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RESEARCH REPORT

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Effects of pupillary light and darkness reflex on the generation of pro- And anti-saccades

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Abstract

Saccades are often directed toward a stimulus that provides useful information for observers to navigate the visual world. The quality of visual signals of a stimulus is influenced by global luminance, and the pupil constricts or dilates after a luminance increase or decrease, respectively, to optimize visual signals for further information processing. Although luminance level changes regularly in the real environment, saccades are mostly studied in the luminance-unchanged setup. Whether pupillary responses triggered by global luminance changes modulate saccadic behavior are yet to be explored. Through varying background luminance level in an interleaved pro- and anti-saccade paradigm, we investigated the modulation of pupillary luminance responses on the generation of reflexive and voluntary saccades. Subjects were instructed to either automatically look at the peripheral stimulus (pro-saccade) or to suppress the automatic response and voluntarily look in the opposite direction from the stimulus (anti-saccade). Level of background luminance was increased (light), decreased (dark), or unchanged (control) during the instructed fixation period. Saccade reaction time distributions of correct pro- and anti-saccades in the light and dark conditions were differed significantly from those in the control condition. Moreover, the luminance condition modulated saccade kinematics, showing reduced performances in the light condition than in the control condition, particularly in pro-saccades. Modeling results further suggested that both pupil diameter and pupil size derivative significantly modulated saccade behavior, though effect sizes were small and mainly mediated by intersubject differences. Together, our results demonstrated the influence of pupillary luminance responses on the generation of pro- and anti-saccades.

KEYWORDS

anti-saccade, global luminance, pupillometry, superior colliculus

Abbreviations: BIC, Bayesian information criterion; FEF, frontal eye field; FP, central fixation point; LC, locus coeruleus; PON, pretectal olivary nucleus; SC, superior colliculus; SCi, superior colliculus intermediated/deep layers; SCs, superior colliculus superficial layers; SRT, saccade reaction time.

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1 | INTRODUCTION

To effectively explore the environment, saccadic eye movements are principally guided toward the objects of interests, providing the high-acuity image to the visual system. However, the visual signal of objects is influenced by the global luminance. The major function of the pupil is to regulate the amount to light projected onto the retina to optimize the trade-off between sensitivity and acuity of image quality for effective visual processing (Campbell & Gregory, 1960; Denton, 1956; Laughlin, 1992; Woodhouse & Campbell, 1975), with constriction to a luminance increase and dilation to a luminance decrease (referred to as the pupillary light and darkness reflexes, respectively) (Barbur et al., 1992; McDougal & Gamlin, 2015; Wang & Munoz, 2014; Wang et al., 2018). While saccades have mostly been studied in the luminance-controlled experiment, in real life, many of saccadic decisions are made while pupil size undergoes changes in response to global luminance. Whether pupil size changes adjusted for global luminance level modulate saccade behavior is yet to be investigated.

A natural task to assess visual performance is to study reflexive and voluntary saccades. Indeed, reflexive and voluntary saccades are commonly observed in viewing natural scenes (Berg et al., 2009), as reflexive saccades are driven by visual stimulation, whereas voluntary saccades require volitional control (Walker et al., 2000). The anti-saccade paradigm is often used to examine reflexive and voluntary saccades (Antoniades et al., 2013; McDowell et al., 2008; Munoz & Everling, 2004), at which subjects are instructed in advance to generate either a pro-saccade (look at the peripheral stimulus) or an anti-saccade (look in the opposite direction of a stimulus) in response to stimulus presentation. Unlike the automatic visuomotor response (reflexive) required in the pro-saccade condition, to complete an anti-saccade, subjects must suppress the automatic saccade and generate a voluntary saccade in the opposite direction of the stimulus. Pupil size has been examined in the pro- and anti-saccade paradigm, with larger pupil dilation observed during preparation for anti-saccades compared to pro-saccades (Dalmaso et al., 2020; Wang et al., 2015). Although these results reveal the modulation of pupil size by saccade planning (cognitive signals), whether pupillary responses evoked by global luminance changes (luminance signals) affect saccade behavior is to be determined. Because reflexive saccades should rely more on visual signals, we hypothesized that pupillary luminance effects should be stronger in pro- compared to anti-saccades.

Previous seminal studies have shown that the optimal size of the pupil for visual detection and discrimination in various luminance levels is close to the natural pupil size at a given luminance level (Campbell & Gregory, 1960; Woodhouse & Campbell, 1975), arguing that pupillary luminance responses serve to adjust pupil size to the optimum to facilitate visual processing. If pupil size affects performances on visual detection and discrimination, pupil size that deviates from the optimum could deteriorate visual processing, resulting in ineffective saccade generation (e.g., slower latency). Besides, saccade behavior may be optimal when the pupil is rather stabilized (e.g., pupil velocity or pupil size derivative close to zero). Therefore, when the pupil is either constricting or dilating, effectiveness of saccade generation could be impaired.

The goal of this study is to understand the influence of pupillary luminance responses induced by varying background luminance on the generation of pro- and anti-saccades (Figure 1). We hypothesize that alternating pupil size via varying background luminance should change saccade performances. Specifically, if the pupil has yet returned to the optimal at stimulus appearance after varying background luminance, saccade behavior should be less effective. The metrics of saccadic eye movements were also analyzed to fully understand pupillary luminance effects on saccade kinematics.

2 | MATERIALS AND METHODS

2.1 | Experimental setup

All experimental procedures were reviewed and approved by the Institutional Review Board of the Taipei Medical University, Taiwan, and were in accordance with the Declaration of Helsinki (World Medical Association, 2001). Thirty-one participants (mean age: 25.1, *SD*: 4 years, and 15 males) were recruited via an advertisement posted on the Taipei Medical University website. Participants had normal or corrected-to-normal vision and were naïve regarding the purpose of the experiment. Participants provided informed consent and were compensated financially for their participation.

2.2 | Recording and apparatus

Participants were seated in a dark room. Eye position and pupil size were measured with a video-based eye tracker (EyeLink-1000 plus, SR Research, Osgoode, ON, Canada) at a rate of 500 Hz with binocular recording (the left eye was used for analysis because it usually had higher accuracy). Stimulus presentation and data acquisition were controlled by EyeLink Experiment Builder and EyeLink software. Stimuli were presented on an LCD monitor at a screen resolution of 1920 × 1,080 pixels (60 Hz refresh rate), subtending a viewing angle of 58° × 32°, with the distance from the eyes to the monitor set at 60 cm.

