Pupil-linked Arousal Signals in the Midbrain Superior Colliculus

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Abstract

■ The orienting response evoked by the appearance of a salient stimulus is modulated by arousal; however, neural underpinnings for the interplay between orienting and arousal are not well understood. The superior colliculus (SC), causally involved in multiple components of the orienting response including gaze and attention shifts, receives not only multisensory and cognitive inputs but also arousal-regulated inputs from various cortical and subcortical structures. To investigate the impact of moment-by-moment fluctuations in arousal on orienting saccade responses, we used microstimulation of the monkey SC to trigger saccade responses, and we used pupil size and velocity to index the level of arousal at stimulation onset because these measures correlate with changes in brain states and locus coeruleus activity. Saccades induced by SC microstimulation correlated with prestimulation pupil velocity, with higher pupil velocities on trials without evoked saccades than with evoked saccades. In contrast, prestimulation absolute pupil size did not correlate with saccade behavior. Moreover, pupil velocity correlated with evoked saccade latency and metrics. Together, our results demonstrated that small fluctuations in arousal, indexed by pupil velocity, can modulate the saccade response evoked by SC microstimulation in awake behaving monkeys. ■

INTRODUCTION

The appearance of a salient stimulus in the environment often elicits an orienting response that includes coordinated eye/head/body movement, as well as attention shifts and pupil dilation (Corneil & Munoz, 2014; Sokolov, 1963; Akert, 1949; Hess, Buergi, & Bucher, 1946). This orienting response can be influenced by attention and arousal (Poe et al., 2020; Sara & Bouret, 2012). However, precisely how arousal and orienting signals interact remains poorly understood.

The superior colliculus (SC) is a key structure in coordinating the orienting response (Wang & Munoz, 2015; Corneil & Munoz, 2014) such as gaze and attention shifts (Krauzlis, Lovejoy, & Zenon, 2013; Gandhi & Katnani, 2011; Sparks, 1986), and is composed of anatomically differentiated superficial (SCs) and intermediate layers (SCi; Edwards, 1980). The SCi receives multisensory, cognitive, and arousal signals from various cortical and subcortical regions (Dash, Peel, Lomber, & Corneil, 2018; Li et al., 2018; Peel, Dash, Lomber, & Corneil, 2017; Stuphorn, Brown, & Schall, 2010; Johnston & Everling, 2009; Wurtz et al., 2001; Hikosaka, Takikawa, & Kawagoe, 2000; Sommer & Wurtz, 2000; Pare & Wurtz, 1997; Edwards, Ginsburgh, Henkel, & Stein, 1979), and efferent neurons of the SCi project directly to the brainstem premotor circuit to initiate the orienting response (Rodgers, Munoz, Scott, Pare, & Paré, 2006; Scudder, Moschovakis, Karabelas, & Highstein, 1996). Moreover, the SCi receives direct projections from the locus coeruleus (LC; Li et al., 2018; Edwards et al., 1979), which is centrally involved in arousal modulation (Joshi, 2021; Joshi & Gold, 2020; Breton-Provencher & Sur, 2019; Larsen & Waters, 2018; Carter et al., 2010; Berridge, 2008; Samuels & Szabadi, 2008a; 2008b; Aston-Jones & Cohen, 2005). Previous studies in awake mice have shown that arousal affects visual activity in the SC (Schröder et al., 2020; Savier, Chen, & Cang, 2019; Ito, Feldheim, & Litke, 2017). How SC motor activity, which is crucial for initiating the orienting response, is modulated by arousal remains unknown. Moreover, species differences between the primate and mouse SC have been extensively documented. For example: The primate SC is innervated by 10% of the retinal ganglion cells (May, 2006), whereas the mouse SC is innervated by 88% of these cells (Ellis, Gauvain, Sivyer, & Murphy, 2016). It is thus important to investigate how arousal can regulate orienting responses organized by the SC in awake behaving monkeys.

Pupil size, controlled by the sympathetic and parasympathetic nervous systems (May, Reiner, & Gamlin, 2019; McDougal & Gamlin, 2015; Loewenfeld, 1999), is long known to provide a window into arousal (Bradshaw, 1967), and a large body of studies have used pupil size to index the level of arousal (Joshi & Gold, 2020; Urai, Braun, & Donner, 2017; Ebitz & Platt, 2015; de Gee, Knapen, & Donner, 2014; Murphy, Vandekerckhove, & Nieuwenhuis, 2014; Eldar, Cohen, & Niv, 2013; Nassar et al., 2012; Aston-Jones & Cohen, 2005). Pupil size

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correlates with various peripheral markers of arousal state, such as heart rate and skin conductance responses, further linking pupil size to arousal (Wang, Baird, et al., 2018; Jennings, van der Molen, & Steinhauer, 1998; Morrow & Steinhauer, 1995; Bond, James, & Lader, 1974; Libby, Lacey, & Lacey, 1973; Colman & Paivio, 1969; Kahneman, Tursky, Shapiro, & Crider, 1969; Scott, Wells, Wood, & Morgan, 1967). Research in behaving animals has shown that pupil size and pupil velocity (i.e., velocity increase—dilation; velocity decrease—constriction) closely couples with changes in brain states and neural activity across various brain regions including the LC (Grueschow et al., 2021; Yüzgeç, Prsa, Zimmermann, & Huber, 2018; Joshi, Li, Kalwani, & Gold, 2016; Reimer et al., 2014, 2016; McGinley et al., 2015; Varazzani, San-Galli, Gilardeau, & Bouret, 2015; Aston-Jones & Cohen, 2005). As arousal is a broad concept, and pupil size and pupil velocity are associated with fluctuations in various neural activity and brain states (Joshi & Gold, 2020; McCormick, Nestvogel, & He, 2020; Joshi et al., 2016; McGinley et al., 2015; Vinck, Batista-Brito, Knoblich, & Cardin, 2015; Reimer et al., 2014), here, we hypothesize that both pupil size and pupil velocity represent effective indices of arousal-mediated brain state (referred to as arousal).

To investigate the modulation of arousal on the orienting response coordinated by the SC, we electrically microstimulated the SCi with trains of pulses, varying the frequency to evoke saccades. Although arousal involves multiple high-level cognitive and affective processes, arousal effects should be revealed in a simple task as well. If moment-by-moment fluctuations in arousal modulate excitability in the SCi, then prestimulation (prestim) pupil size and pupil velocity, indices of arousal at stimulation onset, should influence the resulting saccade responses induced by SCi microstimulation. We found that prestim pupil velocity, but not absolute pupil size, modulated evoked saccade responses. Our results reveal moment-by-moment arousal modulation in the SC in awake behaving monkeys that influences orienting responses.

