Coordination of Pupil and Saccade Responses by the Superior Colliculus

Chin-An Wang[1,2,3] and Douglas P. Munoz[1]

Abstract

■ The appearance of a salient stimulus evokes saccadic eye movements and pupil dilation as part of the orienting response. Although the role of the superior colliculus (SC) in saccade and pupil dilation has been established separately, whether and how these responses are coordinated remains unknown. The SC also receives global luminance signals from the retina, but whether global luminance modulates saccade and pupil responses coordinated by the SC remains unknown. Here, we used microstimulation to causally determine how the SC coordinates saccade and pupil responses and whether global luminance modulates these responses by varying stimulation frequency and global luminance in male monkeys. Stimulation frequency modulated saccade and pupil responses, with trial-by-trial correlations between the two responses. Global luminance only modulated pupil, but not saccade, responses. Our results demonstrate an integrated role of the SC on coordinating saccade and pupil responses, characterizing luminance independent modulation in the SC, together elucidating the differentiated pathways underlying this behavior. ■

INTRODUCTION

A series of responses, including saccadic eye movements and pupil dilation, are evoked by the presentation of a salient stimulus as part of the orienting response (Sokolov, 1963; Akert, 1949; Hess, Bürgi, & Bucher, 1946). Recent evidence, particularly in monkeys, has shown that pupil dilation is evoked by presentation of a visual target, enhanced by acoustic stimuli, modulated by stimulus saliency, and triggered by microstimulation of the superior colliculus (SC; Wang, Blohm, Huang, Boehnke, & Munoz, 2017; Wang, Boehnke, Itti, & Munoz, 2014; Wang & Munoz, 2014; Wang, Boehnke, White, & Munoz, 2012), a midbrain sensorimotor center that is phylogenetically conserved and causally involved in producing orienting responses (Wang & Munoz, 2015; Corneil & Munoz, 2014; Krauzlis, Lovejoy, & Zénon, 2013; Gandhi & Katnani, 2011; Hall & Moschovakis, 2003). Pupil size and saccadic eye movements are becoming popular and promising indices of cognitive and disease processes (Eckstein, Guerra-Carrillo, Miller Singley, & Bunge, 2017). Are the neural mechanisms underlying the cognitive modulation for pupil size similar to those for saccades? Furthermore, what is the role of the SC in coordinating saccade and pupil responses?

The SC is organized into a retinotopic map of contralateral visual space and has anatomically and functionally differentiated superficial (SCs) and intermediate/deep (SCi) layers (White & Munoz, 2011). The SCs receives visual signals from the retina and visual cortex, whereas the SCi receives multisensory and cognitive inputs from various cortical and subcortical areas (Beninato & Spencer, 1986; Wurtz & Albano, 1980; Graybiel, 1978; Edwards, 1975), including structures and neuromodulatory systems involved in the control of pupil size, such as the locus coeruleus (LC), FEF, and cholinergic projections from the pedunculopontine tegmental nucleus (PPTN; Joshi & Gold, 2020; Joshi, Li, Kalwani, & Gold, 2016; Lehmann & Corneil, 2016; Nelson & Mooney, 2016; Reimer et al., 2016; Aston-Jones & Cohen, 2005). Moreover, the SCi projects to the premotor circuitry in the brainstem that initiates the orienting response (Corneil & Munoz, 2014; Gandhi & Katnani, 2011; Sparks, 1986). Electrical microstimulation of the SCi in monkeys induces saccades (Robinson, 1972), and the properties of the evoked movements are modulated by stimulation parameters and the location of stimulation within the SC, with larger saccade responses (e.g., peak velocity) evoked using stronger stimulation parameters and larger amplitude saccades evoked by moving toward the caudal SCi (Stanford, Freedman, & Sparks, 1996). Weak microstimulation in the SCi can evoke pupil dilation without inducing saccades (Joshi et al., 2016; Wang et al., 2012). If the saccade and pupil responses are coordinated by the SCi (referred to as the common drive hypothesis), then varying stimulation parameters and changing stimulation sites should modulate not only saccades but also pupil responses.

Besides orienting, pupil size also changes to regulate the amount of light entering the retina to optimize visual sensitivity and acuity (Laughlin, 1992; Woodhouse, 1975), with smaller pupil sizes for higher luminance levels and larger pupil size for lower luminance levels. This luminance response is controlled by the balance of activity between the parasympathetic and sympathetic nervous systems (McDougal & Gamlin, 2015; Loewenfeld, 1999). Specifically,

[1]Queen's University, Kingston, Canada, [2]Taipei Medical University, [3]National Central University

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higher parasympathetic activity occurs during higher luminance levels, causing pupil constriction, whereas higher sympathetic activity occurs during lower luminance levels leading to pupil dilation. The SCs receives direct retinal projections, including those from intrinsically photosensitive retinal ganglion cells (Hannibal et al., 2014), which are important for luminance encoding and regulating the pupil light reflex (Münch & Kawasaki, 2013; Do & Yau, 2010; Gamlin et al., 2007; Dacey et al., 2005). Although visual signals such as visual contrast play an important role in the SC (Marino et al., 2012), the functional role of global luminance signals in the SC is yet to be explored.

Using microstimulation of the SCi with a systematic variation of stimulation frequency and background luminance, we investigate the role of the SCi in coordinating saccade and pupil responses at different luminance levels. If the SCi coordinates saccades and pupil responses, then responses evoked by SCi microstimulation should be correlated on trial-by-trial basis. Additionally, if the SCi is modulated by luminance levels, then background luminance should affect both pupil and saccade responses evoked by SCi microstimulation (Figure 1A). If, by contrast, the luminance signals sent to the SCi are functionally insignificant, then only the evoked pupil response.

METHODS

Animal Experimental Setup

Experiments were performed on two male rhesus monkeys (*Macaca mulatta*; 10 and 11 kg). The protocols used in this study were approved by Queen's University Animal Care Committee in accordance with the Canadian Council on Animal Care policies for the use of laboratory animals. The methods of surgical procedures, techniques for extracellular neuronal recording, and data collection have been described in detail previously (Marino, Rodgers, Levy, & Munoz, 2008). Eye position and pupil size were measured by a video-based eye tracker (Eyelink-1000, SR Research) at a rate of 1000 Hz with monocular recording (right pupil). Pupil area values recorded from the eye tracker were converted to pupil diameter (see details in Wang & Munoz, 2014). Stimulus presentation and data acquisition were controlled by a UNIX-based real-time data control system (REX; Hays, Richmond, & Optican, 1982). Spikes, eye position, and pupil diameter were recorded in a multichannel data acquisition system (Plexon). Stimuli were presented on a CRT monitor at a screen resolution of 1024 × 768 pixels (75 Hz noninterlaced), subtending a viewing angle of 54° × 44°.

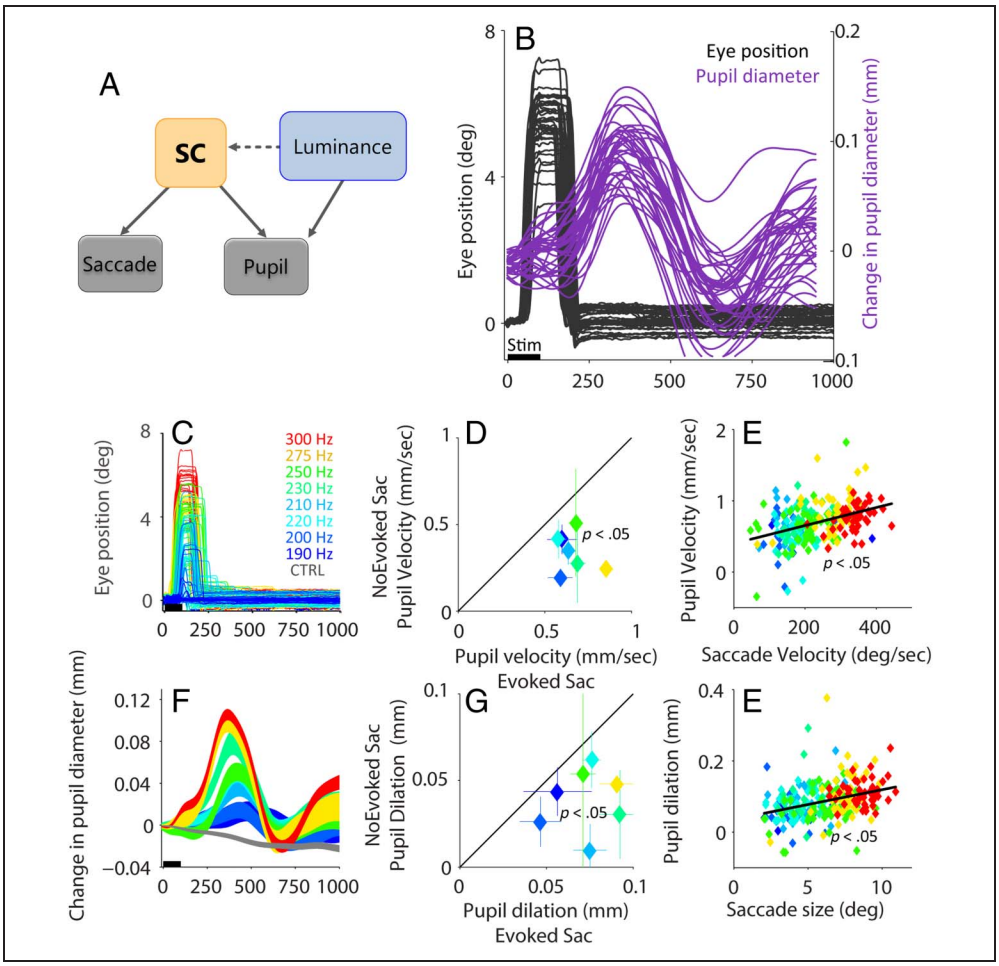

Figure 1. Effect of SCi microstimulation on saccade and pupil responses from an example site. (A) Illustration of hypotheses on the modulation of the SC on saccade and pupil responses by luminance. (B) Temporal dissociation between evoked saccades (only horizontal eye position) and pupil responses. (C, F) Effects of stimulation frequency on (C) saccade and (F) pupil responses. (D, G) Pupil responses between trials with evoked saccades and trials without evoked saccades in (D) velocity and (G) magnitude. (E, H) Trial-by-trial correlation between normalized pupil and saccade responses in (E) velocity and (H) magnitude. In C and F, the black bar on *x*-axis indicates the time line of microstimulation. The shaded colored regions surrounding the pupil response represent ±*SE* range in different conditions. CTRL = control (no stimulation); Stim = microstimulation.

