Neuropsychologia 80 (2016) 176–184

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease

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ARTICLE INFO

Article history:
Received 29 June 2015
Received in revised form
19 November 2015
Accepted 23 November 2015
Available online 26 November 2015

Keywords:
Superior colliculus
Frontal eye field
Motor preparation
Oculomotor
Reaction times
Pupillary response
Preparatory set
Executive function

ABSTRACT

Pupil size is an easy-to-measure, non-invasive method to index various cognitive processes. Although a growing number of studies have incorporated measures of pupil size into clinical investigation, there have only been limited studies in Parkinson's disease (PD). Convergent evidence has suggested PD patients exhibit cognitive impairment at or soon after diagnosis. Here, we used an interleaved pro- and anti-saccade paradigm while monitoring pupil size with saccadic eye movements to examine the relationship between executive function deficits and pupil size in PD patients. Subjects initially fixated a central cue, the color of which instructed them to either look at a peripheral stimulus automatically (pro-saccade) or suppress the automatic response and voluntarily look in the opposite direction of the stimulus (anti-saccade). We hypothesized that deficits of voluntary control should be revealed not only on saccadic but also on pupil responses because of the recently suggested link between the saccade and pupil control circuits. In elderly controls, pupil size was modulated by task preparation, showing larger dilation prior to stimulus appearance in preparation for correct anti-saccades, compared to correct pro-saccades, or erroneous pro-saccades made in the anti-saccade condition. Moreover, the size of pupil dilation correlated negatively with anti-saccade reaction times. However, this profile of pupil size modulation was significantly blunted in PD patients, reflecting dysfunctional circuits for anti-saccade preparation. Our results demonstrate disruptions of modulated pupil responses by voluntary movement preparation in PD patients, highlighting the potential of using low-cost pupil size measurement to examine executive function deficits in early PD.

1. Introduction

Pupil size is controlled by the balanced activity between the sympathetic and parasympathetic systems, and is widely used to index cognitive and neural processing (e.g., Ebitz and Platt, 2015; Eldar et al., 2013; Nassar et al., 2012), in addition to its well-known illumination-dependent modulation (Loewenfeld, 1999). Measurement of pupil size has been increasingly implemented in clinical investigation (e.g., Bremner, 2009; Daluwatte et al., 2013; Frost et al., 2013; Karatekin et al., 2010). Parkinson's disease (PD), a neurodegenerative disorder, is characterized by motor symptoms attributed to the loss of dopaminergic neurons in the pars compacta of the substantia nigra (Greenfield and Bosanquet, 1953). Although recent evidence has suggested the importance of characterizing deficits in executive functions for early diagnosis (Leh et al., 2010; Muslimovic et al., 2005; Rodriguez-Oroz et al., 2009), to date cognitive deficits in PD have not been explored with measures of pupil size.

The interleaved pro- and anti-saccade task has been used extensively to study executive control deficits (Munoz and Everling, 2004; Munoz et al., 2007) because subjects require flexible executive control to generate either an automatic or voluntary movement according to the task condition. Specifically, participants are instructed prior to peripheral stimulus appearance either to look at the stimulus automatically (pro-saccade), or to suppress the automatic saccade and instead generate a voluntary response in the opposite direction (anti-saccade). Modulation of pupil size by pro- and anti-saccade preparation was recently demonstrated

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http://dx.doi.org/10.1016/j.neuropsychologia.2015.11.019
0028-3932/

in healthy young adults (Wang et al., 2015): pupil size was larger prior to stimulus appearance for correct anti-saccade trials, compared to correct pro-saccade or erroneous anti-saccade trials, and pupil size negatively correlated with correct anti-saccade reaction times. These findings suggest that pupil size is linked to voluntary saccade preparation, supporting the suggested connection between the saccade and pupil control circuits (Wang and Munoz, 2015).

PD patients display deficits in executive control in the anti-saccade task, producing more anti-saccade errors and longer saccadic reaction times (SRT) for correct anti-saccades (e.g., Amador et al., 2006; Antoniades et al., 2015a, 2015b; Cameron et al., 2010; Chan et al., 2005; Hood et al., 2007; Rivaud-Pechoux et al., 2007; Srivastava et al., 2014; Terao et al., 2013). In functional magnetic resonance imaging (fMRI) studies, these deficits are particularly pronounced in frontal areas (Cameron et al., 2012). In age-matched controls, there is higher preparatory activation in correct anti- compared to pro-saccade preparation, and the level of preparatory activity negatively correlates to SRT. However, PD patients reveal insignificant differences in preparatory signals between anti- and pro-saccade preparation, and a poor correlation between preparatory activity and SRT (Cameron et al., 2012).

If the saccade and pupil control circuits are linked (Wang and Munoz, 2015), then deficits in voluntary motor preparation in PD patients should be revealed by not only saccadic, but also pupillary responses. Here, we investigate the relationship between task preparation and pupil size in PD patients, using an interleaved pro- and anti-saccade paradigm, and hypothesize that the modulation of pupil size by voluntary motor preparation will be diminished in PD patients. Our results show that PD patients display atypical pupil responses attributed to deficits of voluntary preparation, suggesting that pupil size can be used to examine cognitive deficits in Parkinson's disease.

2. Materials and methods

2.1. Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board in accordance with the Declaration of Helsinki. Participants were naïve regarding the purpose of the experiment and provided informed consent with compensation for their participation. Twenty-two PD patients (mean age=67.4 years, range: 50–83) were recruited from the Movement Disorder Clinic at Kingston General Hospital by neurologist and co-author GP. Patients underwent an evaluation of motor function (United Parkinson's Disease Rating Scale, UPDRS), cognitive status (Montreal Cognitive Assessment, MoCA), and disease severity based on the modified Hoehn and Yahr staging (Goetz et al., 2004). Although a score of 26 or higher in MoCA is considered cognitively normal, a cut-off score of 24 was chosen due to the simplicity of the task. Every subject corrected their errors by making a secondary saccade to the correct location, which confirmed their understanding of task instructions. PD patients in this study were considered mild/moderate stage based on a mean Hoehn and Yahr score of 2.4 (SD $\pm$ 0.6). Clinical data and participant demographics are shown in Table 1. Nineteen age-matched controls (mean age 68.6 years; range: 49–76) were also collected. These participants were spouses or friends of the PD participants or community members who responded to print advertisements. The control group did not differ significantly from the patient group in terms of age or years of education. Participants with co-morbid neurological, psychiatric, or ophthalmic conditions, such as macular degeneration or cataracts, were excluded.