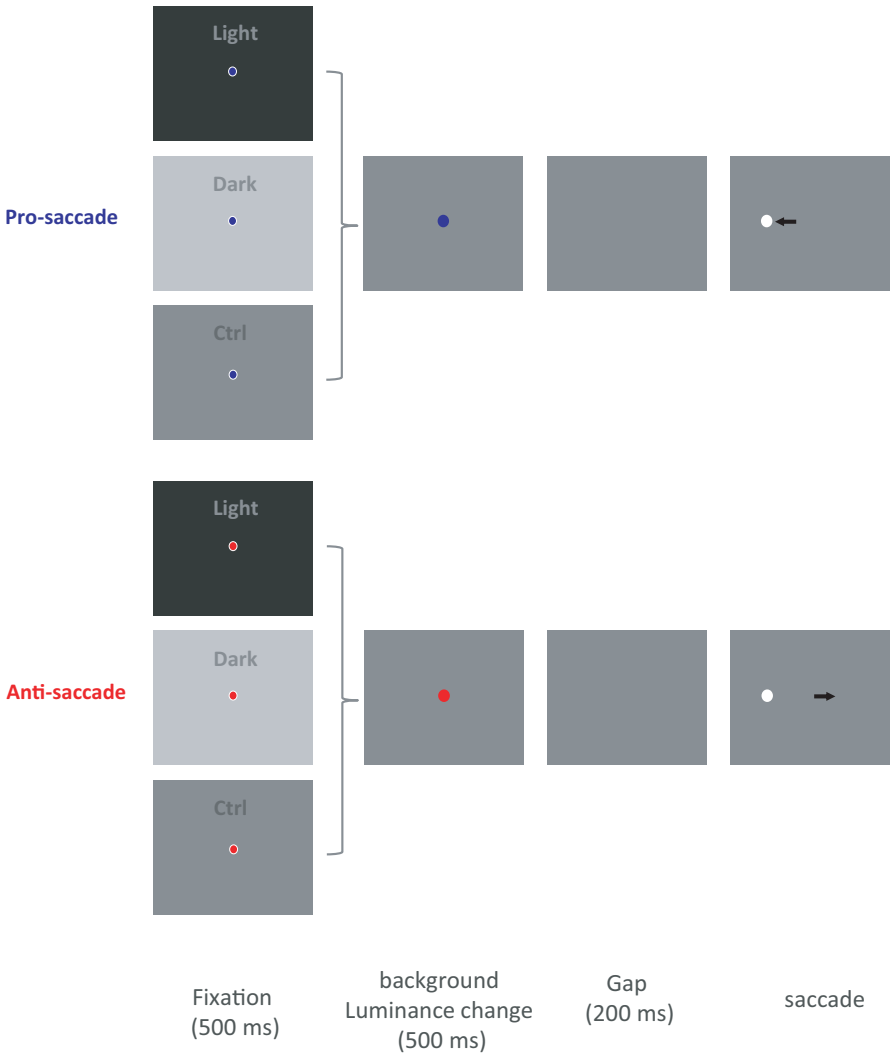


FIGURE 1 Experimental paradigm. Each trial began with a central colored fixation point (two isoluminant colors at 25 cd/m^2 for pro- and anti-saccade conditions, respectively) on a background. After 500 ms the background luminance level was changed to gray (10 cd/m^2) and simultaneously the white rim of the FP (0.1°, 25 cd/m^2) was changed to the instructed color for 500 ms. A blank screen was presented for 200 ms (gap) before target stimulus presentation, and participants were required to move their eyes to the target in the pro-saccade condition, or look away to the opposite location in the anti-saccade condition, after target stimulus appearance. Light: light reflex condition. Dark: darkness reflex condition. Ctrl: control condition (no luminance changes)

2.3 | Interleaved pro- and anti-saccade task (Figure 1)

Each trial began with the appearance of a central fixation point (FP) (0.5° diameter, 0.1° white rim with centered color, the luminance level of white or colored part of the FP was 25 cd/m^2) on a background. The trial condition was revealed via the FP color (the luminance level of the two FP colors were matched, and the colors for pro- or anti-saccade conditions were counterbalanced across participants). On pro-saccade trials, participants were instructed to look toward the peripheral stimulus as soon as the FP disappeared. On anti-saccade trials, participants were instructed to look in the opposite direction of the stimulus as soon as the FP disappeared. In the control (Ctrl) condition (33.3% of the trials), after 500 ms of central fixation on a neutral gray background (10 cd/m^2), the white rim of the FP (0.1°, 25 cd/m^2) was changed to the instructed color and the background luminance level was remained. After another 500 ms of central fixation, the FP disappeared for 200 ms (gap) before the peripheral stimulus appeared (0.5° diameter; yellowish dot with luminance 270 cd/m^2) to the left or right of the FP (8° eccentricity on the horizontal axis). The gap period between FP disappearance and peripheral stimulus appearance was inserted to induce more directional errors in the anti-saccade condition. The gap period between FP disappearance and peripheral stimulus appearance was inserted to induce more directional errors in the anti-saccade condition. Moreover, visual signals from the FP as well as the target should be modulated by pupil size. The insertion of a gap can reduce fixation-related activity related to the FP (e.g., Dorris & Munoz, 1995), allowing us to examine the influence of pupil size on visual activity evoked by a target stimulus. The identical configuration was used as in the control condition except that the initial background luminance level was 5 cd/m^2 (50% contrast relative to the gray background) in the light reflex condition (Light) and 15 cd/m^2 (50% contrast relative to the gray background) in the darkness reflex condition (Dark). The experiment consisted of 360 trials. Task condition (pro- and anti-saccade), background luminance condition (Ctrl, Light, and Dark), and stimulus location

(left and right) were randomly interleaved. Saccades toward either the right or left direction were combined for data analysis. Note that pupil size is modulated by arousal level (Aston-Jones & Cohen, 2005). Sudden changes in the visual information could induce arousal changes, to minimize the influence of arousal particularly when changing background luminance, we changed the color of a FP rim in all luminance conditions (see Figure 1), so that there were transient visual changes in the fovea in three luminance conditions.

2.4 | Data analysis

Saccade reaction time (SRT) was defined as the time from peripheral target appearance to the onset of the first saccade away from fixation defined by the moment when the eye velocity exceeded 30°/s, and with an amplitude greater than 3°. Saccade amplitude, saccade peak velocity, and endpoint saccade accuracy (angular deviation of the end position of the saccade from the correct saccadic location) of the first saccade were also analyzed. Trials were scored as correct if the first saccade after stimulus appearance was in the correct direction (toward the stimulus in the pro-saccade condition; away from the stimulus in the anti-saccade condition). Direction errors were identified as the first saccade after target appearance in the wrong direction (e.g., toward stimulus on anti-saccade trials). To maintain an accurate measure of pupil size, trials with an eye position deviation of more than 2° from the central FP or with detected saccades (>2° amplitude) during the required period of central fixation were excluded from analysis. When blinks were detected, pre- and post-blink pupil values were used to perform a linear interpolation to replace pupil values during the blink period (Karatekin et al., 2010; Nassar et al., 2012; Wang et al., 2018). Trials were discarded when two blinks occurred within a time interval of less than 500 ms. Trials in which a saccade was made prior to the disappearance of the FP or there was failure to initiate a saccade within 800 ms after the disappearance of the FP, were excluded from the analysis. The saccades with SRTs < 90 ms were considered as anticipatory in the paradigm of pro- and anti-saccades (Munoz et al., 1998) because the proportion of anti-saccade error trials was similar to that of correct anti-saccade trials, and these saccades (1.4%) were excluded from analyses. The above criteria resulted in the removal of 7.35% of trials. Besides pupil diameter data, we also computed instantaneous pupil diameter derivative (i.e., velocity, referred to as pupil size derivative) to further examine instantaneous pupillary changes. An epoch from 50 ms prior to stimulus onset was used to compare pupil diameter and pupil diameter derivative at stimulus onset between the pro- and anti-saccade conditions in the different luminance conditions. Note that outlier values beyond ±3.4 standard deviation were also excluded from analysis. For analysis there remained at least 10 correct trials for each condition. Thus, four participants were excluded, leaving 27 participants for final analysis. We followed the procedures of baseline-correction (subtractive baseline-correction) used previously in the same paradigm of pro- and anti-saccades (Dalmaso et al., 2020; Jainta et al., 2011; Wang et al., 2015), and were recommended by recent research on pupillometric analyses (Mathôt et al., 2018). For each trial, a baseline value was determined by averaging pupil size from 50 ms before to the appearance of the stimulus presentation. Pupil values were subtracted from this baseline value.