Procedure, SC Recording, and Stimulation

Monkeys were seated in a primate chair with their heads restrained facing the video monitor. We lowered tungsten microelectrodes (impedance: 0.1–1 MΩ, Frederick Haer) to locate the SC. We mapped the visual response fields of the SC using a visual mapping task (Marino et al., 2012) and identified the depth of the SCi (intermediate layers of the SC) using a delayed saccade task. Once the SCi was localized, it was microstimulated (250–300 Hz pulse train for 100 msec with alternating 0.3-msec anode plus 0.3-msec cathode pulses), and threshold for saccades was determined when the stimulation current in the SCi evoked saccades 50% of the time (range: 5–50 μA). The optimal locations of the response fields of SCi neurons were in close agreement with the vector of eye movement elicited with suprathreshold SCi stimulation and ranged between 3° and 20° eccentricity.

Experimental Task

The monkeys were trained to perform a simple fixation task. They had to maintain gaze within 1.5° of a central fixation point (FP; 0.5° diameter; 20 cd/m^2, isoluminant color of the background) at the center of the screen on a gray background (20 cd/m^2) for a few seconds to obtain a liquid reward. After the monkey maintained fixation for 1–1.5 sec, a train of stimulation pulses was delivered on 50% of the trials, and the monkeys had to maintain fixation for another 1.5–2 sec, regardless of microstimulation. Saccades were often evoked after electrical stimulation (latencies usually less than 100 msec). Monkeys had to move their eyes back to the FP within 500 msec after microstimulation, and both monkeys usually moved their eyes back to the FP within 300 msec after microstimulation.

Two microstimulation experiments were conducted. In the first experiment, stimulation frequency was manipulated (100-msec stimulation train duration). After determining the saccade threshold current, usually at 300-Hz stimulation, we systematically varied the frequency of stimulation, ranging from 150 to 300 Hz and used ~150% of the saccade threshold current to regularly evoke saccades, particularly under high-frequency stimulation. At each stimulation site, we microstimulated at three to eight different frequency levels. The order of frequency levels across blocks was varied across days. Microstimulation was delivered to 24 sites (9 and 15 in Monkeys A and B, respectively).

In the second experiment, the level of global luminance was manipulated by changing the background luminance level of the computer screen. We thus refer to background luminance of the screen as global luminance. Stimulation levels were fixed across various background luminance conditions (>250-Hz stimulation frequency and 100-msec stimulation duration). The monkey had to maintain gaze within 1.5° of a central FP (0.5° diameter; isoluminant color difference from background) at the center of the screen with background luminance of 2.5, 20, or 40 cd/m^2. The order of luminance levels across blocks was varied across days. Microstimulation was delivered to 16 sites (6 and 10 in Monkeys A and B, respectively) at three to five background levels (2.5, 5, 10, 20, and 40 cd/m^2). There were at least 20 correct trials in all conditions.

Data Analysis

Trials with blinks or an eye position deviation of more than 1.5° from the central FP or with the detected saccades (> 2°) during the required period of central fixation were excluded from analysis, except for microstimulation-related (evoked and return) saccades. The recorded pupil size depends on the subject's gaze angle in a video-based eye tracker so that pupil size data can be distorted by eye movements and eccentric eye positions. Because of applying suprathreshold microstimulation, saccades were often evoked after stimulation and eye position returned to center within 300 msec. To maintain an accurate measure of the pupil, we mainly used pupil peak dilation and velocity measures because they regularly occurred after 300 msec of microstimulation, and at this time, the eyes had returned to the FP, so that the pupil could be accurately measured. The difference in the efferent delays of the saccade and pupillary responses are primarily caused by the different muscle types being innervated: smooth muscle controlling the pupil and extraocular fast twitch skeletal fibers for the saccades. Nevertheless, the pupil response is temporally dissociated from the saccade response (see Figure 1B for an example).

Because the pupil response is consensual (Wang & Munoz, 2014; Wang et al., 2012), only pupil diameter of the right eye was recorded for data analysis. Following the procedures of baseline correction used previously (Wang et al., 2012, 2014), original pupil diameter values were subtracted from the baseline pupil diameter value determined by averaging pupil size from 200 msec before to the onset of microstimulation for each trial. To normalize pupil and saccade measurements across conditions for population analyses (frequency, background luminance), all measured values were divided by the median value of the highest frequency condition (lowest luminance level for the other experiments). To be included for condition-based analyses, each condition (frequency/background luminance) had to have more than 15 remaining trials, except where indicated. Evoked saccade RT was defined as the time after microstimulation to the first saccade away from central fixation that exceeded 30°/s. The highest three frequency conditions were selected for some analyses to examine the relationship between saccade and pupil responses, because there were more numerous trials with evoked saccades in the higher frequency conditions.

Results are shown as mean ± *SEM*. We performed correlational analyses and a two-tailed Student's *t* test, except where indicated. Bayesian *t* tests, where appropriate, were also performed to inform statistical significance for pairwise comparisons, with a scale factor $r = .707$ (Rouder, Speckman, Sun, Morey, & Iverson, 2009). Moreover,

Cohen's *d*, where appropriate, was calculated to estimate effect size (Hentschke & Stüttgen, 2011). In the background luminance experiment, we used a bootstrap method to inform the statistical significance of the comparison by performing a random sampling of pupil values derived from each recording trial with 1000 repetitions (Wang et al., 2014). This resulted in a normally distributed cluster of points centered on the mean of selected pupil values (clusters not shown, normal distribution was verified by the Kolmogorov–Smirnov test). Statistical tests were performed using JASP Team (2019) and MATLAB (The MathWorks, Inc.).

RESULTS

Correlation between Saccade and Pupil Responses via Varying Train Frequency

If the mechanisms of initiation of saccade and pupil dilation are shared through the SCi, then the comparable modulation of saccade and pupil responses by varying stimulation frequency should be observed. More specifically, the common drive hypothesis postulates that the same efferent neurons in the SCi project to both saccade and pupil control circuits. Therefore, trial-by-trial correlations between saccade and pupil responses induced by SCi microstimulation should be observed. For example, if there are stronger output signals from the SCi, this signal should drive larger saccade and pupil responses. Moreover, because of a gating role of the omnipause neurons (e.g., Scudder, Kaneko, & Fuchs, 2002), signals must surpass the threshold to evoke saccades. Thus, pupil dilation on trials with an evoked saccade should be larger than that on trials without an evoked saccade. To test these predictions, monkeys were trained to perform a simple fixation task in which they were required to maintain fixation upon a central FP. Microstimulation was delivered to 24 sites in the intermediate layers (SCi; 9 in Monkey A, 15 in Monkey B) on 50% of trials (see Methods for details). Figure 1B shows an example of individual saccade and pupil responses induced by SCi microstimulation (300 Hz, 40 μA, 100 msec). Microstimulation evoked saccades (black traces in Figure 1B) toward the location that corresponds to the stimulated SC position with a mean latency of 42 msec (22–63 msec) after stimulation onset. The monkey then quickly returned his eyes to the central FP with a mean latency of 125 msec (87–152 msec) measured after the previous saccade offset. Pupil dilation was also evoked after microstimulation, but the pupil response onset latency was slower, starting near 200 msec and peaking near 300 msec after the stimulation, because of the longer efferent delay of the pupil control circuit (Wang et al., 2012). We focused here on initial pupil dilation because pupil dilation has long been characterized as a component of orienting (Sokolov, 1963; Ferrier, 1876). Moreover, pupil dilation dynamics evoked by SCi microstimulation (Wang et al., 2012) is similar to those evoked by salient stimuli (Wang et al., 2014), suggesting that similar orienting processes may be involved between two observed pupil dilation. Also, pupil dilation is related to aspects of cognition (van der Wel & van Steenbergen, 2018; Beatty, 1982). Eye movements and variations in eye position could diminish the accuracy of pupil size measurements. Because the eyes of monkeys almost always returned to central FP within 300 msec after stimulation onset (Figure 1B), to maintain the accuracy of pupil measurement, we measured pupil peak velocity and dilation (which occurred at around 300–500 msec after stimulation onset) to correlate pupil responses with saccade responses (see Methods).

Changes in stimulation frequency altered saccade and pupil responses in a systematic and coordinated manner, as shown in Figure 1C–H for this example stimulation site. Consistent with the literature (Stanford et al., 1996), increasing stimulation frequency systematically increased the probability of evoking a saccade (low to high frequency: 13%, 33%, 48%, 64%, 81%, 92%, 98%, and 100%), decreased the latency (low to high frequency, mean value: 86.3, 72.1, 69.3, 78.2, 67.2, 54.0, 41.7, and 41.8 msec), and increased saccade amplitude (Figure 1C; low- to high-frequency conditions: 3.8°, 4.1°, 4.6°, 4.2°, 4.7°, 6.1°, 7.6°, and 8.7°). Microstimulation also resulted in transient pupil dilation, followed by constriction (purple traces in Figure 1B). Importantly, these pupil responses were also systematically modulated by stimulation frequency, with larger peak dilation observed for higher stimulation frequencies (Figure 1F; low to high frequency in magnitude: 0.048, 0.052, 0.080, 0.073, 0.099, 0.072, 0.105, and 0.109 mm).