METHODS

Animal Experimental Setup

Experiments were performed on two male rhesus monkeys (*Macaca mulatta*; 11 and 12 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 on 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). We followed Eyelink's suggested method to transfer output pupil area values recorded from the eye tracker to actual pupil size in diameter (see details in the work of 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°.

Procedure, SC Recording, and Stimulation

Monkeys were seated in a primate chair with their heads restrained facing the video monitor. Once the SC had been located by single neuron recording and the visual response fields were mapped using a visual mapping task (Marino et al., 2012), monkeys performed a delayed saccade task to characterize the types of neurons. Each trial started with fixation of a central fixation spot (0.5° diameter, 30 cd/m^2) against a black background for 500–800 msec, and then a target stimulus (0.5° diameter, 30 cd/m^2) appeared in the response field of the neuron. After a delay (500–800 msec), the fixation spot was removed and the monkey was required to generate a saccade toward the target. Because target presentation was temporally dissociated from the saccade, the visual and motor components of the discharge were isolated and easily distinguished. Spike rasters were generated in real time to confirm the presence or absence of visual and motor activity.

We lowered tungsten microelectrodes (impedance: 0.1–1 MΩ, Frederick Haer) to determine the depth of the SCi (intermediate layers of the SC) defined as the point at which neurons had pronounced increases in discharge related to the initiation of saccades (Sparks, 1978; Schiller & Koerner, 1971; Wurtz & Goldberg, 1971). Once the SCi was confirmed, the SCi was microstimulated (> 250-Hz pulse train for 100 msec with alternating 0.3-msec anode plus 0.3-msec cathode pulses) and the threshold current for eliciting 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 ranging between 3° and 20° eccentricity.

Experimental Task

Two 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, an isoluminant pinkish color relative to 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 then monkeys had to maintain fixation for another 1.5–2 sec regardless

of microstimulation. Because of involving suprathreshold microstimulation, saccades were regularly evoked after electrical stimulation (latencies regularly 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 FP within 300 msec after microstimulation.

In the experiment, stimulation frequency was manipulated (100-msec stimulation train duration). After determining the saccade threshold current, we systematically changed 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. From each stimulation site, we microstimulated at least three frequency levels (three to eight frequency levels). The order of frequency levels across blocks was varied across days. There were at least 20 correct trials in all conditions. Microstimulation was delivered to 24 sites (9 and 15 in Monkeys A and B, respectively). In the second experiment, stimulation duration was manipulated (>250-Hz stimulation frequency).

Data Analysis

A subset of these results was published previously, focusing on the coordination between saccades and pupil responses evoked by microstimulation (Wang & Munoz, 2021a). The arousal effects that we focus on here should also influence pupil responses evoked by microstimulation. However, because SCi stimulation also triggers saccadic eye movements, there were an insufficient number of trials in each condition to accurately measure pupil size after microstimulation, to provide enough statistical power to examine the modulation of arousal on pupil responses evoked directly by the microstimulation. Therefore, here, we only focused on the evoked saccade response. 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 microstimulation-related (evoked and return) saccades. It is known that the size of the pupil depends on the subject's gaze angle in a video-based eye tracker, and pupil-size data can be distorted by eye movements. Because of applying suprathreshold microstimulation, saccades were often evoked after stimulation in this study. To maintain an accurate measure of pupil size, we analyzed the prestim pupil velocity epoch from 50 msec to microstimulation onset (average pupil velocity from 0 to 50 msec before stimulation onset), and examined the relationships between the prestim pupil velocity and saccade behavior evoked by SCi microstimulation. The prestim epoch was specifically selected to represent the arousal level at the moment of microstimulation onset without diminishing the accuracy of pupil size measurement caused by saccades evoked by the microstimulation. Because the pupil response is consensual (Wang, Tworzyanski, Huang, & Munoz, 2018; Wang & Munoz, 2014; Wang, Boehnke, White, & Munoz, 2012), only pupil diameter of the right eye was recorded for data analysis. Median values from each site were used for population analysis to avoid overweighted bias from extreme values.

Pupil size (referred to as absolute pupil diameter) and pupil velocity were used to index arousal level because pupil size is correlated with various peripheral markers (Wang, Baird, et al., 2018; Jennings et al., 1998; Morrow & Steinhauer, 1995; Bond et al., 1974; Libby et al., 1973; Colman & Paivio, 1969; Kahneman et al., 1969; Scott et al., 1967) and pupil velocity (pupil size derivative) is linked to fluctuations in various neural and neuromodulatory mechanisms (Joshi & Gold, 2020; Joshi et al., 2016; McGinley et al., 2015; Vinck et al., 2015; Reimer et al., 2014). Evoked saccade latency was defined as the time after microstimulation to the first saccade away from central fixation that exceeded 30°/sec (latency range: 20–150 msec) and its saccade amplitude over 2° visual angle. In saccade probability analysis of the stimulation frequency experiment (Figures 1 and 2), the frequency condition from each site giving rise to the closest 50% evoked saccade probability was used to have more number of trials in both evoked saccade and without evoked saccade conditions (saccade probability: mean = 57.15%, *SEM* = 3.07%, $n = 24$), as varying stimulation frequency systematically alters saccade responses (Stanford, Freedman, & Sparks, 1996). In the saccade analysis, the highest frequency condition (240–300 Hz; Figure 4) was used to illustrate the effects. We performed correlational analyses and a two-tailed Student t test except where indicated. Moreover, Cohen's d, where appropriate, was calculated to estimate the effect size (Hentschke & Stüttgen, 2011). Furthermore, we specifically used generalized linear mixed models to examine the prestim pupil effects on the saccade response between the two monkeys that allowed us to use pupil size/velocity (or stimulation frequency) as fixed predictors and to consider data from all trials while taking intersite variability into account (Pinheiro & Bates, 2000). With generalized linear mixed models, all frequency conditions were used to examine the relationships between prestim pupil velocity and saccade behavior including probability, latency, amplitude (saccade size in degree), velocity (deg/sec), and main sequence slope (peak velocity [deg/sec] / amplitude). We specifically used the main sequence slope to examine the saccade velocity response between different conditions to accommodate the main sequence effects mediated by differences in saccade amplitude (van Opstal & Goossens, 2008; Bahill, Clark, & Stark, 1975).