Patients did not interrupt their medications for the study because anti-saccade deficits are pronounced even while taking dopaminergic medications (e.g., Briand et al., 1999; Chan et al., 2005; Cameron et al., 2012; Hood et al., 2007). It is also important to note

Table 1
Clinical information of Parkinson's disease subjects. A: anticholinergic; E: entacapone; Eq.: equivalent; L: levodopa; L-CR: levodopa controlled-release; LED: Levodopa Equivalent Dose; M: amantadine; mg: milligrams; Med.: medications; Mo.: months; MoCA: Montreal Cognitive Assessment; P: pramipexole; R: ropinirole; S: rasagiline; SD: standard deviation; UPDRS; United Parkinson's Disease Rating Scale; Yrs: years.

Patients	Sex	Age (yrs)	Education (yrs)	MoCA	Mo. since diagnosis	UPDRS Score (Part II)	UPDRS Score (Part III)	Hoehn-Yahr Stage	Med.	LED (in mg)
1	M	63.5	12.0	27	59	12	41	2.0	L, L-CR	575
2	M	67.7	10.0	28	8	5	21	2.0	R, P	250
3	M	65.7	18.0	29	24	10	15	2.0	L, R	420
4	M	73.6	11.0	25	104	12	36	2.0	L, L-CR, P, A, S	1100
5	M	73.1	17.0	26	51	7	32	2.0	P, A	100
6	F	56.5	12.0	28	87	5	11	2.0	L, L-CR,P	775
7	M	50.9	12.0	28	12	6	17	1.5	P	125
8	M	78.9	19.0	26	147	15	43	3.0	L, L-CR, P, M, E	1248
9	M	74.7	17.0	25	166	14	47	3.0	L, S, E	1198
10	F	73.0	11.0	26	6	8	16	2.5	P	50
11	M	69.6	17.0	28	85	7	21	2.0	L, P	700
12	M	70.9	18.5	25	78	6	19	2.5	L, L-CR, P	1450
13	F	63.7	17.0	28	60	11	26	2.5	L, L-CR, P	537.5
14	F	72.2	12.0	26	37	7	21	2.0	L, R	280
15	M	55.9	18.0	24	250	24	56	4.0	L, P, A	2080
16	M	63.1	16.0	27	64	19	53	3.0	L, L-CR	1250
17	F	83.6	13.0	26	2	11	41	3.0	L	250
18	M	70.3	18.0	26	29	3	22	2.0	L, P	350
19	M	62.8	12.0	28	158	18	37	3.0	L, L-CR, M	550
20	F	56.3	17.0	28	47	16	36	3.0	L, L-CR, P	725
21	F	68.9	15.0	30	55	9	11	2.0	L, P	475
22	F	69.0	17.0	30	78	8	26	2.0	L, L-CR, P	575
mean (n=22)	14M; 8F	67.4	15.0	27	73	11	29.5	2.4		685
Controls mean (n=19)	9M; 10F	68.6	15.5	27						

that scores of UPDRS were higher (worse) in the current study than in our previous study (both on and off medication conditions) (Cameron et al., 2012), suggesting that the severity levels of current patients were more similar to the previous off-medication condition, even though current patients were medicated. Moreover, one previous study examined newly diagnosed PD patients who were not yet taking any medications (Micieli et al., 1991), and demonstrated larger baseline pupil diameter and diminished light reflex responses in PD patients (similar to our results), compared to controls, suggesting that abnormal pupil responses in PD cannot be explained by dopaminergic medication.

2.2. Recording and apparatus

Eye position and pupil size were measured with a video-based binocular eye tracker (Eyelink-1000, SR Research, Osgoode, ON, Canada) at a rate of 500 Hz with binocular recording (left eye position and pupil size were analyzed). Stimulus presentation and data acquisition were controlled by Eyelink Experiment Builder and Eyelink software. Stimuli were presented on a 17-inch LCD monitor at a screen resolution of 1280 × 1024 pixels (60 Hz refresh rate), subtending a viewing angle of 32 × 26°, and distance from the eyes to the monitor was set at 58 cm. We used a previously described method to transfer output pupil area values recorded from the eye tracker to actual pupil size in diameter (for details: Steiner and Barry, 2011; Wang and Munoz, 2014).

2.3. Pro- and Anti-saccade task

Participants were seated in a dark room and the experiment consisted of 120 trials. Each trial began with the appearance of a central fixation point (FP) (0.5° diameter, ~42 cd/m^2) on a black background (0.1 cd/m^2) (Fig. 1A). The trial condition was revealed via FP color (pro-saccade: red FP; anti-saccade: green FP; luminance level was matched). After 2000 ms, the FP disappeared and a peripheral stimulus appeared simultaneously (0.5° diameter; gray dot with luminance 42 cd/m^2) to the left or right of the FP (10° eccentricity on the horizontal axis). On pro-saccade trials, participants were instructed to look towards the peripheral stimulus as soon as it appeared. On anti-saccade trials, participants were instructed to look in the opposite direction of the stimulus as soon as it appeared. Trial condition (pro- and anti-saccade) and stimulus location (left and right) were randomly interleaved, and there were 30 trials for each combination. Note that participants were required to complete a series of experiments, and the current study only focused on the anti-saccade task.