To examine the trial-by-trial correlation between saccade and pupil responses, we divided pupil responses according to the likelihood of evoking saccades. Trials with saccades were associated with larger pupil velocities and greater dilation (Figure 1D, velocity, $t(6) = 5.05$, $p < .01$; Figure 1G, magnitude, $t(6) = 3.86$, $p < .01$). We also examined the correlation between saccade and pupil responses across individual trials when a saccade was evoked and found that trials with larger saccade responses had larger pupil responses (Figure 1E in velocity, $R = .4$, $p < .001$; Figure 1H in magnitude, $R = .34$, $p < .001$).

Saccade and pupil responses evoked by microstimulation were highly correlated across our sample of stimulation sites ($n = 24$) in two monkeys (Figure 2). Stimulation frequency systematically modulated the probability of evoking a saccade (Figure 2A). A generalized linear model was used to characterize this relationship by applying a binomial distribution (saccade evoked or not: 1 or 0) and a logistic link function (a logistic fit). The fitted model yielded an R^2 value of .99 (data from data source Figure 2), suggesting that saccade probability can almost be fully explained by the model of using stimulation frequency as a predictor. Figure 2B summarizes pupil dynamics following microstimulation (22 sites for which we had four or more stimulation frequency conditions were included in Figure 2B, and 2 sites that only had three stimulation frequency conditions were thus excluded from analysis, $n = 22$; individual monkey

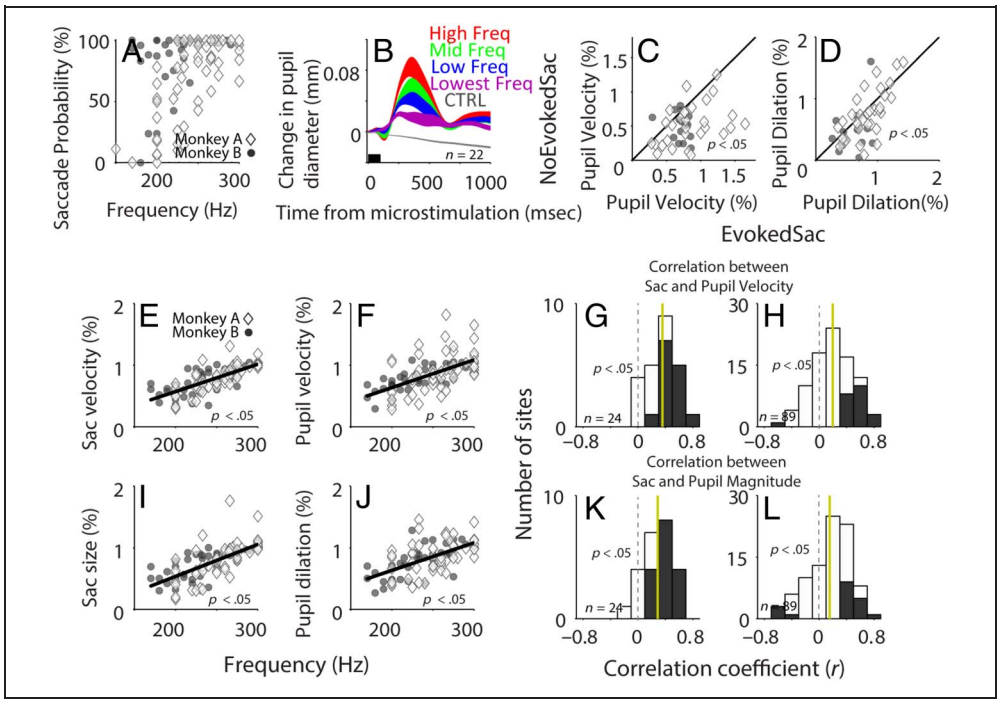

Figure 2. Summary of SCi microstimulation on saccade and pupil modulation. (A) Correlation between stimulation frequency and evoked saccade probability. (B) Pupil responses after microstimulation in four highest frequency and control (no microstimulation) conditions on data collapsed across monkeys and stimulation sites (n = 22). (C, D) Pupil responses collapsed across monkeys and stimulation sites (n = 24) between trials with evoked saccades and trials without evoked saccades in (C) velocity and (D) magnitude. (E, F, I, J) Effect of stimulation frequency on evoked saccade and pupil responses in (E, F) velocity and (I, J) magnitude. (G, K) Distribution of correlation coefficients for the relationship between evoked saccade and pupil responses in (G) velocity and (K) magnitude (n = 24). (H, L) Distribution of correlation coefficients for the relationship between evoked saccade and pupil responses in each frequency condition in (H) velocity and (L) magnitude (n = 89). In A, E, F, I, and J, black lines indicate the regression line. In B, the black bar on x-axis indicates the time line of microstimulation. The shaded colored regions surrounding the pupil response represent $\pm SE$ range for different conditions. In G, H, K, and L, the vertical black dotted and yellow solid line represent a zero and median value of correlation coefficient. Filled bars indicate sites with statistically significant correlation ($p < .05$). n = number of sites; CTRL = control (no stimulation).

data revealed the same stimulation frequency modulation in two monkeys), showing that pupil dilation scaled with stimulation frequency (high to low frequency and control: mean pupil size at an epoch of 250–350 msec after stimulation onset: 0.075, 0.053, 0.041, 0.021, and −0.006 mm). To illustrate the results across microstimulation sites, we normalized the data by dividing saccade/pupil values by the median value in the highest frequency condition (see Methods). The common drive hypothesis (Figure 1A) predicts that pupil responses should be larger on trials in which saccades were evoked, and this is what we observed. Pupil responses evoked by microstimulation were larger on trials with saccades, compared with trials without saccades (Figure 2C in velocity, $t(47) = 3.4$, $p < .01$; Figure 2D in magnitude, $t(47) = 2.55$, $p < .05$). Saccade and pupil responses were both systematically influenced by stimulation frequency (velocity: saccade, Figure 2E, $R = .75$; pupil, Figure 2F, $R = .57$; magnitude: saccade, Figure 2I, $R = .69$; pupil, Figure 2J, $R = .61$, all $p < .001$). Consistent with the common drive hypothesis, trial-by-trial correlational analyses collapsed across all frequency conditions from each stimulation site (n = 24) showed a reliable positive correlation between pupil and saccade responses (histograms of the correlation coefficients are shown in Figure 2G, K), and the mean correlation coefficient was .36 in velocity with significant correlations ($p < .05$) obtained for 58% (14/24) of the stimulation sites (Figure 2G), parried t test of R values against zeros, $t(23) = 7.6$, $p < .001$, and .29 in magnitude with significant correlations obtained for 67% (16/24) of the stimulation sites (Figure 2K), $t(23) = 7.1$, $p < .001$. Again, these results were not an artifact of inaccurate measurement of pupil size because pupil responses following the return saccade onset were clearly modulated by stimulation frequency with larger dilation observed for higher stimulation frequencies.

To further examine the correlation between saccade and pupil responses from individual frequency conditions at each site, we split trials according to median saccade peak velocity or magnitude. Although the variation across trials was reduced in a given frequency condition, trials with larger saccade responses still had larger pupil responses: large saccade velocity, 0.85 mm/s pupil velocity, and small saccade velocity, 0.73 mm/s pupil velocity, $t(88) = 4.94$, $p < .001$; magnitude: large saccade size, 0.095 mm diameter, and small saccade size, 0.077 mm diameter, $t(88) = 5.58$, $p < .001$. Figure 2H and L shows summary histograms of correlation coefficients for all conditions, revealing in general positive correlations between saccade and pupil responses in velocity (significant positive correlations for 24% [21/89] of the individual stimulation/conditions), mean correlation coefficient of .2, $t(88) = 6.5$, $p < .001$, and in magnitude (significant positive correlations for 17% [15/89] of the stimulation/conditions), mean correlation coefficient of .15, $t(88) = 4.6$, $p < .001$, though there were a few sites having significant negative correlations (velocity: 1%, 1/89; magnitude: 4%, 4/89). Together, these results demonstrate positive trial-by-trial correlations between saccade and pupil responses evoked by the SCi

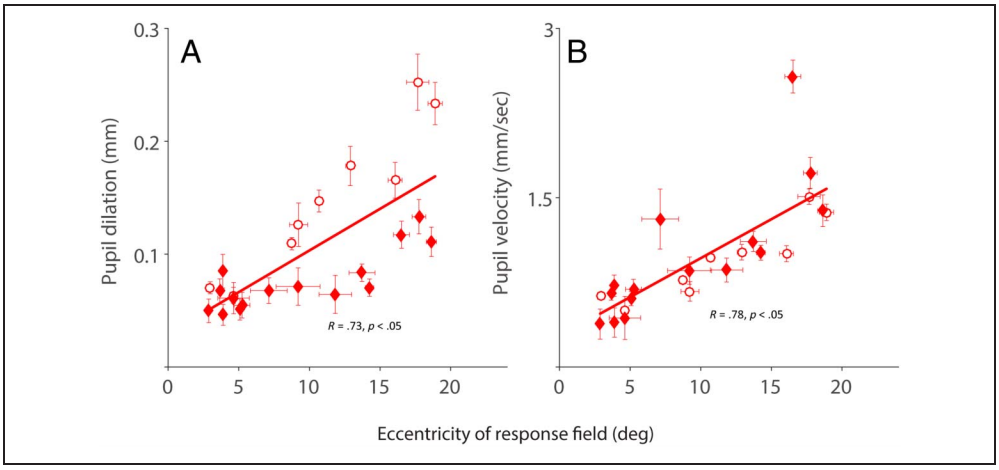

Figure 3. Effects of stimulation-evoked pupillary response as a function of the eccentricity of stimulation site. Correlation between the eccentricity of stimulation site and evoked pupillary response in the three highest frequency conditions in (A) magnitude and (B) velocity (n = 24). Lines indicate the regression line. Monkey A: ◊, Monkey B: ○.

microstimulation. Similar results were obtained with varying stimulation duration.