RESULTS

Modulation of Evoked Saccade Probability by Prestim Pupil Size and Velocity

As illustrated in Appendix Figure A1 for a few single trials, absolute pupil diameter (referred to as pupil size)

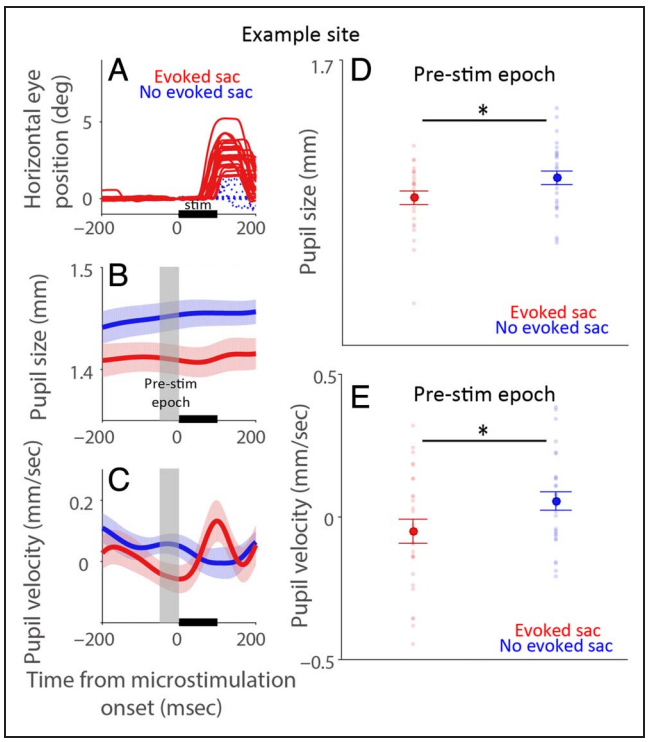

Figure 1. Effect of pre-stimulation pupil size and velocity on saccade probability induced by SCi microstimulation in an example site. (A) Horizontal eye position following microstimulation in an example site in trials with or without an evoked saccade. (B) Dynamics of pupil size in an example site in trials with or without an evoked saccade. (C) Dynamics of pupil velocity in an example site in trials with or without an evoked saccade. (D) Pupil size in the pre-stim epoch between trials with or without an evoked saccade. (E) Pupil velocity in the pre-stim epoch between trials with or without an evoked saccade. In (A–C), the black bar on the *x* axis indicates the time of microstimulation. In B and C, the shaded colored regions surrounding the pupillary response represent ± standard error range for different conditions. The pre-stim (−50 to 0 msec) epoch before microstimulation onset is shaded in gray. In (D–E), the error bar represents ± standard error across trials. The colored circle represents mean value for each condition, and the small dot represents value for each trial. *Indicates differences are statistically significant. Stim = microstimulation.

fluctuates constantly (Appendix Figure A1A), and these momentary changes can be calculated with pupil size derivative (referred to as pupil velocity, Appendix Figure A1B). If moment-by-moment fluctuations in arousal signals, indexed by prestim pupil size or velocity, impact SC excitability, then they should impact saccade probability evoked by microstimulation (see Methods section). Figure 1A–C shows horizontal eye position traces, pupil size and velocity dynamics for trials with saccades (red traces) and without saccades (blue traces) induced by SCi microstimulation from an example site (210 Hz, 40 μA, 100 msec; see Methods section for saccade threshold criteria). Using these parameters of stimulation, the probability of evoking a saccade was 48%, yielding enough trials in both conditions (with and without saccades) for statistical comparisons. As displayed in Figure 1B, prestim pupil sizes were different between the two conditions, with significantly larger pupil sizes on trials without saccades compared with trials with saccades (Figure 1D: prestim pupil size: no sac: mean = 1.45, *SEM* = 0.014 mm; sac: mean = 1.41, *SEM* = 0.014 mm; $t(52) = 2.11$, $p = .039$, $d = 0.57$). Prestim pupil velocities were also different between the two conditions (Figure 1C), with significantly higher pupil velocities on trials without saccades compared with trials with saccades (Figure 1E: prestim pupil velocity, no sac: mean = 0.056, *SEM* = 0.032 mm/sec; sac: mean = −0.05, *SEM* = 0.042 mm/sec; $t(52) = 2.06$, $p = .045$, $d = 0.55$).

To examine whether prestim pupil size and velocity affected saccade probability evoked by SCi microstimulation at the population level, pupil size and velocity dynamics between the two conditions were separated for each monkey (Figure 2). As shown in Figure 2A–B, pupil size dynamics were not reliably different between the two conditions across two monkeys, and pupil sizes at the prestim epoch were not different between the two conditions in

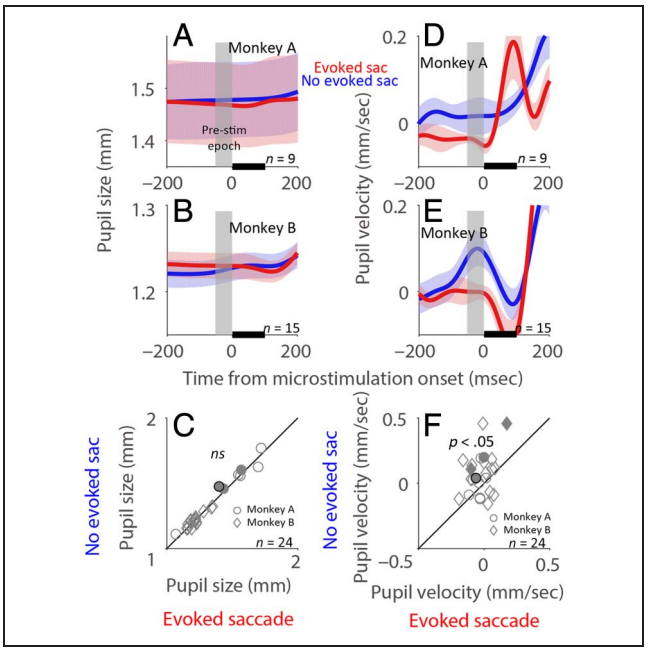

Figure 2. Effect of prestim pupil size and velocity on saccade probability induced by SCi microstimulation. (A–B) Dynamics of pupil size in trials with or without an evoked saccade on Monkey A (A) and Monkey B (B). (C) Pupil size in the pre-stim epoch between trials with or without an evoked saccade collapsed across monkeys and stimulation sites ($n = 24$). (D–E) Dynamics of pupil velocity in trials with or without an evoked saccade on Monkey A (D) and Monkey B (E). (F) Pupil velocity in the pre-stim epoch between trials with or without an evoked saccade collapsed across monkeys and stimulation sites ($n = 24$). In A, B, D, E, the black bar on the *x* axis indicates the time of microstimulation. The shaded colored regions surrounding the pupillary response represent ± standard error range for different conditions. The pre-stim (−50 to 0 msec) epoch before microstimulation onset is shaded in gray. In C,F, filled shapes indicate sites with statistically significant differences ($p < .05$). Example site is indicated with a black circle. *ns* = not statistically significant.

