Pupil light reflex in Parkinson’s disease patients with and without freezing of gait symptoms

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Abstract:
PURPOSE: Freezing of gait (FOG) is considered as a motor disorder that affects some Parkinson’s disease (PD) patients; however, sensory systems may also be involved in FOG. The pupil light reflex (PLR) is a reliable measure of the autonomic nervous system. Different dilation and constriction pupil parameters may be used to investigate the integrity of the autonomic nervous system in PD patients with and without FOG symptoms. This study aimed to look at the integrity of autonomic nervous system and to investigate the nonmotor functions mediated by the cholinergic system in Parkinson’s patients with and without FOG symptoms.

METHODS: Constriction and dilation pupil light reflexes were measured by using a handheld pupillometer. Twenty-two patients with FOG symptoms, 25 patients without FOG symptoms, and 25 aged‑matched healthy controls participated in this study.

RESULTS: The results showed that most of the constriction parameters and dilation latency of both patient groups differed significantly from healthy controls. FOG patients showed larger pupil size under light condition and larger deficits in constriction latency than nonFOG patients. Both the groups of PD patients had longer dilation latencies than healthy controls.

CONCLUSION: This study suggests that the cholinergic autonomic nervous system is affected in PD patients more than the adrenergic system. FOG patients had larger impairments in nondopaminergic mediated functions such as pupil light reflexes, which suggests that FOG patients have greater impairment in functions that involve cholinergic neurotransmitters.

Keywords: Autonomic nervous system, freezing of gait, nonmotor, Parkinson’s disease, pupil light reflex, sensory

INTRODUCTION
Parkinson’s disease (PD) is usually described as a motor disorder disease that affects the central and peripheral nervous systems. Patients with PD are characterized by having body motor dysfunctions such as bradykinesia, muscle rigidity, resting tremor, and postural instability. The main cause of the PD motor disorders is believed to be due to reduction of the dopamine neurotransmitter through cell death within the basal ganglia complex in midbrain.¹⁻⁴

PD patients are also characterized by nonmotor symptoms and signs that are believed to be due to cholinergic system dysfunctions. Deficits in the cortical cholinergic systems are linked to learning and executive functions. Calabresi et al.⁵ hypothesize that some of the cognitive deficits in PD patients are due to a combination of dopamine and acetylcholine depletion because an increase in dopamine is not sufficient to affect certain cognitive performance, and acetylcholinesterase inhibitors are useful in the treatment of dementia associated with PD. They further hypothesized that at the cellular level, dopamine and acetylcholine interact to produce the synaptic changes associated with learning and memory.⁵ This interaction is altered in PD and so these patients experience problems with working memory and learning tasks. Given these findings, it is not surprising that different
sensory and cognitive functions are impaired along with motor functions in PD,

Within the autonomic nervous system, acetylcholine
dysfunctions include problems in cardiovascular, sexual and
urinary gastrointestinal, respiratory, and thermoregulation
systems. In the visual system, different parameters of pupil
light reflex (PLR) are affected in PD patients. Previous
studies showed that the constriction latency, amplitude
of constriction, maximum constriction velocity (MCV),
and maximum constriction acceleration are affected in PD
patients. These studies suggest that a dopamine deficiency
in the retina or cortex is not responsible for the changes
in the different pupillometric parameters because there
was no correlation with any other motor symptoms of the
disease. Furthermore, there are more PLR parameters
affected in cognitive impaired PD patients than those patients
who have normal cognitive function. PLR parameters of
cognitive impaired PD patients were similar to the pupil
dysfunction reported in Alzheimer’s disease patients. This
suggests that both the groups of patients have the same
central cholinergic (parasympathetic) deficit in the acetylcholinergic
pathways in the frontal lobe.

Freezing of gait (FOG) is one of the motor disturbances
associated with PD disease. It is defined as discontinuous
or interrupted episodes of inability to produce or maintain a
forward movement or to make a turn. The episodes usually
last a few seconds. Although FOG is considered classically
as motor dysfunction in PD patients, it is now hypothesized
that impairment of different nonmotor systems may contribute
to FOG.

Amboni et al. reported that FOG and its severity are associated
with frontal cognitive dysfunction and the severity of the
frontal cognitive dysfunction, respectively. It is possible that
these frontal lobe dysfunctions are a result of an acetylcholine
deficit. Furthermore, the deficit in this neurotransmitter may
be throughout the central nervous system and so patients who
experience gait freezing may show a greater impairment of
parasympathetic function (e.g., PLR) than those PD patients
who do not experience gait freezing. Since there are no
comparisons between FOG PD and non-FOG PD patients
using PLR parameters, to our knowledge, we measured various
PRL parameters to determine whether FOG PD patients have
a more generalized cholinergic deficit, or a deficit in both the
parasympathetic and sympathetic systems innervating the eye.