Site-specific Effects in Saccade and Pupil Responses

The SCi is organized into a retinotopically coded motor map, and different sites evoke different amplitude and direction saccades (Robinson, 1972) because different sites project disproportionally to the omnipause and burst neurons (Büttner-Ennever, Horn, Henn, & Cohen, 1999; Moschovakis, Dalezios, Petit, & Grantyn, 1998; Moschovakis, Kitama, et al., 1998). Although unidentified, this pattern of anatomical relationship may also be present in the SCi projections to the pupil control circuit; that is, regions in the SCi map that code for larger amplitude saccades (i.e., caudal SC) may also code for larger pupil dilation, yielding more and/or stronger projections from the caudal SC to the

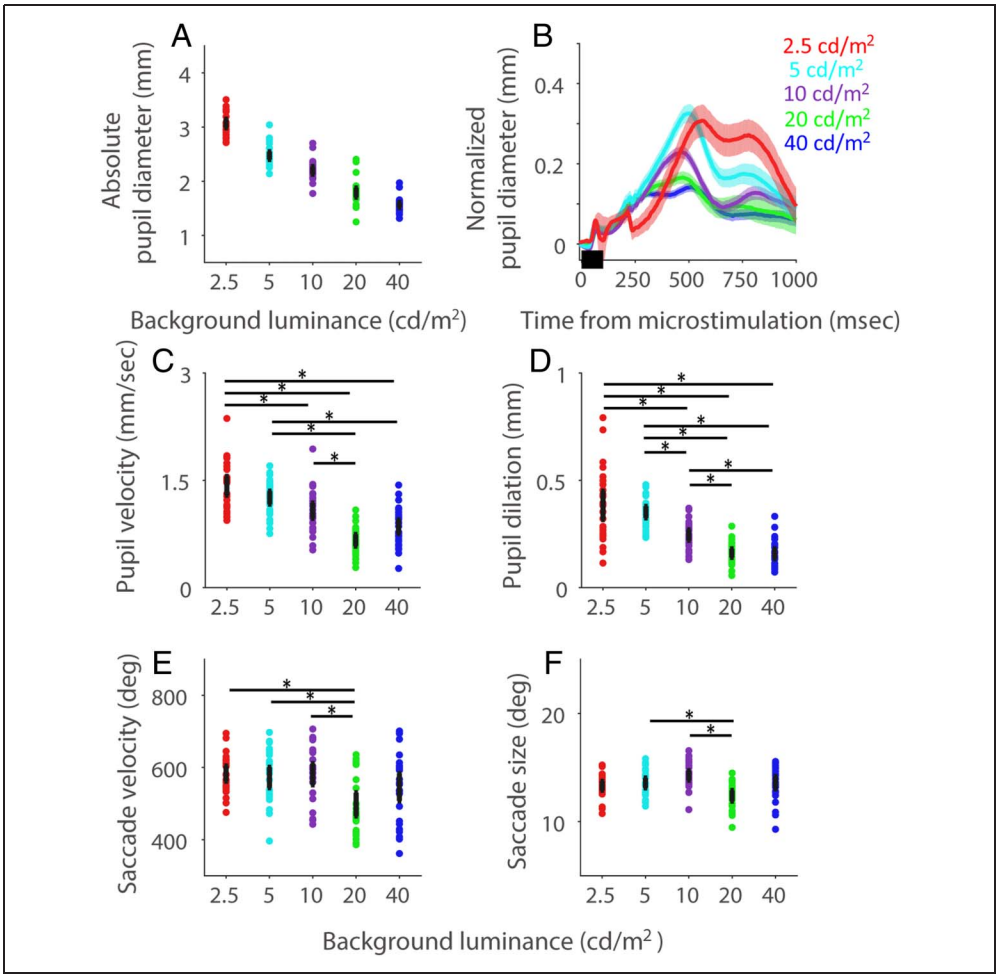

Figure 4. Examples showing background luminance effects on saccade and pupil responses. (A) Effects of background luminance on absolute pupil diameter at an example site. (B) Pupil responses after microstimulation in five background luminance conditions. (C, D) Pupil responses after microstimulation in different background luminance conditions with respect to (C) velocity and (D) magnitude. (E, F) Saccade responses after microstimulation in different background luminance conditions with respect to (E) velocity and (F) magnitude. In A and C–F, the thick black and gray circles represent an average and individual trial values of measurements. In B, the black bar on x-axis indicates the time line of microstimulation. The shaded colored regions surrounding the pupil response or error bar represent ±95% confidence interval for different conditions derived from the bootstrap analysis. n = number of sites; * = differences were statistically significant according to bootstrapping.

pupil control circuit. Because pupil size is unidimensional, we used eccentricity of the response field determined by the vector of saccade elicited with suprathreshold SCi stimulation (see Methods) to investigate the relationship between pupil dilation magnitude and evoked saccade size. The magnitude of the evoked pupil dilations was correlated with response field eccentricity (Figure 3A in magnitude: $R = .73$, $p < .001$; Figure 3B in velocity: $R = .78$, $p < .001$): larger dilation and faster velocities were indeed observed for sites with larger vectors of evoked saccades (magnitude: Monkey A, $R = .95$; Monkey B, $R = .87$, all ps $< .001$; velocity: Monkey A, $R = .91$; Monkey B, $R = .78$, all ps $< .005$). Therefore, our microstimulation results demonstrate the site-specific modulation of both saccade and pupil responses.

Modulation of Pupil but Not Saccade Responses by Background Luminance

The major function of changes in pupil size is to regulate the amount of light projected onto the retina (McDougal & Gamlin, 2015; Loewenfeld, 1999). However, whether global luminance signals play a role in modulating the SC is yet to be explored. Varying background luminance changes the balance of activity in the pupil control pathway (Loewenfeld, 1999). The pupil responses evoked by the SCi should thus be affected. More importantly, if the SCi is also involved in luminance encoding, as suggested by the results of Hannibal et al. (2014), then varying background luminance should also modulate saccade responses evoked by SCi microstimulation. To investigate the influences of background luminance on pupil and saccade responses evoked by SCi microstimulation, monkeys performed the same fixation task described above. However, this time background luminance was varied, and microstimulation parameters were fixed for each recording site (stimulation duration: 100 msec; stimulation frequency range: 240–300 Hz). Changes in background luminance systematically changed pupil diameter, as shown in Figure 4 for an example stimulation site. Consistent with the literature (Loewenfeld, 1999), increasing background luminance systematically reduced baseline pupil diameter with mean values of 3.07, 2.47, 2.2, 1.79, and 1.56 mm in the 2.5, 5, 10, 20, and 40 cd/m^2 background conditions, respectively (Figure 4A; differences were all statistically significant between any of two conditions according to bootstrapping, see Methods). Importantly, pupil responses evoked by SCi microstimulation were also systematically

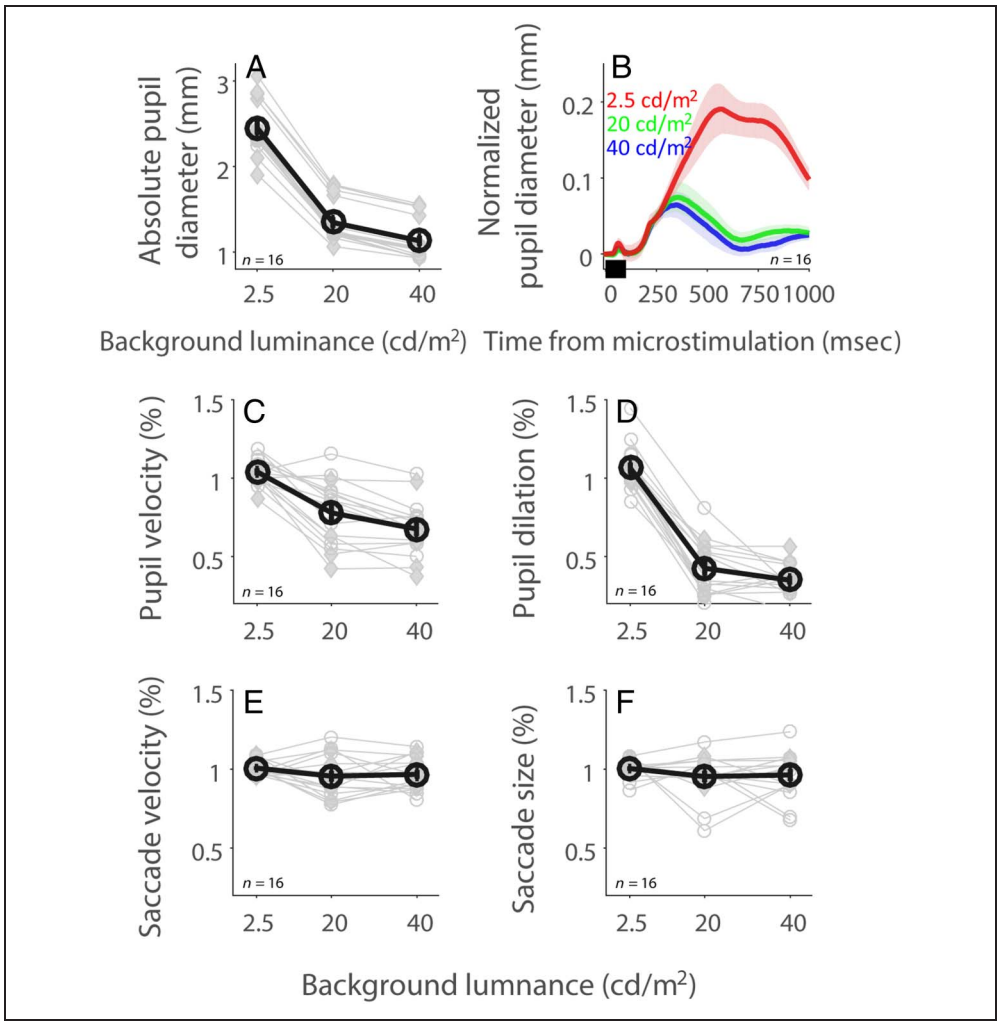

Figure 5. Summary of background luminance on saccade and pupil responses. (A) Effects of background luminance on absolute pupil diameter collapsed across monkeys and stimulation sites ($n = 16$). (B) Pupil responses after microstimulation for three background luminance conditions. (C, D) Pupil responses after microstimulation for different background luminance conditions in (C) velocity and (D) magnitude. (E, F) Saccade responses after microstimulation in different background luminance conditions in (E) velocity and (F) magnitude. In A and C–F, the thick black and gray circles represent an average and individual site values of measurements. In B, the black bar on x-axis indicates the time line of microstimulation. The shaded colored regions surrounding the pupil response represent $\pm SE$ range for different conditions. n = number of sites. Monkey A: ◊, Monkey B: ○.