Table 1. Multilevel Model for Saccade Probability

	Saccade Probability	*Regression Coefficient*	*SE*	*t*	*df*	*p*
Monkey A	(Intercept)	0.4534	0.2335	1.9414	342	.0530
	Velocity	−0.6474	0.4167	−1.5537	342	.1212
Monkey B	(Intercept)	0.2419	0.1421	1.7026	346	.0895
	Velocity	−0.9592	0.3530	−2.7175	346	.0069
Monkey A	(Intercept)	1.6183	1.2130	1.3341	342	.1831
	Size	−0.7788	0.8040	−0.9686	342	.3334
Monkey B	(Intercept)	−1.9058	1.7612	−1.0821	346	.2800
	Size	1.7160	1.4332	1.1973	346	.2320

our sample sites (Figure 2C: prestim pupil velocity: no sac: mean = 1.31, *SEM* = 0.038 mm; sac mean = 1.32, *SEM* = 0.038 mm; $t(23) = 0.95$, $p = .35$, $d = 0.033$, $N = 24$). In contrast, the same pattern of pupil velocity dynamics between the two conditions was observed across two monkeys around microstimulation onset (Figure 2D and E). Almost all stimulation sites in our sample (20/24) produced numerically higher pupil velocities on trials without saccades compared with trials with saccades (Figure 2F, significant differences from 4/24 stimulation sites). This pattern of results was significant across 24 stimulation sites from two monkeys, with significantly higher pupil velocities on trials without saccades compared with trials with saccades (Figure 2F: prestim pupil velocity: no sac: mean = 0.075, *SEM* = 0.034 mm/sec; sac mean = −0.02, *SEM* = 0.018 mm/sec; $t(23) = 2.98$, $p = .0067$, $d = 0.72$, $N = 24$). Together, these results suggested that pupil velocity, not pupil size, around microstimulation onset correlated with saccade probability induced by SCi microstimulation.

To examine whether the same results were obtained across two monkeys, we used generalized linear mixed models with a binomial distribution (saccade evoked or not, 1 or 0) and a logit link function (a logistic fit) that allowed us to consider data from all trials while taking intersite variability into account. Specifically, we investigated the contribution of pupil velocity (or size) on saccade probability based on a model taking as a fixed predictor pupil velocity (or pupil size). Sites were included as a random intercept. The dependent variable, y, was saccade probability. The linear mixed model was as follows:

$$\text{Model } 1 : y = \beta_s + \beta_1 \textit{Velocity}$$

$$\text{Model } 2 : y = \beta_s + \beta_1 \textit{Size}$$

where β_s is a Gaussian random variable fitted for each site as an individual offset and β_i are the standard coefficients of the statistical model (intercept and slopes). Although a consistent tendency of prestim pupil velocity effects was shown in two monkeys (Table 1), prestim pupil velocity significantly affected saccade probability in only one monkey (Monkey A: $\beta_1 = -1.55$, $p = .12$, with adjusted R^2 being .071; Monkey B: $\beta_1 = -2.71$, $p = .0069$, with adjusted R^2 being .033). In pupil size analysis, prestim pupil size did not affect saccade probability in both monkeys (Monkey A: $\beta_1 = -0.97$, $p = .33$, with adjusted R^2 being .069; Monkey B: $\beta_1 = 1.19$, $p = .23$, with adjusted R^2 being .012). Therefore, although prestim pupil velocity affected saccade probability at the population level, these results need to be considered with caution, because they were small and only significant in one monkey. Because the effects of pupil size were not significant, we only focused on pupil velocity for the following analyses.

Modulation of Evoked Saccade Latency by Prestim Pupil Velocity

If the SC is influenced by fluctuations in arousal, that is, correlated with fluctuations in pupil velocity, then prestim pupil velocity should also influence the latency of the stimulation-evoked saccades. To investigate the influence of arousal modulation on saccade latency, trials with evoked saccades were first divided into two groups (median-split) according to the prestim pupil velocity (higher and lower pupil velocity conditions). Note that pupil size is modulated by various factors (Loewenfeld, 1999), as the pupil would certainly constrict following an increase in background luminance, even if the arousal level at that point in time is high. This suggests that a decrease in pupil velocity (or size) does not necessary

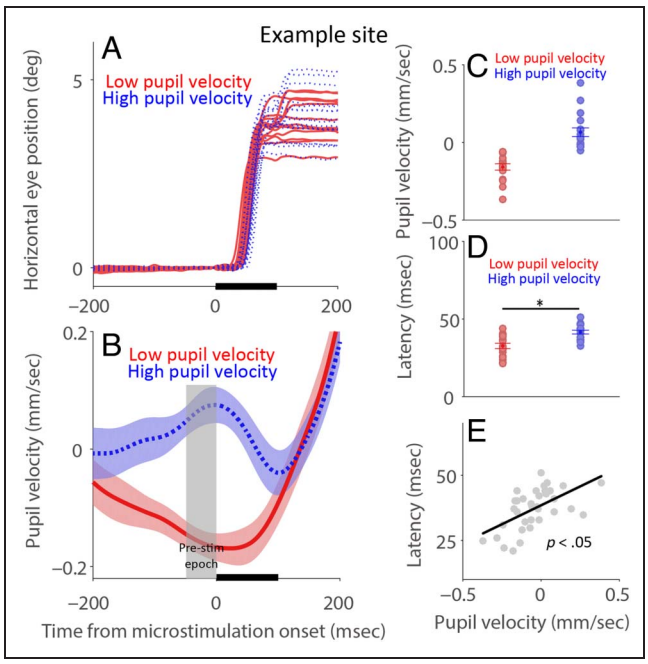

Figure 3. Effect of pupil velocity on saccade latency induced by SCi microstimulation in an example site. (A) Horizontal eye position following microstimulation in trials with lower or higher pupil velocities. (B) Dynamics of pupil velocity in trials with lower or higher pupil velocities. (C) Pupil velocity in the prestim epoch between the lower and higher pupil velocity conditions. (D) Saccade latencies between the lower and higher pupil velocity conditions. (E) Trial-by-trial correlation between pupil velocity and saccade latency evoked by microstimulation. In (A–B), the black bar on the *x* axis indicates the time of microstimulation. In B, the shaded colored regions surrounding the pupillary response represent ± standard error range for different conditions. In (C–D), the error bar represents ± standard error across sites. The colored circle represents mean value for each condition, and the small dot represents mean value for each stimulation site. *Indicates differences are statistically significant. In (E), the black line indicates the regression line.