2.4. Data analysis

Saccade reaction time (SRT) was defined as the time from the target appearance to the first saccade away from FP (eye velocity exceeded 30°/s). 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 stimulus appearance that was executed in the wrong direction (e.g., toward stimulus on anti-saccade trials). The saccades with SRTs < 100 ms (< 0.1%) were classified as anticipatory (Munoz et al., 1998) and excluded from analysis. Because there were no directional biases, saccades for the right or left direction were collapsed.

Trials with an eye position deviation of more than 2° from the central FP during the required period of central fixation (150–2100 ms after FP appearance) were excluded from analysis. When blinks were detected, following the literature, pre- and post-blink pupil values were used to perform a linear interpolation to replace

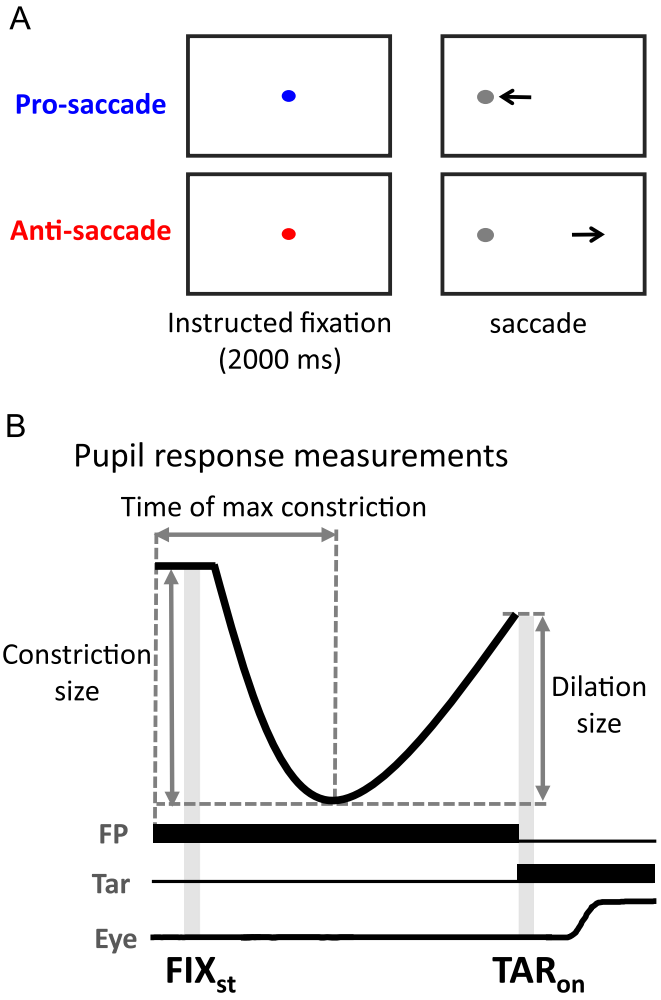

Fig. 1. (A) Each trial started with a central colored fixation point (42 cd/m^2: two isoluminant colors for pro- and anti-saccade conditions, respectively) on a black background, a peripheral stimulus was presented after 2000 ms. Participants were required to move their eyes to the stimulus in the pro-saccade condition, but move to the opposite location in the anti-saccade condition. Note that the displayed FP colors here are only for illustration of the paradigm. (B) Three pupillary measurements were used to analyze constriction and dilation pupil responses: constriction size, time of max constriction, dilation size. Two selected epochs for pupil analyses: FIX$_{st}$ (fixation start): 150–300 ms after fixation onset; TAR$_{on}$ (target onset): 0–100 ms after stimulus onset. FP: fixation point, Tar: target, Eye: eye position.

pupil values during the blink period (e.g., Karatekin et al., 2010; Nassar et al., 2012). Normal changes in pupil size are usually moderate: human pupil constriction velocity was ~1 mm/s even after an increase of whole background luminance (Wang and Munoz, 2014). To reduce pupil size noise due to an inaccurate measurement, trials were discarded when the velocity of pupil size during the required period of central fixation exceeded 5 mm/s (excluded 9.4% of trials), on the assumption that changes in human pupil size could possibly reach this velocity only under the strongest pupillary light reflex condition. Five participants (three from PD group) were excluded from analysis because of insufficient number of correct trials per condition ($N < 10$). The number of direction errors was relatively small in the current study. To increase the statistical power in error-related analyses, participants with more than five direction error trials were included for this analysis ($N > 5$), and nine participants (four from PD group) were excluded. Because there were relatively few direction errors, the current study focused mainly on the comparison between correct pro- and anti-saccade trials.

Pupil size is distorted by eye position because the size of the

pupil depends on the angle of the eyeball relative to the video-based eye tracker. To maintain an accurate measure of pupil size, the selected epochs for pupil analysis were either during the central fixation period or before saccade initiation when eye position was located at the center of the screen. Specifically, two epochs were selected for analysis (Fig. 1B): the start of visual fixation epoch (FIX_{st}: 150 – 300 ms after fixation onset) and a target onset epoch (TAR_{on}: 0 – 100 ms after stimulus onset). It is important to note that pupil size in the TAR_{on} epoch was not confounded with pupil responses evoked by visual stimulus presentation because the pupil response latency in humans is longer than 150 ms (Wang and Munoz, 2014).

Following a large body of literature, we examined relative pupil diameter using baseline-correction (e.g., Bala and Takahashi, 2000; Moresi et al., 2008; Wang et al., 2012). The baseline pupil diameter value was determined by averaging pupil size from the first 150–300 ms after fixation onset (FIX_{st}), and for each trial, original pupil diameter values were subtracted from this baseline pupil diameter value. Pupil size is sensitive to level of illumination; the light reflex drives constriction following increases in illumination (Loewenfeld, 1999), and the appearance of the FP (with a higher luminance value relative to background) changed overall illumination, resulting in pupillary light responses. Pupil size during the instructed fixation period (after fixation appearance) was therefore influenced by the light reflex. To capture pupil dynamics during the instructed fixation period, we analyzed both constriction and dilation components of pupil responses (Fig. 1B). Note that constriction and dilation components of pupil responses may reflect different processes mediated by the parasympathetic or sympathetic pathway (Bradley et al., 2008). The constriction size and time of maximum constriction were defined as the pupil size and the time when the pupil reached to the greatest constriction after FP appearance, respectively. The dilation magnitude was defined as the pupil size during the TAR_{on} epoch minus the pupil size at the time of greatest constriction during fixation, reflecting the increase of pupil size after initial constriction. It has been shown previously that the dilation component is more related to saccade preparation (Wang et al., 2015).