modulated by background luminance levels (Figure 4B). Increasing background luminance produced lower pupil velocities (Figure 4C; low to high background luminance: mean values: 1.42, 1.26, 1.07, 0.66, and 0.85 mm/s) and less dilation (Figure 4D; low to high background luminance: mean values: 0.38, 0.35, 0.25, 0.16, and 0.16 mm). In contrast, saccade responses were not systematically modulated by background luminance, with mean peak velocities of 583°/s, 572°/s, 581°/s, 498°/s, and 546°/s (Figure 4E) and saccade sizes of 13.3°, 13.6°, 14.3°, 12.3°, and 13.6° (Figure 4F) in the 2.5, 5, 10, 20, and 40 cd/m^2 background conditions, respectively, although some comparisons were statistically significant.

Figure 5 summarizes the effects of SCi microstimulation on saccade and pupil responses in different background conditions (2.5, 20, and 40 cd/m^2) collapsed across all stimulation sites tested with luminance changes from two monkeys (n = 16; note that this was minimal data set for all possible sites and some sites; e.g., Figure 4 had more than three luminance values). Pupil diameter (Figure 5A; saccade: $F(2, 30) = 1417.86$, $p < .001$; Bonferroni-corrected comparisons: all comparisons, $p < .05$) before microstimulation was clearly modulated by background luminance, with absolute pupil sizes of 2.45, 1.35, and 1.13 mm for 2.5, 20, and 40 cd/m^2, respectively. Figure 5B shows the normalized pupil diameter produced by SCi microstimulation for three background conditions (stimulation vs. no stimulation), revealing larger responses for lower luminance conditions. To quantify these orienting responses, we normalized these responses (see Methods). As predicted, evoked pupil responses were systematically modulated by background luminance (Figure 5C: velocity, $F(2, 30) = 44.163$, $p < .001$, and all comparisons, $p < .01$; Figure 5D: magnitude, $F(2, 30) = 221.934$, $p < .001$, and comparisons between 2.5 cd/m^2 and others, $p < .05$), with larger pupil dilation evoked with lower background luminance. In contrast, the probability of evoked saccades was not influenced by different background luminance (2.5, 20, and 40 cd/m^2: 94%, 92%, and 91%), $F(2, 30) = 0.538$, $p = .59$. Moreover, neither the velocity (Figure 5E; $F(2, 30) = 1.486$, $p = .24$, and all comparisons, $p > .37$) nor magnitude (Figure 5F: $F(2, 30) = 0.999$, $p = .38$, and all comparisons, $p > .5$) of the saccades were modulated by background luminance levels. These results characterize the influence of luminance signals on pupil, but not saccade, responses evoked by SCi microstimulation.

DISCUSSION

The goal of this study was to understand the role of the SCi in the coordination between saccades and pupil dilation during the orienting response and to determine whether background luminance interacts with these evoked responses (Figure 1A). Varying stimulation frequency systematically modulated the evoked saccade as well as the pupil responses, with larger saccade and pupil responses observed for higher stimulation frequencies. Trial-by-trial correlation was also observed: Trials with larger saccade responses had larger pupil responses. Furthermore, microstimulation of SCi sites, which produced larger amplitude saccades, also evoked larger pupil dilation. These results together demonstrate saccade and pupil movements are coordinated through the SCi, likely via a shared common output signal derived from the SCi. However, varying background luminance only influenced evoked pupil responses, implying that luminance information was not processed directly in the SCi, although the SC does receive direct retinal projections (Hannibal et al., 2014).

Circuits for Saccade and Pupil Control by the SC

The SCi integrates sensory, motor, and cognitive signals from various cortical and subcortical areas and projects directly to the premotor brainstem circuitry to initiate the orienting response (Wang & Munoz, 2015; Corneil & Munoz, 2014). Although the role of the SCi in the control of saccade and pupil responses has been developed, it has yet to be determined whether the same SCi efferent projection drives both saccade and pupil responses (the common drive hypothesis) or, alternatively, that saccade and pupil responses are mediated by different sets of axons emerging from the SCi. The connections between neurons in the SCi and brainstem reticular formation for control of saccades is well established (Horn, 2006; May, 2006; Sparks, 2002). The central mesencephalic reticular formation (cMRF) is one of the collicular targets involved in horizontal saccade control (Cohen & Büttner-Ennever, 1984), and research using intra-axonal recording and horseradish peroxidase injection has revealed that saccade-related long-lead burst neurons in the SCi with axon collaterals terminating in the cMRF also commonly project to the pontine premotor centers for saccade control (Scudder, Moschovakis, Karabelas, & Highstein, 1996; Grantyn & Grantyn, 1982). Moreover, it has recently shown that cMRF also projects directly to the Edinger–Westphal nucleus (May, Warren, Bohlen, Barnerssoi, & Horn, 2016), a critical structure in the pupil control circuit (Wang & Munoz, 2015; Corneil & Munoz, 2014). In addition, the SC projects directly and indirectly via the cMRF to the medullary reticular formation (Perkins, Warren, & May, 2009) and so may influence preganglionic sympathetic motoneurons via this route. However, connections to the motoneurons controlling dilation via these routes remain to be demonstrated. These results and trial-by-trial correlations together suggest that the same efferent projection derived from the SCi could possibly drive both saccade and pupil premotor circuits to produce coordinated saccade and pupil responses. We found that microstimulation of the SCi produced trial-by-trial correlations between saccade and pupil responses, suggesting that common output signals derived from the SCi drive both downstream premotor circuits. Although trial-by-trial correlation between

saccadic and pupil responses could theoretically be explained by assuming different SCi efferents are activated via current spreading, anatomical data on SCi efferents supports the common drive hypothesis.

Monkeys returned their eyes back to the central FP (return saccade) after a saccade evoked by SCi microstimulation. The properties of the return saccade are very similar to the evoked saccade, albeit traveling in the opposite direction. Moreover, pupil size should also be modulated in a manner that correlates with the return saccade. Because of the speed of these two saccades, it appears that the pupil effects were combined. Certainly, robust trial-by-trial correlations were still observed even though we only compared dilation to the properties of the stimulation evoked saccades. Future studies are thus needed to explore how a sequence of saccades might modulate pupil response dyanamics.

Notably, although the visual information was changed after evoking a saccade, the accompanying pupil dilation was unlikely explained by changes in visual information processing due to saccades evoked for several reasons. First, because of using an isoluminant FP, the overall luminance level was unchanged by evoking saccades. Therefore, the primitive visual factor that affects pupil size was carefully controlled. Although it can still be argued that other visual information that changes after an evoked saccade mediates observed pupil dilation, this account is difficult to reconcile with the magnitude of the modulation produced by varying stimulation frequency. Because any changes in visual processing should be similar after an evoked saccade in different stimulation frequency conditions and evoked saccade latencies were slightly larger by decreasing stimulation frequency (saccade RT differences < 50 msec), varying stimulation frequency should only affect pupil dilation responses in the temporal domain, but not in the magnitude domain. However, here we found that the magnitude of evoked pupil dilation was also modulated by stimulation frequency.

Different regions in the SC motor map project disproportionally to omnipause neurons and excitatory/inhibitory burst neurons to trigger saccades with different amplitudes (Büttner-Ennever et al., 1999; Moschovakis, Dalezios, et al., 1998; Moschovakis, Kitama, et al., 1998; Gandhi & Keller, 1997). Although unidentified, this pattern of anatomical relationship may also be present in the SCi projections to the pupil control circuit; that is, regions in the SCi map that code for larger amplitude saccades (i.e., caudal SC) also code larger pupil dilation, yielding more and/or stronger projections from the caudal SC to the pupil control circuit. Although the results here support this idea, that is, SC sites that evoked larger size saccades also induced larger pupil dilation, pupil dilation induced by subthreshold SCi microstimulation was not modulated by SC location (Wang et al., 2012). Interestingly, these differences were observed in behavioral experiments. When the task required maintenance of central fixation, pupil dilation, though evoked, was not modulated by stimulus eccentricity (Figure 2G in Wang et al., 2014). In contrast, when the monkey required to move the eyes to visual target (step task), pupil dilation was modulated by stimulus eccentricity, with larger pupil dilation in trials with larger eccentricitic stimuli. Why are these effects different between supra- and subthreshold microstimulation (or with and without evoking a saccade)? We think that there are at least two possibilities. First, the eccentricity effect required a higher level of SCi activity, and thus, subthreshold microstimulation (or stimulus appearance without evoking a saccade) was too weak to produce this modulation, though pupil dilation was still evoked. Second, the eccentricity effect was conditionally dependent upon saccade generation, and saccade generation recruits additional brain structures such as frontal cortex and cerebellum (Robinson & Fuchs, 2001; Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998) or other processes such as arousal necessary to produce this effect. For example, arousal level could be higher when the derailment of the eyes from the central FP is larger, producing larger pupil dilation in more eccentricitic sites. Future research is required to test these possibilities and explore the anatomical relationship between different regions in the SC and the connections to the pupil control circuit.