indicate a lower arousal level. Therefore, we consider that pupil velocity is a relative value, instead of absolute value, for arousal level, that is, trials with lower pupil velocities have lower arousal level, compared with, trials with higher pupil velocities. As shown in Figure 3 from an example stimulation site (300 Hz, 40 μA, 100 msec), changes in the prestim pupil velocity correlated with saccade latencies evoked by SCi microstimulation (Figure 3A and B). Pupil velocities for pupil lower and higher velocity conditions were −0.16 ± 0.02 mm/sec and 0.065 ± 0.028 mm/sec, respectively (Figure 3C). Importantly, evoked saccade latencies were significantly faster in the lower velocity condition than in the higher velocity condition (Figure 3D: lower velocity: 33 ± 1.7 msec; higher velocity: 42 ± 1.2 msec; $t(34) = 4.38$, $p = .00011$, $d = 1.43$). Saccade latencies also correlated with prestim pupil velocities on a trial-by-trial basis (Figure 3E: $R = .578$, $p = .00022$), implying that trial-by-trial fluctuations of arousal level linked to pupil velocity can partly explain the variability of saccade latency evoked by SCi microstimulation.

To examine relationships between the pupil velocity and saccade latency induced by SCi microstimulation in the population analysis, the highest frequency condition across stimulation sites was used. Pupil velocity dynamics according to the prestim pupil velocity (median-split) is displayed in Figure 4A. Pupil velocities were 0.19 ± 0.023 and −0.19 ± 0.017 mm/sec for the higher and lower velocity conditions, respectively (Figure 4B). Saccade latencies between the lower and higher velocity conditions were generally different (Figure 4C), with faster latencies in the lower velocity condition (i.e., most data points above unity line; lower velocity: 41 ± 1.82 msec; higher velocity: 44 ± 1.83 msec; $t(23) = 3.47$, $p = .0021$, $d = 0.3$). Figure 4D shows summary histograms of trial-by-trial correlation coefficients for sampled sites separately for two monkeys, demonstrating a positive correlation between pupil velocity and saccade latency (median correlation coefficient: 0.12, $t(23) = 3.8$, $p = .00085$, $d = 1.09$, two-tailed paired *t* test of *R* values against zeros; Monkey A: correlation coefficient: .17, $t(8) = 2.6$, $p = .032$, $d = 1.16$;

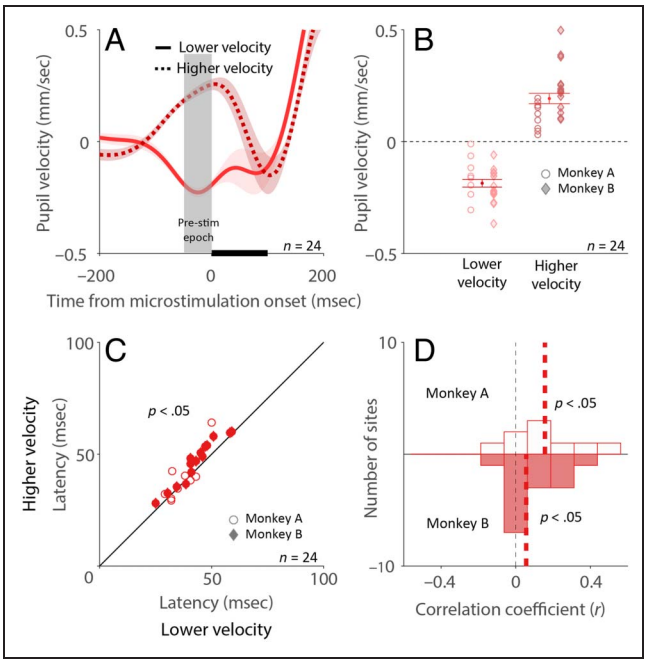

Figure 4. Effect of pupil velocity on saccade latency induced by SCi microstimulation. (A) Dynamics of pupil velocity in trials with lower or higher pupil velocities. (B) Pupil velocity in the prestim epoch between the lower and higher pupil velocity conditions. (C) Saccade latencies between the lower and higher pupil velocity conditions. (D) Distribution of correlation coefficients for the relationship between pupil velocity and saccade latency for the highest frequency condition. In (A), the black bar on the *x* axis indicates the time of microstimulation, and the shaded colored regions surrounding the pupillary response represent ± standard error range for different conditions. In (B), the circle and error bar represent mean value ± standard error across site. The large shape represents value for each site. In (D), the vertical colored dotted lines represent the median correlation coefficients.

Table 2. Multilevel Model for Saccade Latency

	Saccade latency	*Regression coefficient*	*SE*	*t*	*df*	*p*
Monkey A	(Intercept)	125.8114	3.8536	32.6474	1134	2.29E-165
	Velocity	5.8708	1.6745	3.5060	1134	4.73E-04
	StimFreq	−0.3105	0.0123	−25.2226	1134	8.63E-112
Monkey B	(Intercept)	138.2133	5.2725	26.2141	864	6.57E-112
	Velocity	4.9930	1.5672	3.1860	864	0.0015
	StimFreq	−0.3105	0.0179	−17.6478	864	9.27E-60

Table 3. Multilevel Model for Saccade Metrics

	Saccade Amplitude	*Regression Coefficient*	*SE*	*t*	*df*	*p*
Monkey A	(Intercept)	−3.7038	1.6363	−2.2635	1134	.0238
	Velocity	0.5518	0.2982	1.8462	1134	.0651
	StimFreq	0.0531	0.0022	24.0903	1134	6.94E-104
Monkey B	(Intercept)	−12.7693	1.5435	−8.2731	864	4.91E-16
	Velocity	0.0099	0.3215	0.0308	864	.9754
	StimFreq	0.0741	0.0037	20.1455	864	2.72E-74
	Saccade Peak Velocity	*Regression Coefficient*	*SE*	*t*	*df*	*p*
Monkey A	(Intercept)	−124.7395	52.0384	−2.3971	1134	.0167
	Velocity	41.0749	9.7943	4.1938	1134	2.96E-05
	StimFreq	1.7876	0.0722	24.7481	1134	1.83E-108
Monkey B	(Intercept)	−330.2768	41.4787	−7.9698	864	5.01E-15
	Velocity	22.2768	7.7916	2.8591	864	.0044
	StimFreq	2.2931	0.0892	25.7091	864	1.05E-108
	Main Sequence Slope	*Regression Coefficient*	*SE*	*t*	*df*	*p*
Monkey A	(Intercept)	39.8666	1.9301	20.6557	1134	1.04E-80
	Velocity	3.0849	0.9182	3.3597	1134	8.06E-04
	StimFreq	−0.0207	0.0067	−3.0675	1134	.0022
Monkey B	(Intercept)	75.2630	4.0003	18.8141	864	1.90E-66
	Velocity	2.5361	1.0969	2.3122	864	.021
	StimFreq	−0.1036	0.0125	−8.2650	864	5.23E-16

Monkey B: correlation coefficient: .099, $t(14) = 2.9$, $p = .013$, $d = 1.01$). Population results again reveal that the arousal fluctuations, indexed by pupil velocity, correlated with saccade latencies evoked by SCi microstimulation.