**Methods**

**Participants**

PD patients and healthy controls were recruited from the
Sun Life Financial Movement Disorders Research
and Rehabilitation Center, Wilfrid Laurier University
(Waterloo, ON) database. The subjects gave informed written
consent before participating. The study followed the tenets
of the Declaration of Helsinki.

The subject groups were as follows:

1. On-medication FOG and non-FOG PD subjects.
   All subjects met the criteria of PD according to the
   MDS-UPDRS scale system. Patients with other
   neurological disorders, brain lesions, or concussions
   were excluded. FOG versus non-FOG subjects were
determined based on the FOG questionnaire for PD
   patients.

2. Age-matched healthy control group. Subjects free from
   any neurological disorders, brain damage history, positive
   history of PD, or concussions.

The exclusion criteria for all participants were a history of
diabetes, nystagmus, strabismus, and corrected visual acuity
worse than 20/30 at distance or near in either eye. The severity
of the disease and the freezing vs. non-freezing patients were
determined first by a qualified examiner according to MDS-
UPDRS scaling system. The cognitive functions of patients
and healthy controls were measured according to The Montreal
Cognitive Assessment Test (MoCA). Twenty-two FOG PD
patients, 25 non-FOG PD patients, and 25 healthy controls
participated in this study.

Table 1 shows the mean values (mean ± 1 standard deviation)
of different demographic characteristics of the participants
and whether the differences were significant between groups.

**Procedures**

The PLRs parameters were measured using a NeurOptics
PLR™ 3000 Pupillometer (NeurOptics, Inc. Irvine, CA, USA).
The PLR-3000 is a handheld monocular pupillometer that can
measure both pupil constriction and pupil dilation parameters.
PLR-3000 records the pupil size using an infrared camera (32
frames/sec) and can measure the pupil size to within ±0.03 mm.

To measure the pupil constriction parameters, bright stimuli
flash against a dark background. To measure pupil dilation
parameters, the subjects adapt to a steady light and then it
is extinguished for a brief period. Table 2 lists all stimuli
characteristics used in this study for the constriction and
dilation conditions.

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**Table 1: Means and standard deviations of the subjects’ demographics**

| Groups                        | FOG          | Non-FOG       | Healthy controls | The differences (P) |
|-------------------------------|--------------|---------------|------------------|---------------------|
| Sample size (n) (male/female) | 22 (14/8)    | 25 (19/6)     | 25 (8/17)        | NA                  |
| Age (%)                       | 72.3 (6.9)   | 67.5 (9.4)    | 70.43 (7.67)     | 0.059               |
| Cognitive MoCA score (%)      | 24.95 (4.27) | 25.76 (2.18)  | 26.48 (2.16)     | 0.221               |
| Severity UPDRS score (%)      | 22.41 (7.94) | 19.96 (9.58)  | NA               | 0.349               |
| Duration of the disease       | 10.52 (6.6)  | 8.09 (6.35)   | NA               | 0.203               |

FOG=Freezing of gait; MoCA=Montreal cognitive assessment; UPDRS=Unified Parkinson’s Disease Rating Scale; NA=Not applicable
**Table 2: Stimuli characteristics used to measure pupil light reflexes**

| Protocol | Constriction condition | Dilation condition |
|----------|------------------------|-------------------|
| Definition | Stimuli brighter than background | Stimuli dimmer than the background |
| Stimulus intensity (uW) | 50 | 0 |
| Background intensity (uW) | 0 | 50 |
| Measurement duration (s) | 5 | 5 |
| Stimulus duration (s) | 0.07 | 1.07 |

**Table 3: Pupil light reflex parameters for the constriction and dilation measurements**

| Parameter | Definition | Unit |
|-----------|------------|------|
| Init | Initial dark-adapted pupil size before constriction | mm |
| End | Pupil diameter at maximum of constriction | mm |
| Constriction (%) | Init-end/Init | Percentage |
| LAT-C | Time to onset of constriction | ms |
| ACV | The average speed of the pupil constriction | mm/s |
| MCV | The maximum speed of the pupil constriction | mm/s |
| Re-ADV | The average speed of the pupillary re-dilation after the pupil has reached the peak of constriction | mm/s |
| 75% recovery time (T75%) | The time to reach 75% of the original baseline pupil diameter after the peak of the constriction | s |
| Init | Initial light adapted pupil size before dilation | mm |
| End | Pupil diameter at peak of dilation | mm |
| Dilation (%) | (Init-end)/Init | Percentage |
| LAT-D | Time to onset of dilation | ms |
| ADV | The average speed of the pupil dilation | mm/s |