We performed a mixed ANOVA (2×2 ANOVA: between-subjects factor: Parkinson's disease/age-matched control $\times$ within-subjects factor: pro-/anti-saccade) for statistical analysis. We further examined the simple main effect to specifically test our hypothesis that the modulation of pupil size by saccade preparation (anti- versus pro-) was impaired in PD patients, but intact in age-matched control subjects.

3. Results

3.1. Saccadic responses in pro- and anti-saccade task

Fig. 2 summarizes the saccade responses for controls and PD patients performing the pro- and anti-saccade task, replicating previous studies (e.g., Amador et al., 2006; Antoniades et al., 2015a, 2015b; Briand et al., 1999; Cameron et al., 2010, 2012; Chan et al., 2005; Hood et al., 2007; Rivaud-Pechoux et al., 2000). In our study, PD patients made more direction errors than controls on anti-saccade trials (Fig. 2A; two-sample one-sided t test: $t(34) = 1.95$, $P < 0.05$). Fig. 2B and C illustrates the cumulative frequency of correct and erroneous SRTs for pro- and anti-saccade conditions for age-matched controls and PD patients. PD patients had faster mean SRTs for correct pro-saccades (Fig. 2B; mean pro-SRTs for control and PD: 252 ms and 241 ms, respectively), although these effects did not reach significance ($t(34) = 0.76$, $P = 0.23$). Contrarily, PD patients had longer mean SRTs for correct anti-saccades (Fig. 2C; mean anti-SRTs for control and PD: 322 ms and 337 ms, respectively), although effects were not significant ($t(34) = 0.81$, $P = 0.21$). Moreover, average SRT for erroneous anti-saccades in PD were shorter than that in controls, although these effects were not significant (control and PD: 255 ms and 243 ms, respectively; $t(30) = 0.63$, $P = 0.26$). Although not statistically significant, saccadic behaviors in PD revealed inferior performance on anti-saccade initiation, which were consistent with previous studies using interleaved pro- and anti-saccade tasks (e.g., Cameron et al., 2010, 2012).

3.2. Pupil size for correct pro- and anti-saccade trials

We hypothesize that because PD patients have deficits in motor preparation for pro- and anti-saccade generation (Cameron et al., 2012), the modulation of pupil size by task preparation should also be altered. To examine the modulation of saccade preparation on pupil dynamics, we analyzed pupil size during the instructed fixation period prior to stimulus appearance in the interleaved pro- and anti-saccade paradigm. Fig. 3A shows relative pupil diameter baseline-corrected to the diameter at fixation onset (see Methods), revealing two components of the pupil response, namely an initial constriction that began shortly after FP appearance followed by pupil dilation. The initial constriction was mainly driven by the changes of luminance level following the presentation of luminant FP, while the dilation was more related to task preparation (Wang et al., 2015). Because different components of pupil dynamics may be related to different processes (Bradley

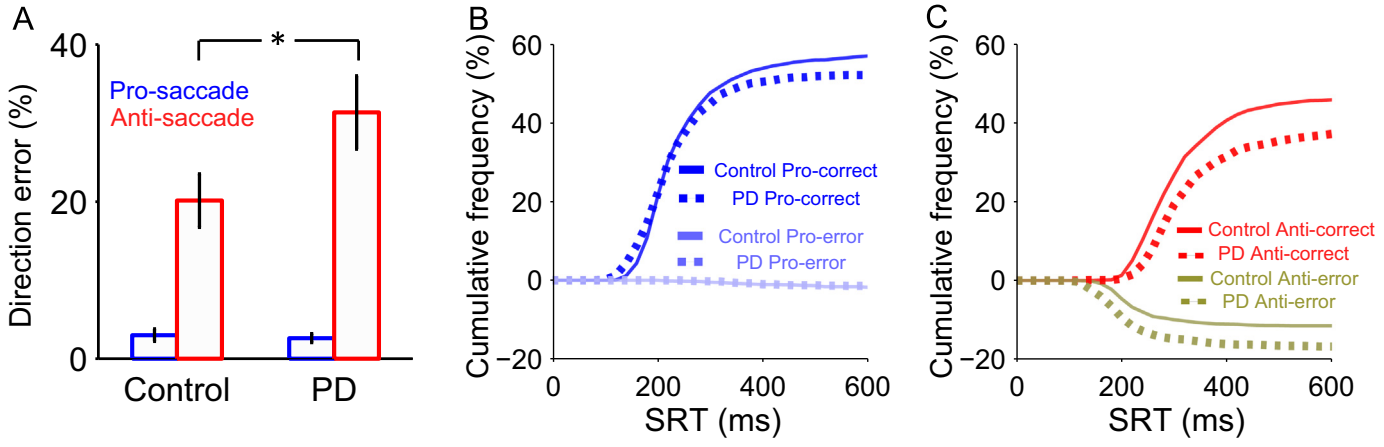

Fig. 2. Saccade behaviors in the pro- and anti-saccade condition. Modulation of task condition between PD patients and controls on (A) direction error rates. Cumulative frequency of SRT between controls and PD patients for (B) correct pro-saccades or (C) correct/erroneous anti-saccades. PD: Parkinson's disease participants, Control: aging control participants, SRT: saccade reaction times, * indicates differences are statistically significant ($P < 0.05$).