A two-way repeated-measure ANOVA was used to examine effects of luminance condition (Ctrl, Light, and Dark) and saccade preparation (pro- and anti-saccade) on the saccade and pupillary response. Effect sizes, where appropriate, were also reported. To examine whether saccade responses are modulated by changes in pupil size in the anti-saccade and the pro-saccade conditions, a two-tailed student *t* test was performed to specifically compare the Ctrl and Light conditions or the Ctrl and Dark conditions. Bayesian *t* tests, where appropriate, were also performed to inform statistical significance for pairwise comparisons, with a scale factor r = 0.707 (Rouder et al., 2009). Statistical tests were performed using JASP Team (2019) and MATLAB (The MathWorks Inc., Natick, MA, USA).

The impact of pupil diameter and pupil size derivative was further analyzed with linear mixed models allowing us to include these variables as fixed effects and a random term capturing differences across participants to account for idiosyncrasy (Pinheiro & Bates, 2000).

First, we tested the influence of pupil diameter and derivative by fitting linear modes including either the diameter alone, the size derivative alone, or the two variables combined. We then assessed which model was the best by taking the minimum BIC (Bayesian Information Criterion). The BIC captures the goodness of the fit while taking into account the number of parameters (Crevecoeur et al., 2017; Murphy, 2012), and the one with the minimum BIC should be retained as it achieves the best balance between explaining the variance in the data without using too many parameters. Notably, baseline-corrected pupil size highly correlated with pupil size derivative at target onset with significant positive trial-by-trial correlations obtained from 96% of subjects and the mean coefficient being 0.57 and 0.57 in the pro- and anti-saccade condition, respectively. In addition, we observed that when fitting a mixed linear model with diameter, pupil size derivative and baseline-corrected pupil size resulted in a partial correlation for baseline-corrected pupil size that was below the levels of variance accounted for by the other predictors. The coefficient for this parameter did not reach significance when the same analysis was conducted on anti-saccade data. Considering this plus the fact that this

parameter exhibited high correlation with pupil size derivative, we chose to keep the latter variable as a predictor in addition to the absolute diameter value.

Second, this analysis was combined with a quantification of the total variance accounted for, and of the partial correlation of the pupil diameter and size derivative which follows Edwards and colleagues (Edwards et al., 2008). Defining y as the dependent variable (SRT, saccade amplitude, peak velocity, or accuracy), we defined the overall R^2 as follows:

$$R^2 = 1 - \frac{Var(\varepsilon)}{Var(y)},$$

where $Var(.)$ indicates the variance of the argument, and ε is the model residuals. This equation calculates how much variance is explained by the model relative to the null model which is simply a constant value for y. Regarding the partial correlations, we followed again Edwards and colleagues and replaced the denominator by the variance of the model obtained leaving one predictor out. For instance, defining $\varepsilon(d)$ as the residuals of the model based on the pupil diameter, and $\varepsilon(d, v)$ as the residuals of the model including diameter and size derivative, then:

$$R_v^2 = 1 - \frac{Var(\varepsilon(d, v))}{Var(\varepsilon(d))},$$

represents the partial correlation of the size derivative.

Finally, the analysis of the possible presence of curvature in the relationship between pupil diameter or size derivative and the different indices was assessed by fitting statistical models with one predictor being the square value of the variables of interest following standard techniques (James et al., 2013). The specific presence of curvature in the data was then assessed by checking whether the p-value associated with the squared-predictor was significantly different from 0. All statistical models were performed with the package "nlme" in R (Pinheiro & Bates, 2000).

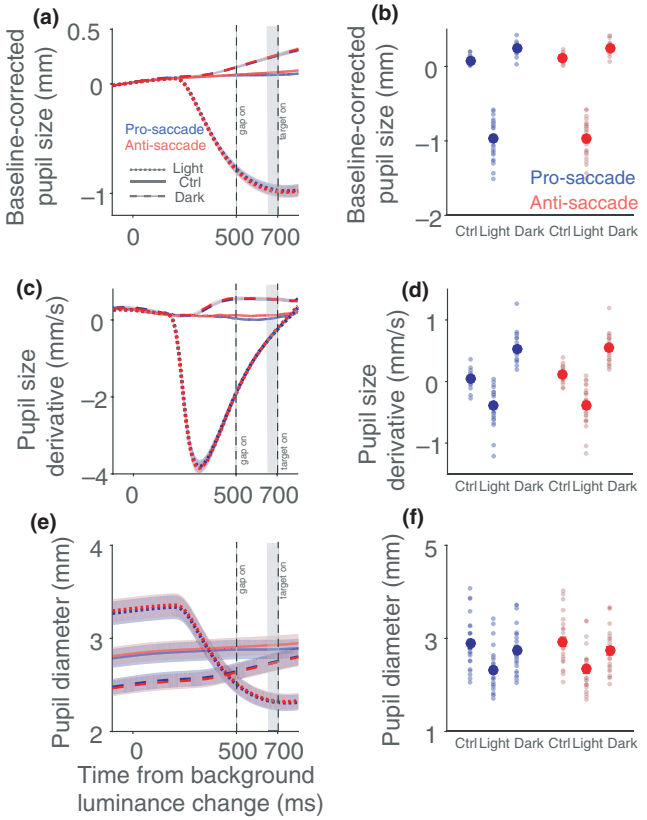


FIGURE 2 Effect of background luminance changes on pupil diameter and pupil size derivative. Pupil dynamics in different background luminance change conditions on baseline-corrected pupil size (A, B), pupil diameter (C, D), and pupil size derivative (E, F) ($n = 27$). Mean pupil size (50 ms before to target stimulus onset) (B), mean absolute pupil diameter (D), and mean pupil size derivative (F) in different background luminance conditions. In A, C, E, the shaded colored regions surrounding the pupillary response curves represent the ± standard error range (across participants) for different conditions. Average pupillary responses at the epoch (50 ms before to target stimulus onset) illustrated by the gray shaded region. In B, D, F, the large circles and error-bars represent the mean values ± standard error across participants. The small-circle represents mean value for each participant. Light: light reflex condition. Dark: darkness reflex condition. Ctrl: control condition (no luminance changes)

3 | RESULTS

3.1 | Pupillary light and darkness responses following background luminance changes