Role of Other Brain Areas in Pupil Control

Pupil size is also modulated by other structures in the brain that possibly contribute to correlations observed here between saccade and pupil responses (Joshi & Gold, 2020; Sara & Bouret, 2012; Nieuwenhuis, De Geus, & Aston-Jones, 2011). Mounting evidence has demonstrated that pupil size covaries with neural activity of the LC in behaving monkeys (Joshi et al., 2016; Varazzani, San-Galli, Gilardeau, & Bouret, 2015; Aston-Jones & Cohen, 2005) and that LC neurons also discharge phasically to task-relevant sensory stimuli (Kalwani, Joshi, & Gold, 2014; Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004; Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Rajkowski, Kubiak, & Aston-Jones, 1994; Swick, Pineda, Schacher, & Foote, 1994; Grant, Aston-Jones, & Redmond, 1988). Furthermore, the cholinergic system also correlates with pupil responses (Reimer et al., 2016) and could also modulate saccade responses through changing cholinergic activity within the SC via input from the PPTN (Watanabe, Kobayashi, Inoue, & Isa, 2005; Li, Endo, & Isa, 2004; Aizawa, Kobayashi, Yamamoto, & Isa, 1999). Pupil dilation is also evoked by subthreshold microstimulation of the FEF (Ebitz & Moore, 2017; Lehmann & Corneil, 2016), a structure involved in attention and gaze shifts (Thompson & Bichot, 2005), although these studies focused mainly on pupil dynamics, instead of the coordination between saccade and pupil responses. Therefore, it is possible that abovementioned structures are involved in coordinating pupil and saccade responses. This raises an interesting possibility that, although saccades are controlled by the SCi, pupil responses could be mediated, not directly by the SCi, but by other structures related to saccade responses. Although this

hypothesis yields the same prediction on the pupil response modulation by stimulation frequency, we think this possibility is less likely because of the following reasons. First, pupil dilation can be evoked by SCi microstimulation in the absence of saccades (Wang et al., 2012), and stimulation frequency (or duration etc) in the FEF can also modulate evoked pupil responses in the absence of saccades (Lehmann & Corneil, 2016), together suggesting that the presence of saccades is not necessary to induce pupil dilation by SCi microstimulation. Second, although weaker, positive correlations between saccade and pupil responses within each frequency condition were still observed here, demonstrating potential coupling between the two responses, even in the absence of the frequency manipulation. Third, because pupil control requires innervation of smooth muscle (McDougal & Gamlin, 2015; Loewenfeld, 1999), the pupil is slower to respond. In other words, although the pupil is slower, most of that increased latency is due to the peripheral effector, not a delay in central processing. Fourth, research that compares several structures, such as the LC, SC, and inferior colliculus in their role on pupil size in behaving monkeys, has shown that the shortest efferent delay between output signals among targeted structures and the pupil response onset latency is the SCi (Joshi et al., 2016). These results suggest that the SCi is the structure that is most closely located to the final common path. Last, and most importantly, the SCi receives inputs from the LC, FEF, and inferior colliculus, as well as cholinergic projections from the PPTN (Beninato & Spencer, 1986; Wurtz & Albano, 1980; Graybiel, 1978; Edwards, 1975). Therefore, it is more likely that the signals from LC, FEF, inferior colliculus, and PPTN are integrated in the SCi to drive coordinated saccade and pupil responses. A recent review article has also postulated some influences from multiple pathways underlying the relationship between the SCi and pupil dilation under different conditions and timescales (Joshi & Gold, 2020).

Global Luminance Effects on Evoked Saccades and Pupil Dilation and Functional Role of Its Coordination

The SC receives retinal projections, including intrinsically photosensitive retinal ganglion cells projections to both the SCs and SCi (Hannibal et al., 2014), which are particularly important to luminance encoding and the pupillary light reflex (Münch & Kawasaki, 2013; Do & Yau, 2010; Gamlin et al., 2007; Dacey et al., 2005). However, it is unclear whether these luminance signals serve a role in signal processing in the SCi. Varying background luminance changes pupil size by regulating the activity balance between the sympathetic and parasympathetic pathways, with greater activation in the sympathetic system, but smaller activation in the parasympathetic system, at lower levels of luminance (Loewenfeld, 1999; Steinhauer & Hakerem, 1992). Here, we found that lowering background luminance systematically increased the degree of pupil dilation evoked by SCi microstimulation, but it did not change the evoked saccade responses. This suggests an independent relationship between the SCi and luminance signal processing. Notably, although the global luminance did not modulate saccades evoked by microstimulation, it may influence saccades that are heavily associated with visual processes, such as visually guided saccades, so future work is required to examine this question.

Pupil dilation can be mediated through inhibiting the parasympathetic system (Barnerssoi, May, & Horn, 2017) and/or activating the sympathetic system (Loewenfeld, 1999; Steinhauer & Hakerem, 1992). According to the modulation of the balanced activity between the sympathetic and parasympathetic pathways by background luminance, pupil dilation should be mediated mainly by the excitation of the sympathetic pathway under lower luminance conditions, but by the inhibition of the parasympathetic pathway under higher luminance conditions. Because dilation here was greater in lower global luminance, such dilation was likely due to sympathetically driven dilator pupillae contraction, which is reduced by antagonism from increased sphincter pupillae contraction at higher luminance levels.

The fact that larger pupil dilations were produced by SCi activation when luminance was lower could be interesting because pupil dilation should theoretically be larger under low light conditions where the pupil is near the mechanical limit of pupil size. Our finding the opposite effect may reflect the functional role of orienting pupil dilation. It has been argued that pupil dilation evoked by salient stimuli serves to slightly increase visual sensitivity (Lynn, 1966), so the size of evoked pupil dilation should be larger under lower luminance conditions because it is particularly needed to increase visual sensitivity under these conditions. Consistently, the observed pupil dilation produced by SCi stimulation was larger under lower background luminance conditions, which is consistent with our previous results with subthreshold microstimulation (Wang et al., 2012). More interestingly, saccade and pupil responses evoked by the SCi, although different in time course, are coordinated. Does the coordination between saccade and pupil responses serve any functional role for visual processing? Although the current study cannot address this question, a potential benefit may be having a larger pupil size after orientation, that is, saccades, resulting in efficient processing of a selected target at the beginning of the foveation. Future research is needed to directly examine the functional role of pupil dilation evoked by salient stimuli and mediated by the SC for visual processing.

Conclusion

The SCi, a hub of sensory and motor processing, integrates sensory and cognitive signals to coordinate the orienting response that includes eye movements and pupil size changes (Wang & Munoz, 2015; Corneil & Munoz, 2014). Here, we demonstrated saccades and pupil dilation evoked

by SCi microstimulation were highly correlated, and SCi site-specific effects were observed in both saccade and pupil responses, together supporting the common drive hypothesis, and arguing that the same efferent projection from the SCi drives both saccade and pupil responses. Moreover, varying background luminance only modulated evoked pupil, but not saccade, responses, implying the functional independence of the SCi and luminance signals. Orienting responses are thought to work together to optimize the body for whatever action is required (Lynn, 1966). Investigation of the various orienting components simultaneously is thus necessary to understand how they are coordinated to optimize performance.

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Reprint requests should be sent to Chin-An Wang, Institute of Cognitive Neuroscience, National Central University, No. 300, Zhongda Road, Zhongli District, Taoyuan City, 320, Taiwan, or via e-mail: joshwang@ncu.edu.tw, or to Douglas P. Munoz, Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada, or via e-mail: doug.munoz@queensu.ca.

Author Contributions

Chin-An Wang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing—Original draft; Writing—Review & editing. Douglas P. Munoz: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing—Original draft; Writing—Review & editing.

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Diversity in Citation Practices

A retrospective analysis of the citations in every article published in this journal from 2010 to 2020 has revealed a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience (JoCN)* during this period were M(an)/M = .408, W(oman)/M = .335, M/W = .108, and W/W = .149, the comparable proportions for the articles that these authorship teams cited were M/M = .579, W/M = .243, M/W = .102, and W/W = .076 (Fulvio et al., *JoCN*, 33:1, pp. 3–7). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

REFERENCES

Aizawa, H., Kobayashi, Y., Yamamoto, M., & Isa, T. (1999). Injection of nicotine into the superior colliculus facilitates occurrence of express saccades in monkeys. *Journal of Neurophysiology*, *82*, 1642–1646. **DOI:** https://doi.org/10.1152/jn.1999.82.3.1642, **PMID:** 10482780

Akert, K. (1949). Der visuelle Greifreflex. *Helvetica Physiologica et Pharmacologica Acta*, *7*, 112–134. **PMID:** 18115765

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450. **DOI:** https://doi.org/10.1146/annurev.neuro.28.061604.135709, **PMID:** 16022602

Aston-Jones, G., Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience*, *14*, 4467–4480. **DOI:** https://doi.org/10.1523/jneurosci.14-07-04467.1994, **PMID:** 8027789, **PMCID:** PMC6577022

Barnerssoi, M., May, P. J., & Horn, A. K. E. (2017). GABAergic innervation of the ciliary ganglion in macaque monkeys—A light and electron microscopic study. *Journal of Comparative Neurology*, *525*, 1517–1531. **DOI:** https://doi.org/10.1002/cne.24145, **PMID:** 27864939, **PMCID:** PMC5808918

Beatty, J. (1982). Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychological Bulletin*, *91*, 276–292. **DOI:** https://doi.org/10.1037/0033-2909.91.2.276, **PMID:** 7071262

Beninato, M., & Spencer, R. F. (1986). A cholinergic projection to the rat superior colliculus demonstrated by retrograde transport of horseradish peroxidase and choline acetyltransferase immunohistochemistry. *Journal of Comparative Neurology*, *253*, 525–538. **DOI:** https://doi.org/10.1002/cne.902530409, **PMID:** 3540040