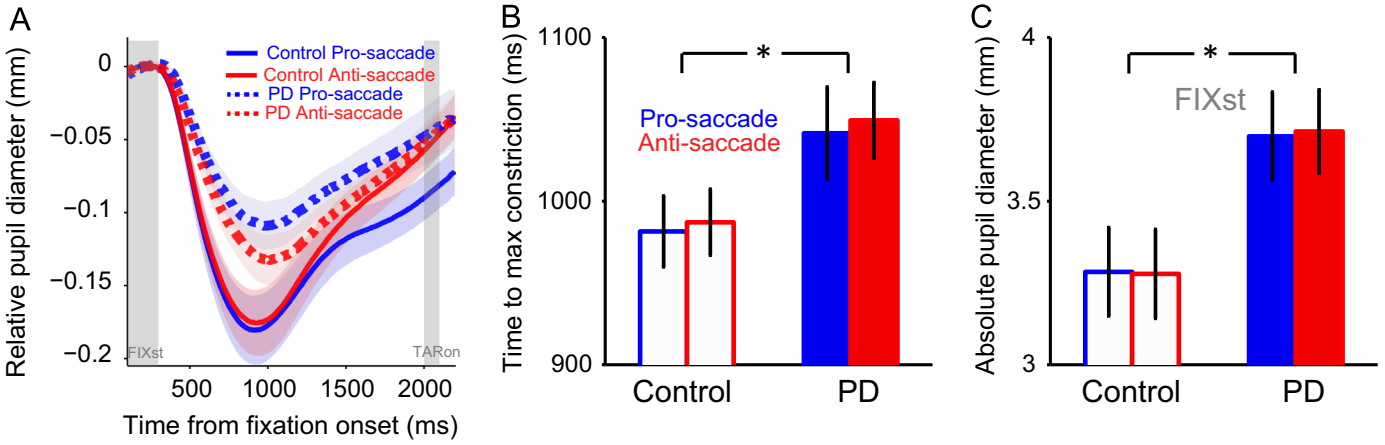

Fig. 3. Pupil size during instructed fixation. (A) relative pupil dynamics between the pro- and anti-saccade condition in patients with Parkinson's disease ($n=19$) and controls ($n=17$). Saccade preparation between patients with Parkinson's disease and controls among trials with correct pro- and anti-saccades on (B) time to max constriction, (C) absolute pupil diameter during the FIX_{on} epoch (150–300 after fixation onset). In A, the shaded colored regions surrounding the pupillary response represent ± standard error range (across participants) for different conditions. The gray area represents the selected epoch for pupil analyses. In B-C, the error-bar represents ± standard error across participants. FIX_{st}: fixation start epoch (150–300 after fixation onset), TAR_{on}: target onset epoch (0–100 after target onset), PD: Parkinson's disease participants, Control: aging control participants, * indicates differences are statistically significant ($P<0.05$).

et al., 2008), we compared between patients and controls using previously established measurements (Fig. 1B, see Methods) to differentiate constriction- from dilation-related processes (Wang et al., 2015).

3.3. Constriction component of pupil responses

PD patients have impairments of pupillary light reflex responses, with reduced constriction size and longer constriction time and latency (Fotiou et al., 2009; Giza et al., 2011, 2012; Micieli et al., 1991; Stergiou et al., 2009). We found that constriction magnitude was reduced in PD patients (constriction size for pro- and anti-saccade trials was 0.21 and 0.21 mm in controls, but only 0.16 and 0.17 mm in PD), although these effects were not significant ($F(1,34)=3.21$, $P=0.08$). The time to maximum constriction was also longer in PD (Fig. 3C: constriction time on correct pro- and anti-saccade trials was 981 and 987 ms in controls, and 1041 and 1049 ms in PD; $F(1,34)=3.92$ $P=0.05$). In addition, absolute pupil diameter at fixation onset (FIX_{st}) was larger in PD (Fig. 3D: diameter on correct pro- and anti-saccade trials was 3.28 and 3.28 mm in controls, and 3.7 and 3.71 mm in PD; $F(1,34)=5.43$, $P<0.05$). Larger absolute pupil diameter could be modulated by prescribed dopaminergic medication (Spiers and Calne, 1969), although the correlation between the dose of levodopa equivalent in PD patients and their absolute pupil diameter was not significant ($R=0.23$, $P=0.34$).

3.4. Dilation component of pupil responses

Pupil dilation is linked to motor preparation (Jainta et al., 2011; Richer et al., 1983; Richer and Beatty, 1985; Wang et al., 2015). To differentiate dilation component from constriction pupil responses, we calculated the dilation size by subtracting pupil size at the time of greatest constriction during fixation from pupil size in the TAR_{on} epoch (Fig. 4A for illustration, see Methods for details). Fig. 4B summarizes pupil dilation magnitude for correct pro- and anti-saccade conditions in controls and in PD patients, illustrating reduced pupil dilation in Parkinson's disease compared to the control group (dilation size in pro- and anti-condition: 0.13 and 0.16 mm for control; 0.11 and 0.12 mm for PD; $F(1,34)=4.61$, $P<0.05$). Most interestingly, there was greater pupil dilation for correct anti- compared to correct pro-saccade preparation in the elderly controls (simple main effects: $F(1,34)=5.82$, $P<0.05$), which is consistent with results from young adults (Wang et al.,