Pupillary light and darkness reflexes are well-documented (Barbur et al., 1992; Wang & Munoz, 2014; Wang, Tworzyanski, et al., 2018). Consistent with the literature, we observed that changes in background luminance levels clearly modulated pupil size (Figure 2a), with pupillary constriction after an increase in background luminance and pupillary dilation after a decrease in background luminance. Baseline-corrected pupil size at the epoch from 50 ms prior to stimulus onset (Target epoch, see Methods) was significantly influenced by background luminance changes (luminance main effect: Figure 2b, $F(2,52) = 441.04$, $p < .001$, $\eta_p^2 = 0.944$). Mean pupil size values in correct pro-saccade trials were 0.08, −0.96, and 0.24 mm in the Ctrl, Light, and Dark conditions, respectively, and were 0.10, −0.98, and 0.25 mm in correct anti-saccade trials in the Ctrl, Light, and Dark conditions, respectively. Pupil size was not modulated by the task type (task type main effect: $F(1,26) = 0.94$, $p = .34$, $\eta_p^2 = 0.035$), and the interaction of task type and luminance conditions was significant ($F(2,52) = 3.989$, $p = .025$, $\eta_p^2 = 0.133$). Moreover, the planned comparisons showed that both light (Pro: $t(26) = 20.453$, $p < .001$, d = 3.94, $BF_{10} > 100$; Anti: $t(26) = 21.445$, $p < .001$, d = 4.13, $BF_{10} > 100$) and dark

(Pro: $t(26) = 12.661$, $p < .001$, d = 2.44, $BF_{10} > 100$; Anti: $t(26) = 12.128$, $p < .001$, d = 2.33, $BF_{10} > 100$) pupil diameter differed significantly from the control condition (divisive baseline-correction results revealed the same effects and are included in supplementary Figure 1).

Similar results were obtained with raw pupil diameter (Figure 2c), with mean pupil sizes at the target epoch in correct pro-saccade trials being 2.88, 2.32, and 2.74 mm, and being 2.93, 2.33, and 2.73 mm in correct anti-saccade trials in the Ctrl, Light, and Dark conditions, respectively (Figure 2d: luminance main effect: $F(2,52) = 268.71$, $p < .001$, $\eta_p^2 = 0.91$). Pupil diameter was marginally modulated by the task type (task main effect: $F(1,26) = 4.08$, $p = .054$, $\eta_p^2 = 0.136$), and the interaction of task type and luminance conditions was significant ($F(2,52) = 7.83$, $p = .001$, $\eta_p^2 = 0.232$). The planned comparisons showed that both light (Pro: $t(26) = 20.65$, $p < .001$, d = 3.97, $BF_{10} > 100$; Anti: $t(26) = 18.69$, $p < .001$, d = 3.6, $BF_{10} > 100$) and dark (Pro: $t(26) = 8.17$, $p < .001$, d = 1.57, $BF_{10} > 100$; Anti: $t(26) = 18.69$, $p < .001$, d = 3.6, $BF_{10} > 100$) pupil diameter differed significantly from the control condition.

To examine instantaneous changes in pupil size, the pupil size derivative (first-order derivative) was analyzed. Pupil derivative dynamics revealed the same pattern of results (Figure 2e). A decrease in pupil size derivative was observed following a background luminance increase, and an increase in pupil size derivative following a background luminance decrease. Mean pupil size derivative at the target epoch in correct pro-saccade trials were 0.04, −0.398, and 0.535 mm/s, and were 0.124, −0.381, and 0.541 mm/s in correct anti-saccade trials in the Ctrl, Light, and Dark conditions, respectively (Figure 2f: luminance main effect: $F(2,52) = 102.628$, $p < .001$, $\eta_p^2 = 0.798$; task main effect: $F(1,26) = 8.536$, $p = .007$, $\eta_p^2 = 0.247$; interaction: $F(2,52) = 6.014$, $p = .012$, $\eta_p^2 = 0.188$). The planned comparisons clearly showed that both light (Pro: $t(26) = 8.356$, $p < .001$, d = 1.608, $BF_{10} > 100$; Anti: $t(26) = 8.378$, $p < .001$, d = 1.612, $BF_{10} > 100$) and dark (Pro: $t(26) = 9.627$, $p < .001$, d = 1.853, $BF_{10} > 100$; Anti: $t(26) = 10.271$, $p < .001$, d = 1.977, $BF_{10} > 100$) pupil size derivative differed significantly from the control condition. In summary, these results suggest that background luminance changes significantly modulated pupillary responses, and baseline-corrected pupil size, raw pupil diameter, and pupil size derivative at target onset in the light and dark conditions were significantly different from those in the control condition.

3.2 | Modulation of pupillary luminance responses on saccadic reaction time and direction error

Saccade behavior in the pro- and anti-saccade task is well-documented (Antoniades et al., 2013; Coe & Munoz, 2017; Everling & Fischer, 1998; Hsu et al., 2020; Munoz & Everling, 2004). To first determine if each SRT distribution condition was derived from the same or different underlying distributions, we analyzed cumulative SRT distributions with a nonparametric Kolmogorov–Smirnov test (Figure 3a and 3b). In correct trials, both Light (Pro: K = 0.76, $p < .001$; Anti: K = 0.88, $p < .001$) and Dark (Pro: K = 0.44, $p < .001$; Anti: K = 0.61, $p < .001$) curves differed significantly from the control condition. In direction-error trials, Light (Pro: K = 0.76, $p < .001$; Anti: K = 0.88, $p < .001$) curves differed significantly from the control condition, but in the dark condition, only anti-saccade trials differed significantly from the control condition (Pro: K = 0.27, $p = .086$; Anti: K = 0.49, $p < .001$). These results generally suggested that SRT distributions were modulated by pupillary luminance responses evoked by the sudden change in background luminance.

Consistent with the literature (Antoniades et al., 2013; Coe & Munoz, 2017; Everling & Fischer, 1998; Hsu et al., 2020; Munoz & Everling, 2004), there were more direction errors in the anti-saccade condition than in the pro-saccade condition (Figure 3c: task type main effect: $F(1,26) = 74.245$, $p < .001$, $\eta_p^2 = 0.741$). In the pro-saccade trials, error rates were 1.846%, 1.394%, and 2.005% for the Ctrl, Light, and Dark conditions, respectively; and they were 19.376%, 21.191%, and 21.298% in the anti-saccade trials for the Ctrl, Light, and Dark conditions, respectively. Other effects were negligible ($p > .37$). Similar error rates were observed between the light or dark condition and the control condition (light: Pro: $t(26) = 1.062$, $p = .298$, d = 0.204, $BF_{10} = 0.339$; Anti: $t(26) = 1.129$, $p = .269$, d = 0.217, $BF_{10} = 0.362$; dark: Pro: $t(26) = 0.361$, $p = .721$, d = 0.069, $BF_{10} = 0.216$; Anti: $t(26) = 1.104$, $p = .280$, d = 0.212, $BF_{10} = 0.353$).

