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

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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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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						