To examine whether the same results can be obtained across two monkeys, we used generalized linear mixed models that allowed us to consider data from all trials while taking microstimulation frequency and intersite variability into account. Specifically, we investigated the contribution of pupil velocity and stimulation frequency on saccade latency. Sites were included as a random intercept. The dependent variable, y, was saccade latency. The predictors were pupil velocity and stimulation frequency. The linear mixed model was as follows:

$$\text{Model } 3 : y = \beta_s + \beta_1 \textit{Velocity} + \beta_2 \textit{Frequency}$$

where β_s is a Gaussian random variable fitted for each site as an individual offset and β_i are the standard coefficients of the statistical model (intercept and slopes). Stimulation frequency significantly modulated saccade latency in both monkeys (Table 2; Monkey A: $\beta_1 = -25.22$, $p = 8E\text{-}112$, with overall adjusted R^2 being .44; Monkey B: $\beta_1 = -17.65$, $p < .001$, with overall adjusted R^2 being .41). More importantly, prestim pupil velocity significantly affected saccade latency in both monkeys (Monkey A: $\beta_1 = 3.51$, $p < .001$; Monkey B: $\beta_1 = 3.17$, $p = .0015$), with faster latencies correlated to lower velocities. Together, these results suggested that prestim pupil velocity consistently modulated saccade latency across two monkeys.

Modulation of Evoked Saccade Metrics by Prestim Pupil Velocity

To further examine whether arousal also affected evoked saccade amplitude, velocity, and main sequence slope (peak velocity/amplitude), we directly used generalized linear mixed models in each monkey separately. We used Model 3, but the dependent variable, y, now was one of three saccade indices: saccade amplitude, saccade peak velocity, and main sequence slope. The predictors were pupil velocity and stimulation frequency. Prestim pupil velocity did not modulate saccade amplitude induced by microstimulation (Table 3; Monkey A: $\beta_1 = 1.85$, $p = .065$, with overall adjusted R^2 being .74; Monkey B: $\beta_1 = 0.031$, $p = .98$, with overall adjusted R^2 being .73). In contrast, saccade peak velocity and main sequence slope were significantly modulated by prestim pupil velocity (peak velocity: Monkey A: $\beta_1 = 4.19$, $p < .001$, overall adjusted $R^2 = .28$; Monkey B: $\beta_1 = 2.86$, $p = .0044$, overall adjusted $R^2 = .79$; main sequence slope: Monkey A: $\beta_1 = 3.36$, $p < .001$, overall adjusted $R^2 = .14$; Monkey B: $\beta_1 = 2.31$, $p = .021$, overall adjusted $R^2 = .39$), with higher saccade peak velocities and steeper slope correlating with higher pupil velocities. These results reveal that arousal fluctuations, indexed by pupil velocity, correlated with the velocity and slope of saccades evoked by SCi microstimulation.

DISCUSSION

The goal of this study was to understand the impact of moment-by-moment fluctuations in arousal on saccade responses induced by microstimulation of the SCi. We found that the arousal level, indexed by pupil velocity, but not by absolute pupil size, correlated with saccade responses evoked by SCi microstimulation. Higher pupil velocities were observed on trials without an evoked saccade compared with those on trials with an evoked saccade, although these effects were statistically significant in only one monkey. Trial-by-trial correlations were observed between pupil velocity and latency of saccades induced by SCi microstimulation, showing higher pupil velocities correlated with slower evoked saccades. Furthermore, higher saccade peak velocities and steeper main sequence slopes were observed on trials with higher pupil velocities. In summary, our results demonstrated pupil-linked arousal modulation in the SCi.

Neural Correlates between Pupil Size and Arousal

In addition to its well-established modulation by luminance (May et al., 2019; McDougal & Gamlin, 2015), pupil size has long been linked to arousal (Bradshaw, 1967). The LC is usually cited as the structure underlying observed relationships between pupil size and changes in the arousal-mediated brain state (Mather, Clewett, Sakaki, & Harley, 2016; Sara & Bouret, 2012; Sara, 2009; Aston-Jones & Cohen, 2005). Studies in behaving animals have shown that noradrenergic neurons of the LC and cholinergic neurons of the basal forebrain are activated during pupil dilation (i.e., higher pupil velocity; Nelson & Mooney, 2016; Reimer et al., 2016), spiking in LC neurons is often followed by pupil dilation, and LC microstimulation evokes pupil dilation (Joshi et al., 2016). Moreover, research in mice has shown that pupil dilation generally correlates with a more active state (McGinley et al., 2015; Vinck et al., 2015; Reimer et al., 2014), such that, during dilation, the intracellular membrane potential is desynchronized in the primary visual and somatosensory cortex, and spontaneous firing is suppressed with enhanced sensory responses in V1. These results are similar to effects from noradrenergic or cholinergic neuron stimulation, with increased cortical neuron responsiveness and signal-to-noise ratio of sensory-evoked responses (Minces, Pinto, Dan, & Chiba, 2017; Martins & Froemke, 2015), together further linking pupil dilation with a release of neuromodulatory transmitters. In addition to this pathway, the nucleus paragigantocellularis (PGi) of the ventral medulla, which is involved in homeostatic functions such as blood pressure regulation and cardiovascular reflexes, is also believed to mediate the arousal-related pupil correlation (Costa & Rudebeck,

2016; Nieuwenhuis, De Geus, & Aston-Jones, 2011). The PGi provides critical inputs to both the LC and the pupil control circuit (Ennis & Aston-Jones, 1988; Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986; Lovick, 1986), possibly linking pupil size with LC activity.