Similar patterns were reflected in SRTs (Figure 3d). Mean SRTs for correct pro-saccades were 155 ms, 160 ms, and 160 ms in the Ctrl, Light, and Dark conditions, respectively, and 229 ms, 231 ms, and 232 ms in correct anti-saccades trials. Consistent with previous studies (Everling & Fischer, 1998; Munoz et al., 1998; Munoz & Everling, 2004), it took longer to generate correct anti- than pro-saccades ($F(1,26) = 163.426$, $p < .01$, $\eta_p^2 = 0.86$). The main effect of background luminance, however, was only approaching significance ($F(2,52) = 2.687$, $p = .096$, $\eta_p^2 = 0.094$). Other effects were negligible ($p > .53$). The simple effects showed significant luminance modulation in pro-saccade trials ($p = .027$), but not in anti-saccade trials ($p = .547$), suggesting that SRTs were significantly modulated by background luminance changes in pro-saccade, but not anti-saccade trials. Consistently, planned comparisons revealed longer pro-saccade latencies in the dark ($t(26) = 2.625$, $p = .014$, d = 0.505, $BF_{10} = 3.45$) than in the control condition, though differences between the light and control condition was less reliable ($t(26) = 1.958$, $p = .061$, d = 0.377, $BF_{10} = 1.06$). Clearly, in anti-saccade trials, both light and dark latencies were not

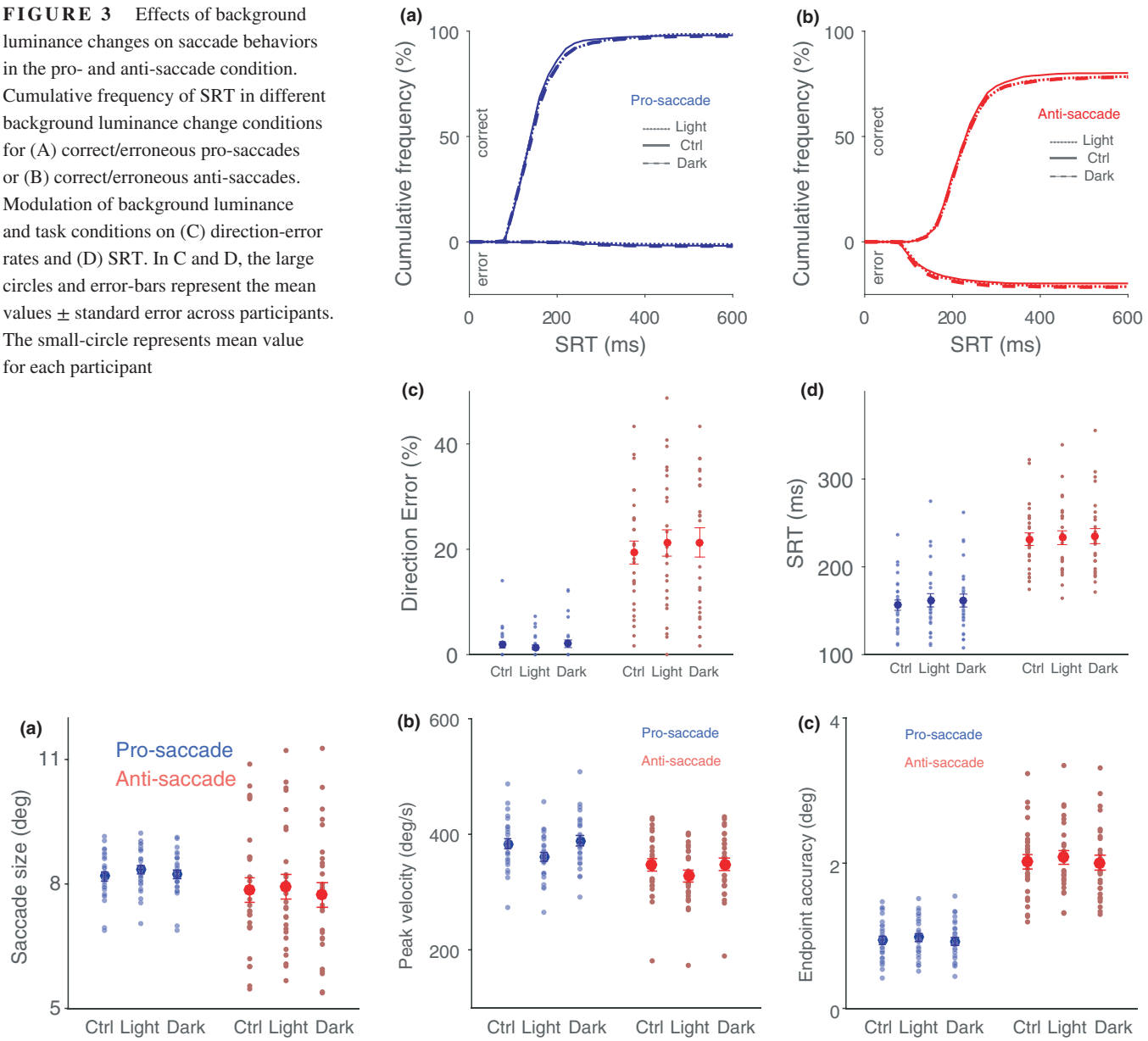


FIGURE 3 Effects of background luminance changes on saccade behaviors in the pro- and anti-saccade condition. Cumulative frequency of SRT in different background luminance change conditions for (A) correct/erroneous pro-saccades or (B) correct/erroneous anti-saccades. Modulation of background luminance and task conditions on (C) direction-error rates and (D) SRT. In C and D, the large circles and error-bars represent the mean values ± standard error across participants. The small-circle represents mean value for each participant

FIGURE 4 Effects of background luminance changes on saccade metrics in the pro- and anti-saccade condition. Modulation of background luminance and task conditions on (A) saccade amplitude, (B) saccade peak velocity, and (C) saccade endpoint accuracy. The large circles and error-bars represent the mean values ± standard error across participants. The small-circle represents mean value for each participant

different from the control condition (light: $t(26) = 0.708$, $p = .485$, d = 0.136, $BF_{10} = 0.256$; dark: $t(26) = 0.914$, $p = .369$, d = 0.176, $BF_{10} = 0.298$).

3.3 | Modulation of pupillary luminance responses on saccadic metrics

To understand the influence of background luminance changes on saccade metrics, we further analyzed saccade amplitude, peak velocity, and endpoint accuracy in correct trials. Saccade amplitude was significantly modulated by background luminance changes (Figure 4a: main luminance effects: $F(2,52) = 6.02$, $p = .004$, $\eta_p^2 = 0.188$), with mean saccade amplitudes for correct pro-saccades were 8.18 deg, 8.34 deg, and 8.23 deg in the Ctrl, Light, and Dark conditions, respectively, and 7.85 deg, 7.93 deg, and 7.73 deg in correct anti-saccades trials. Effects of task type and interaction were not significant (all ps > 0.13). The simple effects showed significant luminance modulation in pro-saccade trials ($p < .001$), but not in anti-saccade trials ($p = .089$), suggesting that saccade amplitude was particularly modulated by background luminance changes in pro-saccade trials. Planned comparisons only showed significantly larger

Condition \Index	SRT	Size	PV	Accuracy
Pro-Saccade	Model 1	Model 1	Model 3	Model 1
Anti-Saccade	Model 3	Model 2	Model 3	Model 1

TABLE 1 Results of the model selection analysis. The table indicate which model was the best across Models 1, 2, and 3 according to the BIC for each parameter and across Pro- and Anti-saccade conditions. Each model was fitted with participants included as a random intercept to account for intersubject variability

pro-saccade amplitude in the light than in the control condition ($t(26) = 5.24$, $p < .001$, d = 1, $BF_{10} > 100$). Other effects were negligible ($p > .1$).