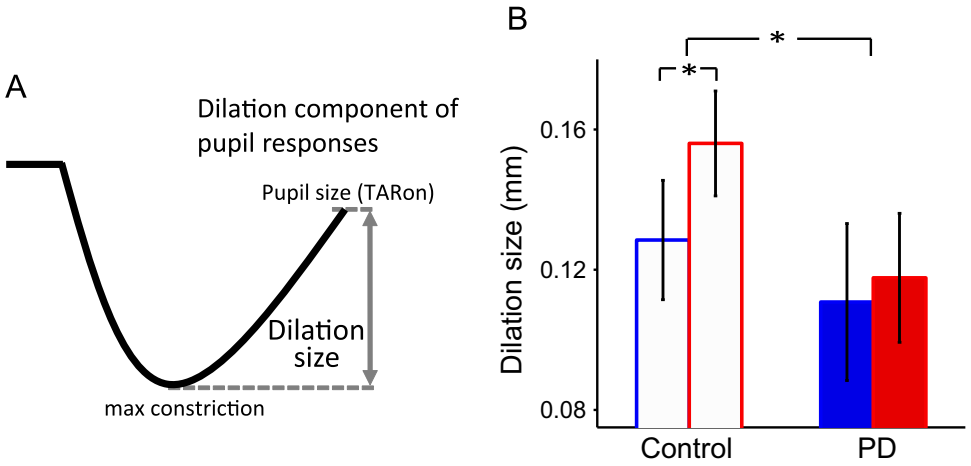

Fig. 4. Effect of saccade preparation on dilation component of pupil responses. (A) illustration of measurement of dilation size. (B)Modulation of saccade preparation between PD patients ($n=19$) and controls ($n=17$) among trials with correct pro- and anti-saccades on dilation size. In B, the error-bar represents ± standard error across participants. TAR_{on}: target onset epoch (0–100 after target onset), PD: Parkinson's disease participants, Control: aging control participants, * indicates differences are statistically significant ($P<0.05$).

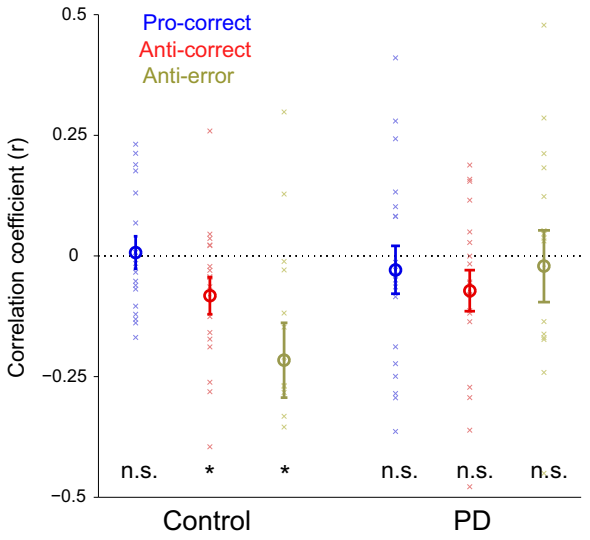

Fig. 5. Correlation between pupil dilation and saccade reaction times. Distribution of correlation coefficients for the relationship between SRT and dilation size for correct pro- and anti-saccades in each participant (control: $n=17$; PD: $n=19$), or for erroneous anti-saccades (control: $n=14$; PD: $n=18$). The vertical colored circles represent the mean value of correlation coefficient across all participants for each condition, and the error-bar represents ± standard error across participants for each condition. The colored X represents correlation coefficient for each participant. The horizontal dotted line represents a zero value of correlation coefficient ($r=0$). PD: Parkinson's disease participants, Control: aging control participants, Pro-correct: correct pro-saccades, Anti-correct: correct anti-saccades, Anti-error: erroneous anti-saccades, * indicates differences are statistically significant ($P<0.05$), n.s.: not statistically significant.

2015), but this modulation was not present in PD patients (simple main effects: $F(1,34)=0.39$, $P>0.5$). All other effects were negligible ($P>0.1$).

Pupil size has been shown to correlate with SRT on correct anti-saccade trials (Wang et al., 2015). If PD patients have deficits in task preparation, this correlation should be diminished. Fig. 5 shows the distribution of the correlation coefficients between dilation magnitude and SRT for each subject. The control participants had significant negative correlations between dilation magnitude and anti-SRT (the mean correlation coefficient: −0.08; paired t test of R values against zeros: $t(16)=-2.2$, $P<0.05$) but no correlation between dilation size and pro-SRT (the mean correlation coefficient: 0.01, $t(16)=0.22$, $P>0.8$). However, the correlation was reduced in PD patients (Fig. 5). Correlation coefficient between dilation magnitude and anti-SRT did not reach significance in PD patients (Fig. 5: mean correlation coefficient: −0.072; $t(18)=-1.7$, $P=0.1$). There was no correlation between dilation size and pro-SRT (mean correlation coefficient: −0.029, $t(18)=0.59$, $P>0.5$). As hypothesized, the correlation between dilation size and correct anti-SRT was intact in age-matched controls, but diminished in PD patients.

3.5. Pupil dynamics during erroneous anti-saccade trials

In young adults, pupil dilation prior to stimulus appearance was reduced when an erroneous pro-saccade was made in the anti-saccade condition (Wang et al., 2015). It is possible that these effects will be eliminated if PD patients have deficits in task preparation. Fig. 6A shows pupil constriction followed by dilation for correct and erroneous trials, and Fig. 6B summarizes pupil dilation magnitude for correct and erroneous anti-saccade trials in controls and in PD patients, showing reduced pupil dilation in PD patients compared to controls (dilation size in anti-correct- and anti-error condition: 0.16 and 0.14 mm in control; 0.11 and 0.10 mm in PD; $F(1,30)=5.21$, $P<0.05$). Importantly, there was larger pupil dilation for correct compared to erroneous anti-saccade preparation in controls (Fig. 6B, simple main effects: $F(1,30)=4.86$, $P<0.05$). However, these effects were greatly attenuated in PD patients (simple main effects: $F(1,30)=1.21$, $P=0.28$). All other effects were negligible ($P>0.1$). The correlational results between dilation size and erroneous anti-SRT also supported this idea, showing negative correlation in age-matched controls (Fig. 5, mean correlation coefficient: –0.22, $t(13)=-2.9$, $P<0.05$), but no correlations were observed in PD patients (Fig. 5, mean correlation coefficient: −0.02, $t(17)=-0.03$, $P>0.7$). These erroneous anti-saccade results suggest that modulation of task preparation on pupil size was disturbed in PD patients. Note that few participants were excluded from erroneous analysis due to insufficient number of trials (see Section 2).