In addition, because the pupil is regulated by autonomic activity, it has long been linked to other peripheral measurements (Loewenfeld, 1999). Studies back to 1960s have concurrently measured various autonomic activities to examine different cognitive modulations (Hess, 1965). For example, larger pupil dilation (i.e., pupil velocity increases) along with larger skin responses and higher heart rates are obtained with more difficult conditions (Kahneman et al., 1969). Similarly, larger pupil dilation after initial light-reflex constriction and larger skin responses are observed when viewing higher arousing pictures (Bradley, Miccoli, Escrig, & Lang, 2008). These studies clearly suggest that pupil dilation (i.e., pupil velocity increases) is linked to autonomic activity. Research further shows that both absolute pupil size and changes in pupil size (i.e., pupil velocity) correlate with peripheral indices on a trial-by-trial basis (Wang, Baird, et al., 2018), together suggesting that both pupil size and velocity can possibly index changes in arousal-mediated brain state.

Neural Mechanisms for Arousal Effects in the Oculomotor Network

Saccades are modulated by arousal level, and studies in a wide range of tasks have generally shown enhanced saccade responses by arousal: Faster saccade RTs and larger saccade peak velocities are observed using arousing stimuli (McSorley & Morriss, 2017; Wang, Blohm, Huang, Boehnke, & Munoz, 2017; DiGirolamo, Patel, & Blaukopf, 2016; Simola, Le Fevre, Torniainen, & Baccino, 2015; Di Stasi, Catena, Cañas, Macknik, & Martinez-Conde, 2013; van Steenbergen, Band, & Hommel, 2011; Crommelinck & Roucoux, 1976). The SCi receives direct projections from the FEF and the lateral intraparietal cortex, and the SCi, together with the FEF and lateral intraparietal cortex, has been causally implicated to the shifts of gaze and spatial attention (Krauzlis et al., 2013; Bisley & Goldberg, 2010; Thompson & Bichot, 2005; Wardak, Olivier, & Duhamel, 2004). The link between pupil size and the SCi (or FEF) has also been developed, as a transient increase in pupil size is observed after weak microstimulation without evoking saccades (Wang & Munoz, 2021a; Ebitz & Moore, 2017; Joshi et al., 2016; Lehmann & Corneil, 2016; Wang et al., 2012). Moreover, the arousal-regulated projections, from the LC and PGi (Edwards et al., 1979), as well as cholinergic projections from the pedunculopontine tegmental nucleus (Beninato & Spencer, 1986; Graybiel, 1978), also converge in the SCi. Therefore, critical control signals related to sensory, arousal, and cognitive processes can be integrated in the SCi to coordinate the orienting response that includes eye/head/body movement, attention shifts, and pupil dilation (Corneil & Munoz, 2014; Sokolov, 1963; Akert, 1949; Hess et al., 1946). Saccadic eye movements induced by SCi microstimulation should thus be modulated by the arousal signal indexed by pupil size and velocity at microstimulation onset.

Here, we found that pupil velocity, not absolute pupil size, correlated with saccades evoked by SCi microstimulation, suggesting that pupil size and velocity may reflect different arousal-related signals processed through the SC. In line with this, research shows that phasic changes in pupil size (corresponding to pupil velocity here) better correlate with activity from noradrenergic projections in cortex, whereas sustained (long-lasting) pupil dilation (corresponding to pupil size here) correlates with cortex activity from cholinergic projections (Reimer et al., 2016). Consistently, recent human studies have also noted the differences on behavioral and electrophysiological effects between tonic and phasic pupil responses (Wang & Munoz, 2021b; Yamagishi & Furukawa, 2020; Van Kempen et al., 2019). As a brief increase in pupil size (e.g., microdilations) and long-lasting pupil dilations may be mediated by different mechanisms, we further explored prestim pupil velocity effects in the context of temporal domain. We found that the prestim pupil velocity effects more effectively affected saccades evoked by SCi microstimulation at the time of microstimulation (Appendix Figure 2), suggesting that the observed prestim pupil velocity effects may be more related to the phasic component of arousal regulation. Note that these effects were not consistent across two monkeys possibly because of small sample sizes; thus, interpretation needs to be careful. As demonstrated (Joshi & Gold, 2020; Joshi et al., 2016), it is important to consider pupil modulations in the long and in the short timescales; our study with a short period of central fixation before microstimulation onset is limited to fully answer this question. Future studies with a long period of central fixation are required to address this question.

Moreover, lower pupil velocity correlated with higher saccade probabilities and faster saccade latencies induced by SCi microstimulation, but higher pupil velocity correlated with higher saccade velocity and a steeper main sequence slope induced by SCi microstimulation. These results seem conflicted and suggest different arousal modulations in different saccade responses induced by SCi microstimulation. However, these findings can be explained by the same arousal effect on the rostral and caudal SCi (described in the following paragraph). It is also important to note that saccade probability or latency correlates to low-frequency activity before saccade initiation (Dorris & Munoz, 1998), whereas saccade peak velocity is more related to high-frequency motor burst activity around saccade onset (Goossens & Van Opstal, 2000). So, although saccades with faster latencies are often concomitant with those with higher peak velocities, saccade latency and velocity are mainly mediated by differentiable characteristics of neural activity.

If, as argued (McGinley et al., 2015; Vinck et al., 2015; Reimer et al., 2014), arousal generally enhances neural activity, SCi activity should increase during higher pupil velocity, compared with lower pupil velocity. Monkeys required to maintain central fixation, and rostral activity induced by the FP (Dorris & Munoz, 1995; Munoz & Wurtz, 1993) should be enhanced during an increase in pupil velocity. The discharge patterns of neurons in the rostral and caudal SCi are reciprocal, presumably because of intracollicular inhibition (Phongphanphanee et al., 2014; Meredith & Ramoa, 1998; Munoz & Istvan, 1998). Enhanced rostral activity should lead to reduced caudal activity, correspondingly resulting in lower evoked saccade probabilities and longer evoked saccade latencies induced by SCi microstimulation, which is precisely what we found. However, arousal effects on caudal SCi activity evoked by microstimulation could affect saccade behavior differently. Activity in the caudal SCi evoked by microstimulation could be enhanced during pupil velocity increases, correspondingly resulting in higher evoked saccade peak velocities. Because both rostral and caudal SCi activity, induced by the FP presence and microstimulation, respectively, were both modulated by arousal in the current task, this leads to these seemingly conflicting results. Future studies that systematically manipulate rostral and caudate activity in the context of arousal effects are needed to test this possibility directly. Nevertheless, our results provide neural substrate underlying effects of arousal on the saccade response coordinated by the SC in behaving monkeys.