Changes in background luminance also affected peak velocity (Figure 4b: luminance main effects: $F(2,52) = 58.723$, $p < .001$, $\eta_p^2 = 0.693$). Mean peak velocities for correct pro-saccades were 384 deg/s, 361 deg/s, and 389 deg/s in the Ctrl, Light, and Dark conditions, respectively, and 347 deg/s, 328 deg/s, and 348 deg/s in correct anti-saccades trials. Peak velocities were smaller in the anti-saccade than in the pro-saccade condition (task type main effects: $F(1,26) = 30.467$, $p < .001$, $\eta_p^2 = 0.540$). The interaction of luminance changes and task was significant ($F(2,52) = 3.395$, $p = .041$, $\eta_p^2 = 0.115$). The simple effects showed significant luminance modulation in both pro-saccade and anti-saccade trials (all $ps < 0.001$). Specifically, significantly larger peak velocities in pro-saccade trials were observed in the control than in the light condition ($t(26) = 7.46$, $p < .001$, d = 1.436, $BF_{10} > 100$), and though less reliable, larger peak velocities in the dark compared to the control condition ($t(26) = 2.286$, $p = .031$, d = 0.440, $BF_{10} = 1.84$). Similar patterns were reflected in anti-saccade trials. Peak velocities in the control condition were significantly larger than those in the light condition ($t(26) = 6.468$, $p < .001$, d = 1.245, $BF_{10} > 100$), but indifferent from the dark condition ($t(26) = 0.476$, $p = .638$, d = 0.092, $BF_{10} = 0.23$).

Endpoint accuracy was almost significantly modulated by luminance changes (Figure 4c: $F(2,52) = 3.112$, $p = .053$, $\eta_p^2 = 0.107$), it was more significantly influenced by the task type ($F(1,26) = 107.169$, $p < .001$, $\eta_p^2 = 0.805$), with more accurate saccades in the pro- than in the anti-saccade condition. The interaction was not significant ($F(2,52) = 0.094$, $p = .872$, $\eta_p^2 = 0.004$). The simple effects showed no significant luminance effects in both pro- and anti-saccade trials ($p > .17$). Effects of all planned comparisons were negligible ($p > .22$).

3.4 | Effects of pupil diameter and pupil size derivative on saccade behavior from linear mixed models

Our foregoing analyses characterized main effects of luminance conditions on saccade kinematics. To further quantify the effect of pupil diameter and pupil size derivative in detail, we used linear mixed models allowing us to consider data from all trials while taking inter-participant variability into account. More specifically, we investigated the influence of pupil diameter and pupil size derivative on saccade behavior (see Methods) based on three models taking as fixed predictor(s) the pupil diameter (Model 1), pupil size derivative (Model 2), or pupil diameter and pupil size derivative together (Model 3). Participants were included as a random intercept, such that fixed biases linked to individuals' traits are included in the model. Model comparison was performed based on BIC criterion. The dependent variable, y, was one of four indices related to each trial, namely SRT, saccade amplitude, saccade peak velocity, and accuracy. The predictors were the pupil diameter (d) and pupil size derivative (v). The linear mixed models were as follows:

$$\text{Model 1: } y = \beta_0 + \beta_S + \beta_1 d + \varepsilon,$$

$$\text{Model 2: } y = \beta_0 + \beta_S + \beta_1 v + \varepsilon,$$

$$\text{Model 3: } y = \beta_0 + \beta_S + \beta_1 d + \beta_2 v + \varepsilon,$$

where ε are Gaussian random variables capturing the model residuals, β_S is a Gaussian random variable fitted for each participant as an individual offset, and β_i are the standard coefficients of the statistical model (intercept and slopes).

As displayed in Table 1, Model 3 was indeed selected in some conditions which confirm that both pupil diameter and pupil size derivative account for some fluctuations of saccade behavior on a trial-by-trial basis. Moreover, Model 1 was picked in three saccade indices in the pro-saccade condition, suggesting pupil diameter played a more important role in pro-saccade trials. In contrast, information of pupil size derivative was useful (Model 2 or Model 3) in three saccade indices in the anti-saccade condition, suggesting pupil size derivative played a more important role in anti-saccade trials. These results were consistent with our hypothesis that reflexive saccades are majorly mediated by visual signals, pupil diameter effects on saccade behavior is thus stronger in the pro-saccade condition than the anti-saccade condition. To further understand whether there are positive or negative relationships between pupil and saccade indices, we fitted Model 3 to all saccade indices in the pro- and anti-saccade conditions. It is important to stress first that considering Model 3 without any subject-specific term yielded clearly significant regressions

for both pro- and anti-saccade instructions (Pro: all $F > 4.5$, $p < .01$, Anti: all $F > 16$, $p < 10^{-6}$), meaning that for all indices and all conditions, pupil diameter or pupil size derivative had a significant impact (Table 2). However, this effect was in part due to intersubject differences. Indeed, by fitting Model 3 again with the random term (β_S), we calculated the total model R^2 as well as the partial R^2 associated with pupil diameter and pupil size derivative and found acceptable R^2 but low partial correlations for these variables. Furthermore, coefficients between pupil diameter and saccade indices were negative in SRT, saccade amplitude, and ending accuracy, but positive in peak velocity, suggesting that larger pupil diameter correlated with saccades with shorter SRTs, smaller saccade amplitude, larger peak velocities, and less accuracy. Similar patterns were observed in anti-saccade trials, except larger pupil diameter negatively correlated with saccade amplitude. Coefficients between pupil size derivative and saccade indices were negative in saccade amplitude and positive in other indices in pro-saccades, suggesting that increases in pupil size derivative correlated with saccades with larger peak velocities, slower SRT, smaller sizes, and less accuracy. Similar patterns were observed in anti-saccade trials, except increases in pupil size derivative negatively correlated with SRT. These results mean that the pupil diameter and pupil size derivative are significantly linked to the indices that characterize saccade behavior, though this dependency was statistically weak and predominantly reflecting intersubject differences.

