, 114–133.

May, P.J. (2006) The mammalian superior colliculus: laminar structure and connections. *Prog. Brain Res.*, **151**, 321–378.

Moresi, S., Adam, J.J., Rijcken, J. & Van Gerven, P.W. (2008) Cue validity effects in response preparation: a pupillometric study. *Brain Res.*, **1196**, 94–102.

Muller, J.R., Philiastides, M.G. & Newsome, W.T. (2005) Microstimulation of the superior colliculus focuses attention without moving the eyes. *Proc. Natl. Acad. Sci. USA*, **102**, 524–529.

Munoz, D.P., Cameron, I.G.M. & Fecteau, J.H. (2005) Training accounts for differences in previous trial effects between humans and monkeys. Program No. 475.9. 2005 Neuroscience Meeting Planner. Society for Neuroscience, Washington, DC [Internet].

Mysore, S.P. & Knudsen, E.I. (2013) A shared inhibitory circuit for both exogenous and endogenous control of stimulus selection. *Nat. Neurosci.*, **16**, 473–478.
Nassar, M.R., Rumsey, K.M., Wilson, R.C., Parikh, K., Heasly, B. & Gold, J.I. (2012) Rational regulation of learning dynamics by pupil-linked arousal systems. *Nat. Neurosci.*, **15**, 1040–1046.
Netser, S., Ohayon, S. & Gutfreund, Y. (2010) Multiple manifestations of microstimulation in the optic tectum: eye movements, pupil dilations, and sensory priming. *J. Neurophysiol.*, **104**, 108–118.
Nisida, I., Okada, H. & Nakano, O. (1960) The activity of the ciliospinal centers and their inhibition in pupillary light reflex. *Jpn. J. Physiol.*, **10**, 73–84.
Peli, E., Yang, J. & Goldstein, R.B. (1991) Image invariance with changes in size: the role of peripheral contrast thresholds. *J. Opt. Soc. Am. A.*, **8**, 1762–1774.
Qiyuan, J., Richer, F., Wagoner, B.L. & Beatty, J. (1985) The pupil and stimulus probability. *Psychophysiology*, **22**, 530–534.
Reinhard, G., Lachnit, H. & Konig, S. (2007) Effects of stimulus probability on pupillary dilation and reaction time in categorization. *Psychophysiology*, **44**, 469–475.
Robinson, D.A. (1972) Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res.*, **12**, 1795–1808.
Savitzky, A. & Golay, M.J.E. (1964) Smoothing and differentiation of data by simplified least squares procedures. *Anal. Chem.*, **36**, 1627–1639.
Sokolov, E.N. (1963) Higher nervous functions: the orienting reflex. *Annu. Rev. Physiol.*, **25**, 545–580.
Sparks, D.L. (1986) Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. *Physiol. Rev.*, **66**, 118–171.
Steiner, G.Z. & Barry, R.J. (2011) Pupillary responses and event-related potentials as indices of the orienting reflex. *Psychophysiology*, **48**, 1648–1655.
Steinhauer, S.R. & Hakerem, G. (1992) The pupillary response in cognitive psychophysiology and schizophrenia. *Ann. NY Acad. Sci.*, **658**, 182–204.
Stelmack, R.M. & Siddle, D.A. (1982) Pupillary dilation as an index of the orienting reflex. *Psychophysiology*, **19**, 706–708.
Verberne, A.J. (1995) Cuneiform nucleus stimulation produces activation of medullary sympathoexcitatory neurons in rats. *Am. J. Physiol.*, **268**, R752–R758.
Wang, C.A., Boehnke, S.E., White, B.J. & Munoz, D.P. (2012) Microstimulation of the monkey superior colliculus induces pupil dilation without evoking saccades. *J. Neurosci.*, **32**, 3629–3636.
Wang, C.A., Boehnke, S.E., Itti, L. & Munoz, D.P. (2014) Transient pupil response is modulated by contrast-based saliency. *J. Neurosci.*, **34**, 408–417.
White, B.J. & Munoz, D.P. (2011) The superior colliculus. In Liversedge, S.P., Gilchrist, I.D. & Everling, S. (Eds), *Oxford Handbook of Eye Movements*. Oxford University Press, Oxford, pp. 195–213.
Wierda, S.M., van Rijn, H., Taatgen, N.A. & Martens, S. (2012) Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution. *Proc. Natl. Acad. Sci. USA*, **109**, 8456–8460.
Winton-Brown, T.T., Fusar-Poli, P., Ungless, M.A. & Howes, O.D. (2014) Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci.*, **37**, 85–94.
Wise, L.Z. & Irvine, D.R. (1983) Auditory response properties of neurons in deep layers of cat superior colliculus. *J. Neurophysiol.*, **49**, 674–685.
Zenon, A. & Krauzlis, R.J. (2012) Attention deficits without cortical neuronal deficits. *Nature*, **489**, 434–437.