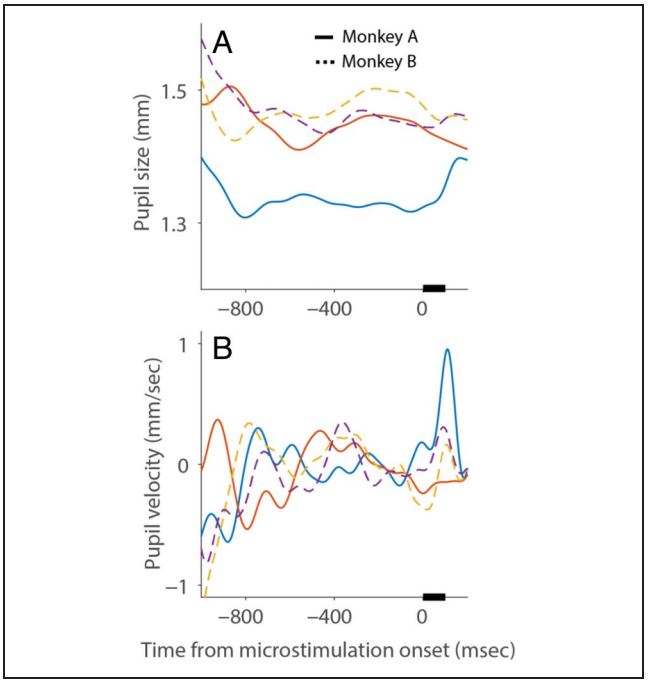

Figure A1. Example trial of pupil size and velocity dynamics. (A) Dynamics of pupil size relative to microstimulation onset in an example trial. (B) Dynamics of pupil velocity relative to microstimulation onset in an example trial.

APPENDIX

Temporal Evolution on Prestim Pupil Velocity Modulation

To examine when the arousal level indexed by pupil velocity correlated with saccades evoked by SCi microstimulation, we separated trials with or without evoked saccades and examined dynamics of pupil velocity responses before microstimulation onset in all sampled sites across two monkeys ($n = 24$). Pupil size and velocity dynamics relative to microstimulation onset are displayed in the following Appendix Figure A2A and B, respectively. To examine the prestim pupil velocity effects temporally, we first compared pupil velocities between these two conditions within the window from 400 msec before microstimulation onset (50-msec intervals, Bonferroni–Holm correction). As displayed in Appendix Figure A2B, the results only showed significantly higher pupil velocities on trials without evoked saccades than with evoked saccades in the last 50-msec time window before stimulation onset ($p = .033$). Similarly, trials with evoked saccades in the highest condition ($n = 24$) were divided into two groups according to evoked saccade latency (median-split). Appendix Figure A2C and D shows dynamics in pupil diameter and velocity before stimulation onset, respectively. Similar patterns of responses between faster and slower saccade latency conditions were obtained. As displayed in Appendix Figure A2D, the comparisons within the window from 400 msec to stimulation onset (50-msec intervals, Bonferroni–Holm correction) only showed significantly higher pupil velocities on trials with slower saccade latencies, compared with faster saccade latencies, in the last 50-msec time window before stimulation onset ($p = .0017$). Together, these results suggested that the arousal level indexed by pupil velocity more effectively affected saccades evoked by SCi microstimulation at the time of microstimulation.

To further examine the size of time window on prestim pupil velocity effects, we performed another analysis where we increased the window size from 50 msec, 100 msec, 200 msec, to 400 msec relative to stimulation onset. Regarding the comparison between saccade and no-evoked-saccade trials onset (Bonferroni–Holm correction), as shown in Appendix Figure A2B, the differences between the two conditions were significant in all window sizes. Similarly, the differences between faster and slower SRT conditions in the highest frequency condition were significant in all window sizes (Appendix Figure A2D). Together, these results suggested that the prestim pupil velocity effects are pronounced regardless of the time window size. Note that these temporal effects were not significant in each monkey data; thus, these effects should be considered with caution.

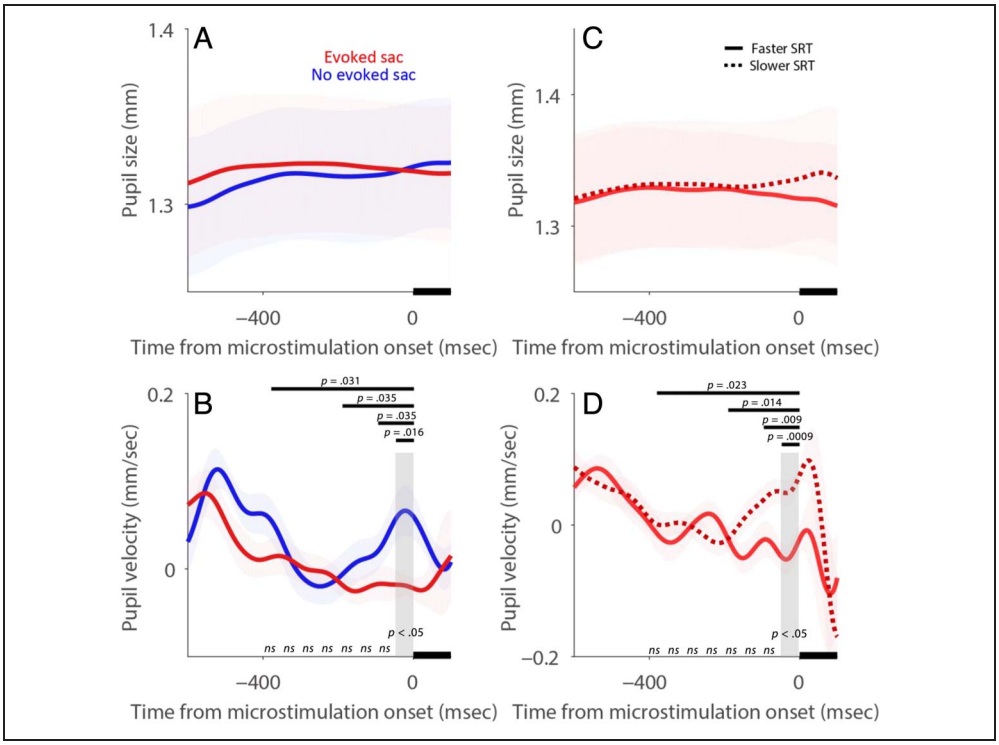

Figure A2. Temporal effect of pupil velocity on saccade behavior induced by SCi microstimulation. Dynamics of pupil size (A) and velocity (B) in trials with or without evoked saccades. Dynamics of pupil size (C) and velocity (D) in trials with faster or slower SRTs. The black bar on *x* axis indicates the time of microstimulation, and the shaded colored regions surrounding the pupillary response represent ± standard error range for different conditions. *ns:* not significant.

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Data Availability

Data are available from the authors upon reasonable request following the publication.

Author Contributions

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

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Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals 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 = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). 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.

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