Büttner-Ennever, J. A., Horn, A. K., Henn, V., & Cohen, B. (1999). Projections from the superior colliculus motor map to omnipause neurons in monkey. *Journal of Comparative Neurology*, *413*, 55–67. **DOI:** https://doi.org/10.1002/(SICI)1096-9861(19991011)413:1<55::AID-CNE3>3.0.CO;2-K

Cohen, B., & Büttner-Ennever, J. A. (1984). Projections from the superior colliculus to a region of the central mesencephalic reticular formation (cMRF) associated with horizontal saccadic eye movements. *Experimental Brain Research*, *57*, 167–176. **DOI:** https://doi.org/10.1007/BF00231143, **PMID:** 6519224

Corneil, B. D., & Munoz, D. P. (2014). Overt responses during covert orienting. *Neuron*, *82*, 1230–1243. **DOI:** https://doi.org/10.1016/j.neuron.2014.05.040, **PMID:** 24945769

Dacey, D. M., Liao, H.-W., Peterson, B. B., Robinson, F. R., Smith, V. C., Pokorny, J., et al. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature*, *433*, 749–754. **DOI:** https://doi.org/10.1038/nature03387, **PMID:** 15716953

Do, M. T. H., & Yau, K.-W. (2010). Intrinsically photosensitive retinal ganglion cells. *Physiological Reviews*, *90*, 1547–1581. **DOI:** https://doi.org/10.1152/physrev.00013.2010, **PMID:** 20959623, **PMCID:** PMC4374737

Ebitz, R. B., & Moore, T. (2017). Selective modulation of the pupil light reflex by microstimulation of prefrontal cortex. *Journal of Neuroscience*, *37*, 5008–5018. **DOI:** https://doi.org/10.1523/JNEUROSCI.2433-16.2017, **PMID:** 28432136, **PMCID:** PMC6596477

Eckstein, M. K., Guerra-Carrillo, B., Miller Singley, A. T., & Bunge, S. A. (2017). Beyond eye gaze: What else can eyetracking reveal about cognition and cognitive development? *Developmental Cognitive Neuroscience*, *25*, 69–91. **DOI:** https://doi.org/10.1016/j.dcn.2016.11.001, **PMID:** 27908561, **PMCID:** PMC6987826

Edwards, S. B. (1975). Autoradiographic studies of the projections of the midbrain reticular formation: Descending projections of nucleus cuneiformis. *Journal of Comparative Neurology*, *161*, 341–358. **DOI:** https://doi.org/10.1002/cne.901610306, **PMID:** 50329

Ferrier, D. (1876). *The functions of the brain.* New York: G. P. Putnam's Sons. **DOI:** https://doi.org/10.1037/12860-000

Gamlin, P. D. R., McDougal, D. H., Pokorny, J., Smith, V. C., Yau, K.-W., & Dacey, D. M. (2007). Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision Research*, *47*, 946–954. **DOI:** https://doi.org/10.1016/j.visres.2006.12.015, **PMID:** 17320141, **PMCID:** PMC1945238

Gandhi, N. J., & Katnani, H. A. (2011). Motor functions of the superior colliculus. *Annual Review of Neuroscience*, *34*, 205–231. **DOI:** https://doi.org/10.1146/annurev-neuro-061010-113728, **PMID:** 21456962, **PMCID:** PMC3641825

Gandhi, N. J., & Keller, E. L. (1997). Spatial distribution and discharge characteristics of superior colliculus neurons antidromically activated from the omnipause region in monkey. *Journal of Neurophysiology*, *78*, 2221–2225. **DOI:** https://doi.org/10.1152/jn.1997.78.4.2221, **PMID:** 9325389

Gaymard, B., Ploner, C. J., Rivaud, S., Vermersch, A. I., & Pierrot-Deseilligny, C. (1998). Cortical control of saccades. *Experimental Brain Research*, *123*, 159–163. **DOI:** https://doi.org/10.1007/s002210050557, **PMID:** 9835405

Grant, S. J., Aston-Jones, G., & Redmond, D. E., Jr. (1988). Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. *Brain Research Bulletin*, *21*, 401–410. **DOI:** https://doi.org/10.1016/0361-9230(88)90152-9, **PMID:** 3145784

Grantyn, A., & Grantyn, R. (1982). Axonal patterns and sites of termination of cat superior colliculus neurons projecting in the tecto-bulbo-spinal tract. *Experimental Brain Research*, *46*, 243–256. **DOI:** https://doi.org/10.1007/BF00237182, **PMID:** 7095033

Graybiel, A. M. (1978). A stereometric pattern of distribution of acetylthiocholinesterase in the deep layers of the superior colliculus. *Nature*, *272*, 539–541. **DOI:** https://doi.org/10.1038/272539b0, **PMID:** 99660

Hall, W. C., & Moschovakis, A. K. (Eds.) (2003). *The superior colliculus: New approaches for studying sensorimotor integration (Methods and new frontiers in neuroscience)*. Boca Raton, FL: CRC Press. **DOI:** https://doi.org/10.1201/9780203501504

Hannibal, J., Kankipati, L., Strang, C. E., Peterson, B. B., Dacey, D. M., & Gamlin, P. D. (2014). Central projections of intrinsically photosensitive retinal ganglion cells in the macaque monkey. *Journal of Comparative Neurology*, *522*, 2231–2248. **DOI:** https://doi.org/10.1002/cne.23588, **PMID:** 24752373, **PMCID:** PMC3996456

Hays, A. V., Jr., Richmond, B. J., & Optican, L. M. (1982). *Unix-based multiple-process system, for real-time data acquisition and control*. El Segundo, CA: Electron Conventions.

Hentschke, H., & Stüttgen, M. C. (2011). Computation of measures of effect size for neuroscience data sets. *European Journal of Neuroscience*, *34*, 1887–1894. **DOI:** https://doi.org/10.1111/j.1460-9568.2011.07902.x, **PMID:** 22082031

Hess, W. R., Bürgi, S., & Bucher, V. (1946). Motorische funktion des Tektal- und tegmentalgebietes (motor functions of tectal and tegmental areas). *Monatsschrift für Psychiatrie und Neurologie*, *112*, 1–52. **DOI:** https://doi.org/10.1159/000148295

Horn, A. K. E. (2006). The reticular formation. *Progress in Brain Research*, *151*, 127–155. **DOI:** https://doi.org/10.1016/S0079-6123(05)51005-7

Joshi, S., & Gold, J. I. (2020). Pupil size as a window on neural substrates of cognition. *Trends in Cognitive Sciences*, *24*, 466–480. **DOI:** https://doi.org/10.1016/j.tics.2020.03.005, **PMID:** 32331857, **PMCID:** PMC7271902

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron*, *89*, 221–234. **DOI:** https://doi.org/10.1016/j.neuron.2015.11.028, **PMID:** 26711118, **PMCID:** PMC4707070

Kalwani, R. M., Joshi, S., & Gold, J. I. (2014). Phasic activation of individual neurons in the locus ceruleus/subceruleus complex of monkeys reflects rewarded decisions to go but not stop. *Journal of Neuroscience*, *34*, 13656–13669. **DOI:** https://doi.org/10.1523/JNEUROSCI.2566-14.2014, **PMID:** 25297093, **PMCID:** PMC4188964

Krauzlis, R. J., Lovejoy, L. P., & Zénon, A. (2013). Superior colliculus and visual spatial attention. *Annual Review of Neuroscience*, *36*, 165–182. **DOI:** https://doi.org/10.1146/annurev-neuro-062012-170249, **PMID:** 23682659, **PMCID:** PMC3820016

Laughlin, S. B. (1992). Retinal information capacity and the function of the pupil. *Ophthalmic & Physiological Optics*, *12*, 161–164. **DOI:** https://doi.org/10.1111/j.1475-1313.1992.tb00281.x, **PMID:** 1408164

Lehmann, S. J., & Corneil, B. D. (2016). Transient pupil dilation after subsaccadic microstimulation of primate frontal eye fields. *Journal of Neuroscience*, *36*, 3765–3776. **DOI:** https://doi.org/10.1523/JNEUROSCI.4264-15.2016, **PMID:** 27030761, **PMCID:** PMC6601743

Li, F., Endo, T., & Isa, T. (2004). Presynaptic muscarinic acetylcholine receptors suppress GABAergic synaptic transmission in the intermediate grey layer of mouse superior colliculus. *European Journal of Neuroscience*, *20*, 2079–2088. **DOI:** https://doi.org/10.1111/j.1460-9568.2004.03668.x, **PMID:** 15450087

Loewenfeld, I. E. (1999). *The pupil: Anatomy, physiology, and clinical applications*. Oxford: Butterworth-Heinemann.

Lynn, R. (1966). *Attention, arousal and the orientation reaction*. Oxford: Pergamon Press.