LAT-C=Latency of constriction; ACV=Average constriction velocity; MCV=Maximum constriction velocity; LAT-D=Latency of dilation; ADV=Average dilation velocity; Re-ADV=Re-ADV; Init=Initial diameter; End=End diameter

Differences between groups were examined using one-way analysis of variance (ANOVA) with Tukey’s post hoc tests to examine all pairwise comparisons between groups. The second analysis examined the associations between different PLRs and the severity, duration, and MoCA scores in PD patients by calculating the Pearson correlation coefficients. IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. was used for this data analysis. The criterion of $P < 0.05$ was used to determine statistical significance.

**Results**

**Constriction pupil light reflex**

Figure 1 shows representative data of the pupil diameter as a function of time after the eye was stimulated with the white light pulse. Table 4 shows means and standard error of the means of different constriction parameters. Table 5 shows the ANOVA results and the pairwise multiple comparisons between groups for those parameters that showed a significant group effect. There was a significant group effect for all the constriction parameters, except the minimum diameter (End) ($F = 2.193, DF = 2, 69, P = 0.119$), and the re-dilation velocity (re-ADV) ($F = 2.112, DF = 2, 69, P = 0.129$). Pairwise comparisons showed, however, that the group effect was primarily due to the differences between the one, or both, of the PD groups and the HC for most parameters. The only significant difference between the FOG and non-FOG PD was the constriction latency (LAT-C), and T 75%.

**Dilation pupil light reflex**

Figure 2 shows representative data of the pupil diameter as a function of time after the light was extinguished for 1.03 s. Table 6 lists the means and standard error of the means of different pupil dilation parameters for all groups. One-way ANOVA showed that the differences between groups were statistically significant for all dilation PLR parameters except the dilation percentage of change (Dia %) ($F = 1.757, DF = 2, 69, P = 0.180$) and the dilation velocity (ADV) ($F = 1.82$, $P = 0.180$) and the re-dilation velocity (re-ADV) ($F = 1.82$, $P = 0.119$). Pairwise comparisons showed, however, that the group effect was primarily due to the differences between the one, or both, of the PD groups and the HC for most parameters. The only significant difference between the FOG and non-FOG PD was the re-dilation velocity (re-ADV) ($F = 2.112, DF = 2, 69, P = 0.129$). Pairwise comparisons showed, however, that the group effect was primarily due to the differences between the one, or both, of the PD groups and the HC for most parameters. The only significant difference between the FOG and non-FOG PD was the constriction latency (LAT-C), and T 75%.
DF = 2, 69, \( P = 0.169 \). Table 7 shows the results and the pairwise multiple comparisons between groups for those parameters who showed significant differences between groups.

### Discussion

Nonmotor symptoms due to ANS dysfunctions have been reported in PD patients.\(^{20}\) Both sympathetic and parasympathetic branches of ANS are known to be affected.\(^{21}\) Measuring the pupil size under light and dark conditions and measuring different PLR parameters is a relatively easy and noninvasive technique to evaluate the integrity of the ANS sympathetic and parasympathetic pathways.\(^{22}\)

The main objectives of this study were to examine both constriction and dilation parameters of the PLR to determine whether the cholinergic mediated (parasympathetic) and adrenergic mediated (sympathetic) ANS were differentially affected in FOG PD and non-FOG patients. In addition,
the previous clinical results might help disentangle the afferent (sensory) PLR versus efferent (motor) PLR pathways. This information would help us to determine whether the problem originates in the retina or in the central nervous system.

Most of constriction parameters and dilation latency among dilation parameters were significantly different for one or both of PD patient groups compared with healthy controls. Our results were in agreement with previous findings for those common constriction parameters.\[11,12\] Others have reported that dopaminergic treatment has no effect on different PLR parameters.\[23\]

Multinomial logistic regressions were conducted for all constriction and dilation PLR parameters separately to determine the best discriminant parameters between groups. The results showed that the final logit regression models adequately fit our data for the constriction parameters (Chi-square test = 96.961, DF = 18, P < 0.0001), and for the dilation parameters (Chi-square test = 27.684, DF = 12, P = 0.006). Table 8 shows the rank order of different PLR parameters that can best discriminate different subject groups. Except the constriction percentages, the average constriction velocity, and MCV, the other constriction parameters were good discriminators between groups. Dilation latency was the only parameter that could discriminate between groups among dilation parameters. These findings suggest that both parasympathetic and sympathetic ANS pathways were affected in PD patients compared with healthy controls, and the parasympathetic ANS pathway is more affected than the sympathetic ANS pathway in PD patients.