Finally, we assessed the possibility that the relationship between trial indices and pupil diameter or pupil size derivative exhibited curvature. We reasoned that if there is an optimal diameter size or optimal pupil size derivative when the pupil is rather stabilized, we should observe an optimal value for which the indices exhibit either a maximum or a minimum. This was assessed by fitting a mode that included the square of the diameter (or pupil size derivative) as a fixed predictor as follows:

$$\text{Model 4: } y = \beta_0 + \beta_S + \beta_1 d + \beta_1 d^2 + \varepsilon$$

$$\text{Model 5: } y = \beta_0 + \beta_S + \beta_1 v + \beta_1 v^2 + \varepsilon$$

Although our results showed some quadratic trends in SRT and ending accuracy in two saccade conditions, these trends were not statistically significant. Specifically, we concentrated on the parameter β_1 of Model 4, since it is responsible for the curvature of this function, and found that it was always associated with t-values lesser than 1.92 ($p > .05$). Moreover, fitting with pupil size derivative and pupil size derivative to the square showed no significant curvature in the data. Together, we found no curvature in the relationship between saccade indices and pupil diameter or pupil size derivative. Notably, it is also possible that the observed trends require a larger sample size or more extreme variations in the luminance condition to have a significant impact on behavior, future studies are needed to test this question.

4 | DISCUSSION

The current study examined the effect of pupillary luminance responses on the generation of reflexive and voluntary saccades in the interleaved pro- and anti-saccade task. Sudden changes in background luminance significantly modulated pupil size, with constriction in response to a luminance decrease and dilation in response to a luminance increase. These pupillary luminance responses influenced saccade behavior. SRT distributions of correct pro- and anti-saccades in the light and dark conditions differed significantly from those in the control condition. Moreover, pupillary luminance changes modulated saccade kinematics, particularly in the pro-saccade condition, showing significantly smaller peak velocities and larger saccade amplitude in the light than in the control condition. Modeling results further suggested that although both pupil diameter and pupil size derivative contributed to saccade behavior, pupil diameter was more important for pro-saccade trials. Together, our results for the first time demonstrated that pupil size adjusted to global luminance changes affects pro- and anti-saccade generation in the gap paradigm.

TABLE 2 Results of the regression analysis. Model 3 was fitted in all cases and the table reports the coefficients that multiply the fixed predictors (a1 for pupil diameter and a2 for the size derivative). Partial correlations were estimated by comparing the model residuals with the predictor of interest relative to the null model where this predictor was removed

	a1	a2	Partial R^2 of diameter	Partial R^2 of size derivative	Total R^2
PRO: SRT	−1.81	3.7×10^{-2}	<0.001	<0.001	0.31
PRO: Size	−0.26	-3.6×10^{-3}	0.01	<0.001	0.26
PRO: PV	15.8	17	0.011	0.023	0.38
PRO: Accuracy	−0.15	0.014	0.007	<0.001	0.15
Anti: SRT	−4.27	−1.29	<0.001	<0.001	0.32
Anti: Size	0.1	−0.11	<0.001	<0.001	0.36
Anti: PV	19.16	17.24	0.003	0.003	0.14
Anti: Accuracy	−0.12	0.001	0.001	<0.001	0.13

4.1 | Modulation of pupillary luminance responses on saccade generation

The pupil responds to global luminance level to moderate a trade-off between sensitivity and acuity of input image for optimizing visual processing (Campbell & Gregory, 1960; Denton, 1956; Laughlin, 1992; Woodhouse & Campbell, 1975). Research that examines visual detection and discrimination under various background luminance levels has found better performances while the artificial aperture of the pupil is close to nature pupil diameter at a given background luminance level (Campbell & Gregory, 1960; Woodhouse & Campbell, 1975). These results not only support the functional role of pupillary luminance responses, but also suggest the modulation of pupil size on visual signals.

The orienting response such as saccades is arguably coordinated by the superior colliculus (SC) (Boehnke & Munoz, 2008; Corneil & Munoz, 2014), a midbrain structure causally involved in gaze and attention shifts (Gandhi & Katnani, 2011; Krauzlis et al., 2013), and/which is greatly modulated by the visual signal. A study that manipulates the visual response of the SC via varying stimulus contrast has shown that the visual signals are greatly modulated by stimulus contrast and correlated strongly with changes in saccade latency and metrics (Marino et al., 2012, 2015). If the visual signal is modulated by the size of the pupil and affects saccade generation, varying pupil size that in turn modulates visual signals should also modulate saccade responses. Consistently, we found that saccade latency and metrics were modulated by pupil size induced by background luminance changes. SRT distributions of pro- and anti-saccades in the light and dark conditions were differed significantly from those in the control condition (Figure 3), and varying background luminance also significantly modulated saccade metrics (Figure 4). More specifically, smaller peak velocities and larger saccade amplitudes were found in the light than in the control condition. Because pupil size was significantly smaller in the light condition as compared to the control condition (decrease around 30%, Figure 2), these results may suggest that smaller pupil size could reduce visual responses evoked by visual stimuli, as the fundamental function of the pupil, and in turn resulting in smaller saccade peak velocities in the context of the pro- and anti-saccade paradigm. Future studies are required to examine this prediction. Although larger saccade amplitude in the light than in the control condition seemed contradicted with this assumption, these saccades were generally overshot (larger than the correct saccade amplitude), and thus, saccades were less accurate in the light than in the control condition (though not statistically significant). Moreover, reflexive saccades are mainly driven by visual information, compared to voluntary saccades. Consistently, our results showed the more reliable luminance modulation in the pro-saccade condition than that in the anti-saccade condition, and pupil diameter was more important in pro-saccade modulation. Notably, although we argue that visual signals are more important for pro-saccade generation, these signals are still essential for anti-saccade generation. To generate an anti-saccade, visual signals of a stimulus, though suppressed, still need to be processed to the certain level, as a go signal, to initiate anti-saccades (Munoz & Everling, 2004). Future research is required to examine these modulations on reflexive and voluntary saccades in other paradigms. Notably, the modulation of pupil diameter on saccade responses was generally small in the current study. It could be because a decrease of pupil size was only 30% and 10% from the control condition in the light and dark conditions, respectively. These changes were rather small in comparison to previous research that uses a great range of artificial pupil diameter, for example, 1–8 diameter that could usually produce ±100% changes from the surface pupil size (Campbell & Gregory, 1960; Woodhouse & Campbell, 1975).

Changing background luminance greatly influenced pupil size derivative at stimulus onset (Figure 2), such that the pupil size derivative around stimulus onset was negative, close to zero, and positive in the light, control, and dark conditions, respectively. To examine the contribution of pupil size derivative in addition to pupil diameter on saccade indices, model selection based on a Bayesian Information Criterion (BIC) was used (Murphy, 2012). We used pupil diameter (Model 1), pupil size derivative (Model 2), or pupil diameter + pupil size derivative (Model 3) on a trial-by-trial basis as independent variables to account for trial-by-trial fluctuation of saccade indices in both correct pro-saccade and anti-saccade trials. Modeling results showed that Model 3 was generally selected by BIC (Table 1), suggesting that both pupil diameter and pupil size derivative uniquely contributed to saccade latency and metrics. Moreover, although these effects were significant, they were generally small and largely mediated by intersubject differences (Table 2). This could be due to the smaller differences in pupil diameter within subjects compared to those between subjects. As mentioned, the percentage change of pupil diameter was only ~ 30% while varying background luminance, but the intersubject differences were larger, as pupil diameter across subjects ranged from around 1.5 to 4 mm.