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. *European Journal of Neuroscience*, *35*, 1738–1752. **DOI:** https://doi.org/10.1111/j.1460-9568.2012.08079.x, **PMID:** 22639796

Marino, R. A., Rodgers, C. K., Levy, R., & Munoz, D. P. (2008). Spatial relationships of visuomotor transformations in the superior colliculus map. *Journal of Neurophysiology*, *100*, 2564–2576. **DOI:** https://doi.org/10.1152/jn.90688.2008, **PMID:** 18753320

May, P. J. (2006). The mammalian superior colliculus: Laminar structure and connections. *Progress in Brain Research*, *151*, 321–378. **DOI:** https://doi.org/10.1016/S0079-6123(05)51011-2

May, P. J., Warren, S., Bohlen, M. O., Barnerssoi, M., & Horn, A. K. E. (2016). A central mesencephalic reticular formation projection to the Edinger-Westphal nuclei. *Brain Structure & Function*, *221*, 4073–4089. **DOI:** https://doi.org/10.1007/s00429-015-1147-z, **PMID:** 26615603, **PMCID:** PMC4884558

McDougal, D. H., & Gamlin, P. D. (2015). Autonomic control of the eye. *Comprehensive Physiology*, *5*, 439–473. **DOI:** https://doi.org/10.1002/cphy.c140014, **PMID:** 25589275, **PMCID:** PMC4919817

Moschovakis, A. K., Dalezios, Y., Petit, J., & Grantyn, A. A. (1998). New mechanism that accounts for position sensitivity of saccades evoked in response to stimulation of superior

colliculus. *Journal of Neurophysiology*, *80*, 3373–3379. **DOI:** https://doi.org/10.1152/jn.1998.80.6.3373, **PMID:** 9862936

Moschovakis, A. K., Kitama, T., Dalezios, Y., Petit, J., Brandi, A. M., & Grantyn, A. A. (1998). An anatomical substrate for the spatiotemporal transformation. *Journal of Neuroscience*, *18*, 10219–10229. **DOI:** https://doi.org/10.1523/JNEUROSCI.18-23-10219.1998, **PMID:** 9822775, **PMCID:** PMC6793294

Münch, M., & Kawasaki, A. (2013). Intrinsically photosensitive retinal ganglion cells: Classification, function and clinical implications. *Current Opinion in Neurology*, *26*, 45–51. **DOI:** https://doi.org/10.1097/WCO.0b013e32835c5e78, **PMID:** 23254557

Nelson, A., & Mooney, R. (2016). The basal forebrain and motor cortex provide convergent yet distinct movement-related inputs to the auditory cortex. *Neuron*, *90*, 635–648. **DOI:** https://doi.org/10.1016/j.neuron.2016.03.031, **PMID:** 27112494, **PMCID:** PMC4866808

Nieuwenhuis, S., De Geus, E. J., & Aston-Jones, G. (2011). The anatomical and functional relationship between the P3 and autonomic components of the orienting response. *Psychophysiology*, *48*, 162–175. **DOI:** https://doi.org/10.1111/j.1469-8986.2010.01057.x, **PMID:** 20557480, **PMCID:** PMC3797154

Perkins, E., Warren, S., & May, P. J. (2009). The mesencephalic reticular formation as a conduit for primate collicular gaze control: Tectal inputs to neurons targeting the spinal cord and medulla. *Anatomical Record*, *292*, 1162–1181. **DOI:** https://doi.org/10.1002/ar.20935, **PMID:** 19645020, **PMCID:** PMC2773470

Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1994). Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. *Brain Research Bulletin*, *35*, 607–616. **DOI:** https://doi.org/10.1016/0361-9230(94)90175-9, **PMID:** 7859118

Rajkowski, J., Majczynski, H., Clayton, E., & Aston-Jones, G. (2004). Activation of monkey locus coeruleus neurons varies with difficulty and performance in a target detection task. *Journal of Neurophysiology*, *92*, 361–371. **DOI:** https://doi.org/10.1152/jn.00673.2003, **PMID:** 15028743

Reimer, J., McGinley, M. J., Liu, Y., Rodenkirch, C., Wang, Q., McCormick, D. A., et al. (2016). Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nature Communications*, *7*, 13289. **DOI:** https://doi.org/10.1038/ncomms13289, **PMID:** 27824036, **PMCID:** PMC5105162

Robinson, D. A. (1972). Eye movements evoked by collicular stimulation in the alert monkey. *Vision Research*, *12*, 1795–1808. **DOI:** https://doi.org/10.1016/0042-6989(72)90070-3, **PMID:** 4627952

Robinson, F. R., & Fuchs, A. F. (2001). The role of the cerebellum in voluntary eye movements. *Annual Review of Neuroscience*, *24*, 981–1004. **DOI:** https://doi.org/10.1146/annurev.neuro.24.1.981, **PMID:** 11520925

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian *t* tests for accepting and rejecting the null hypothesis. *Psychonomic Bulletin & Review*, *16*, 225–237. **DOI:** https://doi.org/10.3758/PBR.16.2.225, **PMID:** 19293088

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: The locus coeruleus mediates cognition through arousal. *Neuron*, *76*, 130–141. **DOI:** https://doi.org/10.1016/j.neuron.2012.09.011, **PMID:** 23040811

Scudder, C. A., Kaneko, C. R., & Fuchs, A. F. (2002). The brainstem burst generator for saccadic eye movements: A modern synthesis. *Experimental Brain Research*, *142*, 439–462. **DOI:** https://doi.org/10.1007/s00221-001-0912-9, **PMID:** 11845241

Scudder, C. A., Moschovakis, A. K., Karabelas, A. B., & Highstein, S. M. (1996). Anatomy and physiology of saccadic long-lead burst neurons recorded in the alert squirrel monkey. I. Descending projections from the mesencephalon. *Journal of Neurophysiology*, *76*, 332–352. **DOI:** https://doi.org/10.1152/jn.1996.76.1.332, **PMID:** 8836229

Sokolov, E. N. (1963). Higher nervous functions: The orienting reflex. *Annual Review of Physiology*, *25*, 545–580. **DOI:** https://doi.org/10.1146/annurev.ph.25.030163.002553, **PMID:** 13977960

Sparks, D. L. (1986). Translation of sensory signals into commands for control of saccadic eye movements: Role of primate superior colliculus. *Physiological Reviews*, *66*, 118–171. **DOI:** https://doi.org/10.1152/physrev.1986.66.1.118, **PMID:** 3511480

Sparks, D. L. (2002). The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience*, *3*, 952–964. **DOI:** https://doi.org/10.1038/nrn986, **PMID:** 12461552

Stanford, T. R., Freedman, E. G., & Sparks, D. L. (1996). Site and parameters of microstimulation: Evidence for independent effects on the properties of saccades evoked from the primate superior colliculus. *Journal of Neurophysiology*, *76*, 3360–3381. **DOI:** https://doi.org/10.1152/jn.1996.76.5.3360, **PMID:** 8930279

Steinhauer, S. R., & Hakerem, G. (1992). The pupillary response in cognitive psychophysiology and schizophrenia. *Annals of the New York Academy of Sciences*, *658*, 182–204. **DOI:** https://doi.org/10.1111/j.1749-6632.1992.tb22845.x, **PMID:** 1497258

Swick, D., Pineda, J. A., Schacher, S., & Foote, S. L. (1994). Locus coeruleus neuronal activity in awake monkeys: Relationship to auditory P300-like potentials and spontaneous EEG. *Experimental Brain Research*, *101*, 86–92. **DOI:** https://doi.org/10.1007/BF00243219, **PMID:** 7843306

Thompson, K. G., & Bichot, N. P. (2005). A visual salience map in the primate frontal eye field. *Progress in Brain Research*, *147*, 249–262. **DOI:** https://doi.org/10.1016/S0079-6123(04)47019-8

van der Wel, P., & van Steenbergen, H. (2018). Pupil dilation as an index of effort in cognitive control tasks: A review. *Psychonomic Bulletin & Review*, *25*, 2005–2015. **DOI:** https://doi.org/10.3758/s13423-018-1432-y, **PMID:** 29435963, **PMCID:** PMC6267528

Varazzani, C., San-Galli, A., Gilardeau, S., & Bouret, S. (2015). Noradrenaline and dopamine neurons in the reward/effort trade-off: A direct electrophysiological comparison in behaving monkeys. *Journal of Neuroscience*, *35*, 7866–7877. **DOI:** https://doi.org/10.1523/JNEUROSCI.0454-15.2015, **PMID:** 25995472, **PMCID:** PMC6795183

Wang, C.-A., Blohm, G., Huang, J., Boehnke, S. E., & Munoz, D. P. (2017). Multisensory integration in orienting behavior: Pupil size, microsaccades, and saccades. *Biological Psychology*, *129*, 36–44. **DOI:** https://doi.org/10.1016/j.biopsycho.2017.07.024, **PMID:** 28789960

Wang, C.-A., Boehnke, S. E., Itti, L., & Munoz, D. P. (2014). Transient pupil response is modulated by contrast-based saliency. *Journal of Neuroscience*, *34*, 408–417. **DOI:** https://doi.org/10.1523/JNEUROSCI.3550-13.2014, **PMID:** 24403141, **PMCID:** PMC6608151

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. *Journal of Neuroscience*, *32*, 3629–3636. **DOI:** https://doi.org/10.1523/JNEUROSCI.5512-11.2012, **PMID:** 22423086, **PMCID:** PMC6703448

Wang, C.-A., & Munoz, D. P. (2014). Modulation of stimulus contrast on the human pupil orienting response. *European Journal of Neuroscience*, *40*, 2822–2832. **DOI:** https://doi.org/10.1111/ejn.12641, **PMID:** 24911340

Wang, C.-A., & Munoz, D. P. (2015). A circuit for pupil orienting responses: Implications for cognitive modulation of pupil size. *Current Opinion in Neurobiology*, *33*, 134–140. **DOI:** https://doi.org/10.1016/j.conb.2015.03.018, **PMID:** 25863645

Watanabe, M., Kobayashi, Y., Inoue, Y., & Isa, T. (2005). Effects of local nicotinic activation of the superior colliculus on saccades in monkeys. *Journal of Neurophysiology*, *93*, 519–534. **DOI:** https://doi.org/10.1152/jn.00558.2004, **PMID:** 15342715

White, B. J., & Munoz, D. P. (2011). The superior colliculus. In S. P. Liversedge, I. D. Gilchrist, & S. Everling (Eds.), *The Oxford handbook of eye movements* (pp. 195–213). New York: Oxford University Press.

Woodhouse, J. M. (1975). The effect of pupil size on grating detection at various contrast levels. *Vision Research*, *15*, 645–648. **DOI:** https://doi.org/10.1016/0042-6989(75)90278-3, **PMID:** 1138478

Wurtz, R. H., & Albano, J. E. (1980). Visual-motor function of the primate superior colliculus. *Annual Review of Neuroscience*, *3*, 189–226. **DOI:** https://doi.org/10.1146/annurev.ne.03.030180.001201, **PMID:** 6774653