Previous studies showed that MCV and maximum constriction acceleration were the best discriminants among PLR constriction parameters between PD patients and healthy controls.\[11,13,14,24\] Several reasons could explain different findings of our study compared with the previous studies. First, the temporal resolution of the pupillometric systems was different. The pupillometer in this study had a frame rate of 32 frames per second, whereas the other pupillometric systems were much faster with a frame rate of 263 frames per second.

Second, different studies used different experimental conditions and different stimulus light intensities. We used 50 mW as the stimulus intensity in this study. It could be that this light level was not sufficient to show PLR dysfunctions among some PD patients. Different stimulus intensities can change different

![Figure 2](image)

**Figure 2:** Pupil size response to light stimulus as a function of time in three different participants representing the three subject groups. The two yellow lines show where the stimulus started and ended, the black vertical line shows the dilation latency. (a) Freezing of gait Parkinson’s disease patient, (b) non-Freezing of gait Parkinson’s disease patient, (c) Healthy control subjects.
Table 6: Means, standard deviations, and standard error means for different dilation pupil light reflexes for all groups

| Group      | Initial (mm) | End (mm) | Amount-dilation (mm) | Dilation (%) | LAT-D (ms) | ADV (mm/s) |
|------------|--------------|----------|----------------------|--------------|------------|------------|
| FOG (n=22) | 2.90         | 3.43     | 0.53                 | 19.25        | 0.40       | 0.87       |
| Mean       | 0.09         | 0.11     | 0.028                | 0.92         | 0.016      | 0.036      |
| SEM        |              |          |                      |              |            |            |
| Non-FOG (n=25) | 2.54     | 2.96     | 0.41                 | 16.81        | 0.39       | 0.74       |
| Mean       | 0.093        | 0.10     | 0.03                 | 1.15         | 0.010      | 0.054      |
| SEM        | 0.06         | 0.09     | 0.03                 | 1.20         | 0.013      | 0.05       |
| HC (n=25)  | 2.53         | 3.02     | 0.48                 | 19.43        | 0.34       | 0.80       |
| Mean       | 0.06         | 0.09     | 0.03                 | 1.20         | 0.013      | 0.05       |
| SEM        |              |          |                      |              |            |            |

Init=Initial diameter; End=End diameter; LAT-D=Latency of dilation; ADV=Average dilation velocity; FOG=Freezing of gait; HC=Healthy controls; SEM=Standard error of mean

Table 7: One way ANOVA tests of dilation pupil light reflexes between groups

| Test        | ANOVA | DF   | P    | Pairwise multiple comparisons (P) |
|-------------|-------|------|------|----------------------------------|
| Init        | 5.517 | 2.69 | 0.006| FOG 0.014*                        |
|             |       |      |      | Non-FOG 0.013*                    |
|             |       |      |      | HC 0.99                           |
| End         | 6.049 | 2.69 | 0.004| FOG 0.05*                         |
|             |       |      |      | Non-FOG 0.018*                    |
|             |       |      |      | HC 0.89                           |
| Amount-dilation | 3.83  | 2.69 | 0.027| FOG 0.021*                        |
|             |       |      |      | Non-FOG 0.56                      |
|             |       |      |      | HC 0.233                          |
| LAT-D       | 5.24  | 2.69 | 0.008| FOG 0.75                          |
|             |       |      |      | Non-FOG 0.009*                    |
|             |       |      |      | HC 0.048*                         |

*Differences between groups is significant at 0.05 significant level. HC=Healthy controls; FOG=Freezing of gait; Init=Initial diameter; End=End diameter; LAT-D=Latency of dilation

FOG PD initial pupil size under light conditions suggests that FOG PD group had a larger sensory deficit due to lower retinal inputs. Although a larger pupil size under light suggests sensory deficits, it has been suggested that larger pupil size under light conditions reflects dysfunctions in the parasympathetic (cholinergic) nervous system due to an acetylcholine (ACh) reduction.[31,32] However, this parameter is not considered as a strong indicator of the cholinergic system dysfunction.[24]

A third parameter that is known to reflect the retinal contribution to PLR is the amount of constriction.[13,24,29] Both PD patient groups had a lower amount of constriction compared with healthy controls, which suggests that either their retinal function or optic nerve function was impaired. Constriction latency (LAT-C) is the fourth indicator of the sensory inputs to the pupil responses.[33-35] This parameter was shown to be one of the strongest discriminators between groups among the constriction parameters.