To investigate whether there are nonlinear relationships between the pupil response and saccade indices, we added a square function separately in pupil diameter and pupil size derivative analysis. If there is optimal pupil size, the optimum should be close to the median of pupil size values in the control condition (no luminance changes), resulting in the nonlinear relationship. Although our results showed no U and inverted U-shaped relationships, as mentioned previously, this could be due to relatively small differences in pupil diameter after background luminance changes across different

conditions. It is thus possible that the range of pupil diameter at stimulus onset across trials was not large enough to reveal the expected nonlinear relationship between pupil diameter and saccade behavior. Future research is required to address this possibility.

It could be puzzling that how could slower pupillary responses influence faster saccade generation? Notably, absolute pupil size could modulate the quality of visual signals induced by a visual target through regulating the amount of lights onto the retina (Campbell & Gregory, 1960; Denton, 1956; Laughlin, 1992; Woodhouse & Campbell, 1975). As mentioned, visual activity evoked by the target in the SC correlates with saccade latency and metrics (Marino et al., 2012, 2015), and these SC visual signals could be modulated by the size of the pupil, and in turn modulates saccade responses. Therefore, by introducing a delay of 500 ms after background luminance changes with a 200 ms gap before target appearance, absolute pupil size was different at target onset in different background luminance conditions, and these pupil size differences could modulate the visual activity in the SC evoked by the target, and affect saccade behavior.

It is interesting to note that consistent with previous studies (Dalmaso et al., 2020; Wang et al., 2015), larger pupil dilation in the anti-, compared to, pro-saccade condition was observed when the global luminance level was unchanged in the control condition (baseline-corrected pupil size: $t(26) = 2.52$, $p = .018$, $d = 0.48$; absolute pupil diameter: $t(26) = 3.35$, $p = .003$, $d = 0.64$; pupil size derivative: $t(26) = 3.30$, $p = .003$, $d = 0.64$). However, this effect was diminished when background luminance was changed. These results suggest that cognitive signals (e.g., saccade preparation) reflected in pupil size could be diluted by pronounced global luminance signals, implicating the importance of maintaining global luminance level for using pupil size to index cognitive processing.

4.2 | Other accounts for pupil modulation on saccade response

Correlation between pupil responses and task performance has been consistently reported (Ebitz & Moore, 2019; Einhäuser, 2017; Mathôt, 2018), and the locus coeruleus (LC) is commonly implicated in the observed relationship (Aston-Jones & Cohen, 2005). Indeed, pupil responses are indicative for arousal level, as research in behaving animals has shown that pupil size correlates with changes in brain states and neural activity across various brain regions including the LC (Aston-Jones & Cohen, 2005; Joshi et al., 2016; McGinley et al., 2015; Reimer et al., 2014, 2016; Varazzani et al., 2015; Yüzgeç et al., 2018), with enhanced sensory responses during pupil dilation compared to constriction (i.e., being dilation), suggesting pupil size derivative as an effective index of arousal level (McGinley et al., 2015; Reimer et al., 2014; Vinck et al., 2015). Varying background luminance could induce larger arousal fluctuations than the control condition, although we also changed the color of central fixation point to minimize the arousal influence across different conditions. The observed relationships between the pupil response and saccade performances could be attributed, at least partly, to the arousal modulation. Future research with simultaneous measurements of the autonomic activity such as galvanic skin and heart responses is needed to answer this question.

4.3 | Neural mechanisms underlying the modulation of pupillary luminance responses on saccade behavior

What neural substrates mediate this behavior? There is evidence that the oculomotor network including the SC and frontal eye field (FEF) is causally involved in the suppression and generation of saccadic eye movement in the anti-saccade paradigm (review: Munoz & Everling, 2004). In addition, these structures along with others are important for saccade kinematics (Robinson & Fuchs, 2001; Sparks, 2002; Sparks & Barton, 1993). Specifically, the superficial layers of the SC (SCs) receives visual signals from the retina and other visual areas such as the pretectal olivary nucleus (PON) (Born & Schmidt, 2008; Gamlin, 2006), a critical structure in the parasympathetic pathway (McDougal & Gamlin, 2015). Moreover, both the SCs and PON receive direct retinal signals from luminance-sensitive neurons (Gamlin, 2006; Hannibal et al., 2014). The intermediated/deep layers (SCi) receives multisensory, cognitive, and arousal signals from the SCs, FEF, LC as well as other cortical and subcortical areas (Edwards, 1975; White & Munoz, 2011), and projects to the premotor brainstem circuit to initiate the orienting response such as saccades (Corneil & Munoz, 2014; Gandhi & Katnani, 2011). Furthermore, recent research has shown pupil dilation evoked by the subthreshold microstimulation of the SCi or FEF (Ebitz & Moore, 2017; Lehmann & Corneil, 2016; Wang et al., 2012). Effects of pupil size by saccade preparation in the pro- and anti-saccade paradigm (Dalmaso et al., 2020; Wang et al., 2015) are similar to effects observed in neural activity of the SCi and FEF performing the same task (Munoz & Everling, 2004). These results not only extend this circuitry to the pupil control pathway, but also demonstrate cognitive modulation (saccade planning) on pupil size via this pathway.

Because the luminance-sensitive neurons in the PON have exhibited the firing rate of cells proportionally to luminance levels to continually monitor luminance changes (Clarke et al., 2003; Gamlin et al., 1995; Pong & Fuchs, 2000), it is possible that neurons in the SCs that receive inputs from luminance-sensitive neurons in the

retina and PON may also contain luminance information. Because the SCi could possibly integrate signals from these luminance-sensitive SCs neurons, saccade behavior is potentially influenced by luminance changes. Alternatively, as described, the quality of visual signals can be modulated by the size of the pupil, it is also possible that saccade kinematics are influenced by the quality of SC visual signals modulated by the size of the pupil. The origin of the effect of luminance on saccadic behavior (sensitivity to light or effect of pupil size) remains to be explored in more detail. Taken together, we argue that the visual response in the SC could be modulated by luminance signals and pupil size, and these visual signals along with cognitive and arousal signals are integrated in the SCi and in turn modulates saccade latency and metrics. Although these SCi output signals should also affect pupil size (Wang et al., 2012), this question is beyond the focus of the current study, and needs to be explored in future research.

5 | CONCLUSION

While there has been considerable progress in understanding saccade behavior in the luminance-controlled environment, little is known about saccadic decision when pupil size is responding to global luminance changes. Here, we demonstrated that saccade behavior was modulated by pupil size adjusted to the level of global luminance, and pupillary luminance responses affected both pro- and anti-saccade behavior. Many of saccade decisions, in the real-world situation, are made when other important factors, for example, vestibular signals, are not well-controlled (Rincon-Gonzalez et al., 2016; Van Beuzekom & Van Gisbergen, 2002a, 2002b). Future research that explores the interactive processes between the oculomotor and other systems is thus important to advance our knowledge of eye movement control in the real world.

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CONFLICTS OF INTEREST

The authors report no potential conflict of interest.

AUTHORS CONTRIBUTION

C.W. and Y.C. designed research; C.W. and Y.C. performed research; C.W. and F.C. analyzed data; C.W. and F.C. wrote the manuscript. All authors provided comments and edits on various drafts of the manuscript.

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DATA AVAILABILITY STATEMENT

Data are available from the authors upon reasonable request.

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