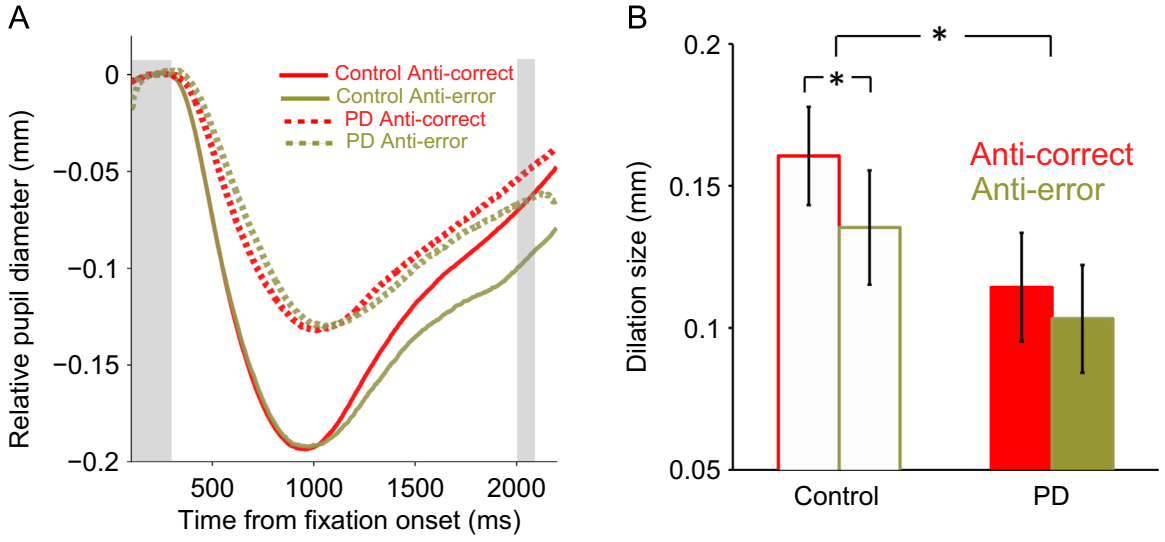

Fig. 6. Pupil size modulation on erroneous anti-saccade trials. (A) relative pupil dynamics between the correct and erroneous anti-saccade trials in PD patients ($n=18$) and controls ($n=14$). (B) dilation size among trials with correct and erroneous anti-saccades. In A, The gray area represents the selected epoch for pupil analyses. In B, the error-bar represents ± standard error across participants. FIX_{st}: fixation start epoch (150–300 after fixation onset), TAR_{on}: target onset epoch (0–100 after stimulus onset), PD: Parkinson's disease participants, Control: aging control participants, Anti-correct: correct anti-saccades, Anti-error: erroneous anti-saccades, * indicates differences are statistically significant ($P<0.05$). n.s.: not statistically significant.

4. Discussion

By combining measurements of pupil size and saccadic behaviors, we demonstrated that pupil responses in the interleaved pro- and anti-saccade paradigm were correlated to saccade preparation. PD patients had disruptions in pupil size modulation during saccade preparation. Contrary to age-matched controls, in PD patients, differences in dilation magnitude were greatly reduced between correct anti- and pro-saccade preparation (Figs. 3 and 4), and the correlation between dilation size and SRT on correct anti-saccade trials was diminished (Fig. 5). Furthermore, differences in dilation size between correct and erroneous anti-saccades were reduced, and the correlation between dilation size and erroneous anti-saccade reaction time was largely disrupted (Fig. 6). Together, our results demonstrate deficits in motor preparation in PD patients, evident by disruptions of pupil size modulation during the instructed fixation period, and suggest that pupil size is an effective index to investigate cognitive impairments in Parkinson's disease.

4.1. Neural substrate linking pupil size and voluntary saccade deficits

A growing number of studies have focused on the cognitive impairments in PD (Leh et al., 2010; Rodriguez-Oroz et al., 2009; Muslimovic et al., 2005). The anti-saccade task has been used to examine executive functions in the oculomotor system, and insights from monkey neurophysiology have suggested two types of preparatory signals involved in saccade preparation that are particularly pronounced in the superior colliculus (SC) and frontal eye fields (FEF) (Munoz and Everling, 2004), essential structures to initiate saccadic eye movements (Schiller et al., 1980). First, fixation-related preparatory activity prior to stimulus appearance is increased during anti- compared to pro-saccade preparation (Everling et al., 1999). It has been argued that this signal is critical for supressing automatic responses on anti-saccade trials. Second, the pre-saccadic activity related to motor preparation increases for saccade neurons, and correlates negatively with SRT (Dorris et al., 1997; Dorris and Munoz, 1998; Everling et al., 1999; Everling and Munoz, 2000).

Similarly, in healthy human fMRI studies, there is higher FEF activation during preparation for anti-saccades compared to pro-saccades, and preparatory activity negatively correlates to SRTs (Alahyane et al., 2014; Connolly et al., 2002, 2005; DeSouza et al., 2003; Manoach et al., 2007). The profile of functional activation is greatly disrupted in PD patients (Cameron et al., 2012). Unlike age-matched controls, they show a similar level of preparatory activity between correct anti- and pro-saccade trials, and poor correlation between FEF preparatory activity and SRT on correct anti-saccades. Moreover, unlike age-matched controls, activation differences between correct and erroneous anti-saccades are greatly reduced.

The SC has recently been linked to pupil control (Wang and Munoz, 2015). Microstimulation of the SC evokes transient pupil dilation (Netser et al., 2010; Wang et al., 2012), and transient pupil responses evoked by SC microstimulation are similar to those evoked by presentation of salient visual and auditory stimuli (Wang and Munoz, 2014; Wang et al., 2014). Because pupil dilation is evoked by SC microstimulation in the areas associated with both fixation- (rostral SC) and saccade-related (caudal SC) processing (Wang et al., 2012), it is possible that pupil size is modulated by both types of preparatory signals. The modulation of pupil size by pro- and anti-saccade preparation was recently demonstrated in healthy young adults (Wang et al., 2015). There was greater pupil dilation in preparation for correct anti-saccades compared to correct pro-saccades, and a negative correlation between the size of pupil dilation and SRT. These results suggest that pupil size is correlated to neural activity related to saccade preparation. Therefore, the dysfunction in preparatory networks in PD should predictively alter their pupil responses.

Correspondingly, PD pupil responses reflected impairments in task preparation. First, unlike age-matched controls, size differences in pupil dilation prior to saccade initiation between correct anti- compared to correct pro-saccade were greatly diminished (Fig. 4B). Second, the correlation between dilation size and SRTs on correct anti-saccades was reduced (Fig. 5). Third, differences in pupil dilation between correct and erroneous anti-saccades were absent (Figs. 5 and 6B). Additionally, PD patients display reduced brain activation in an interleaved pro- and anti-saccade paradigm (Cameron et al., 2012), and consistently, we found reduced dilation size (Figs. 4B and 6B). Overall, the pupil results presented here are consistent with previous fMRI results, demonstrating pronounced impairments on preparation for voluntary movements in PD patients.

4.2. Other pathways influencing pupil size in Parkinson's disease

Although motor symptoms caused by the degeneration of dopaminergic neurons in the substantia nigra are the diagnostic focus of Parkinson's disease, some pre-clinical features associated with other pathological events occur in a prodromal period and ensuring PD diagnosis (Hawkes et al., 2010). The significant loss of noradrenergic and dopaminergic neurons in the locus coeruleus has been characterized in PD (Cash et al., 1987; Zarow et al., 2003), and one recent study has shown an important role of noradrenergic dysfunction in cognition in PD (Kehagia et al., 2014). The locus coeruleus is importantly involved in the control of pupil size, arguably via arousal mechanisms (Aston-Jones and Cohen, 2005; Sara and Bouret, 2012). Therefore, the disruptions in pupil size modulation observed in the current study could also be associated to dysfunctions in the locus coeruleus. Moreover, because the SC also receives inputs from the locus coeruleus (Wang and Munoz, 2015), it is also possible that the abnormality in pupil size modulation in PD may be mediated through the locus coeruleus connections to the SC and frontal cortex. Future research is required to address this question.

4.3. Relationship between processing load and pupil dilation

Pupil size has been linked to processing load, and previous studies have shown that increased processing demands on cognitive tasks correlate with increased pupil diameter (e.g., Beatty, 1982; Granholm et al., 1996; Verney et al., 2001). According to this hypothesis, because task difficulty is higher in the anti-saccade condition, pupil dilation on anti-saccade trials should be larger, compared to pro-saccade trials. If pupil size is correlated with processing load, it can be argued that availability of more processing resources are correlated to larger pupil size. Therefore, insufficient processing resources, as revealed with smaller pupil size should result in erroneous saccades, inferring smaller pupil dilation on erroneous, compared to correct trails in the anti-saccade condition. In contrast, more processing resources revealed with larger pupil size should result in faster SRT on correct trials, a negative correlation between pupil dilation and correct anti-SRT. However, this idea is hard to explain the same modulation of pupil dilation by ensuing SRTs on “erroneous” anti-saccade trials (Figs. 5 and 6). Specifically, if pupil size is correlated to the level of processing resources, better preparation (among anti-error trials) revealed by larger pupil size should result in slower anti-error SRTs (even pupil size was generally smaller on error trials). However, the same effects of SRT, larger pupil dilation observed with faster SRTs, were demonstrated in both correct and erroneous anti-saccades, suggesting that the observed pupil size differences cannot simply explain by processing load hypothesis.

4.4. Integrating pupil size and saccadic eye movements in clinical investigation

Saccadic eye movements have been used as an effective biomarker to examine various diseases using different behavioral paradigms. In PD, a bulk of results have demonstrated saccade deficits in the anti-saccade task, showing more direction errors and longer reaction times in the anti-saccade condition, compared to control participants (Amador et al., 2006; Briand et al., 1999; Cameron et al., 2010, 2012; Chan et al., 2005; Hood et al., 2007; Rivaud-Pechoux et al., 2000, 2007). However, because preparatory processes cannot be observed from only eye movement recording before saccade initiation, these saccade-related behavioral impairments could be the result of deficits in the execution rather than preparation of correct anti-saccades. Measures of pupil size provide an online assessment of preparatory processes prior to saccade initiation, implicating the correlation between voluntary saccade deficits and movement preparation.

Pupil size is regulated by an integral activity between the sympathetic and parasympathetic pathways (Loewenfeld, 1999). It has been used as an effective evaluation of function in the autonomic nervous system that, unlike the oculomotor system, acts largely unconsciously (Bremner, 2009). Many disorders are associated to dysfunction of the autonomic system (Mathias and Bannister, 2013). The combination of pupil size and saccadic eye movements in behavioral paradigms provides a possibility to index both cognitive and autonomic functions, potentially producing more effective biomarkers for various diseases in clinical investigation. One study has combined measurements of pupil size and eye movements to examine emotional processing in PD, highlighting the possibility of this approach (Dietz et al., 2011).

5. Conclusion

The anti-saccade task has been used extensively to investigate voluntary control of executive functions in healthy as well as in clinical populations (Hutton and Ettinger, 2006; Munoz et al., 1998; Munoz and Everling, 2004; Everling and Fischer, 1998). Pupil size, an easy-to-measure technique and freely available to most modern video-based eye tracking systems, has long been used as an effective indicator of cognitive and neural processing (Beatty, 1982; Hess and Polt, 1960; Hess and Polt, 1964; Kahneman and Beatty, 1966; Kahneman et al., 1967). In the current study, the anti-saccade paradigm with pupil size measurements was used, showing the disrupted modulation of pupil size by voluntary saccade preparation in PD patients, and these results highlight the promised potential of using this low-cost approach to help identify cognitive impairment in early Parkinson's disease.

Acknowledgment

We thank Ann Lablans, Sean Hickman, and Mike Lewis for outstanding technical assistance, as well as members of the Munoz lab for comments on an earlier version. This work was supported by Canadian Institutes of Health Research Grant (MOP-97741 and MOP-136972). D.P.M. was supported by the Canada Research Chair Program.

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