The longer constriction latency (LAT-C) that was found in FOG subjects could be due to deficits in sensory retinal functions. Supporting this evidence is the results from a study by Salter et al.[30] They measured constriction PLR parameters using the same device in multiple sclerosis (MS) patients with optical neuritis. Their MS patients had reduced high contrast visual acuity, low contrast visual acuity and contrast sensitivity. In addition, all constriction parameters were found to be significantly affected in MS patients compared with the healthy controls. Moreover, the reduction in constriction percentage, average constriction velocity, and MCV along with the increase in constriction latency found in the MS group was comparable to the changes found in our PD patients results. They also reported that thinning in different retinal layers including total macular volume due to optic neuritis could predict the deficits in different constriction PLR parameters. Lagreze and Kardon also found a correlation between the estimated ganglion cell loss and the relative afferent pupillary defect in optic neuritis.[33]

In his review, Simao summarized a number of studies reporting a thinning of the retinal nerve fiber in similar regions of the eye in PD patients.[38] It is possible that this retinal deficit underlies the deficits in pupil function. Nevertheless, he pointed out that the amount of thinning was not correlated with visual function or duration of the disease and so more study about the proposed linkage is required.
Retinal inputs to PLR response are a combination of the signals originating at the rods and cones and the intrinsic response of the intrinsically photosensitive retinal ganglion cells (ipRGCs), which project to the pretectum. Although the role of the ipRGCs in the PLR response is still being studied, it appears that these cells play a major role in maintaining the steady-state size of the pupil. There is evidence that ipRGCs may be damaged in open-angle glaucoma (ONG). The differences between red and blue postillumination pupil responses were reduced in patients with ONG relative to controls. A smaller difference between the postillumination responses is believed to indicate damage to ipRGCs. The input into the ipRGCs includes dopaminergic amacrine cells and so it is possible that the larger mean pupil size under light adaptation found in the FOG-PD arises from reduced dopaminergic inputs into these cells in addition to reduced input from the photoreceptor pathways.

Nevertheless, we cannot completely rule out a motor pathway dysfunction. A lack of correlation between the PRL and VEP latencies was also reported in MS patients when the disease was inactive. A study was done on rats found that the number of retinal photoreceptors does not predict the PLRs, which suggests the PLR is not a good indicator of the integrity of retinal photoreceptor cells. Although none of these findings exclude the possibility that the ganglion cells to the pretectum are affected differentially relative to the cells projecting to the LGN, it does raise the question as to whether there is also a motor dysfunction.

The result that the initial pupil size under dark adaptation was smaller in the non-FOG PD group suggests a motor deficit in this group of PD patients. A smaller pupil size in darkness is a sign of either increase in parasympathetic influence or reduction in sympathetic input.

Nevertheless, this imbalance was not evident in the minimum pupil size during constriction or the during the light-adapted state before the dilation was measured, which suggests that the result could be due to other factors such as attention or general arousal level. As to why these levels would be different in the non-FOG subjects is uncertain.

The MCV was slower in the two PD groups, which suggests a parasympathetic deficit. However, previous studies have shown that there is a positive and significant relationship between pupil response velocities with the amplitude size change. This means that if constriction amplitude is lower for a certain disease patient, then it is expected that their constriction velocity is slower and there is no new information gained by looking at each parameter. There was a positive and significant relationship between pupil constriction velocities and the amplitude size change and both PD groups also had significantly smaller constriction amplitudes. Linear regression results of MCV versus amplitude of constriction were significant \( r \geq 0.818, P > 0.001 \) for all subject groups.

Scatterplots of these relationships are shown in Figure 3 for all subject groups. All groups showed the expected strong and significant relationships between MCV and constriction amplitude. The FOG PD group has a flatter slope for pupil constriction than the other two groups. The results should be interpreted cautiously because these data are across subjects and not within, but it suggests that the subjects in the FOG

| Test | \( \chi^2 \) | DF | \( P \) |
|------|----------|----|-----|
| Intercept | 0.276 | 2 | 0.871 |
| Re-ADV | 20.332 | 2 | 0.000* |
| LAT-C | 15.413 | 2 | 0.000* |
| Amount of Constriction | 13.754 | 2 | 0.001* |
| End | 12.088 | 2 | 0.002* |
| Init | 11.732 | 2 | 0.003* |
| T 75% recovery | 10.349 | 2 | 0.006* |
| Constriction (%) | 3.912 | 2 | 0.141 |
| MCV | 3.658 | 2 | 0.161 |
| ACV | 2.182 | 2 | 0.336 |
| Intercept | 5.289 | 2 | 0.071 |
| LAT-D | 7.648 | 2 | 0.022* |
| Amount of dilation | 3.803 | 2 | 0.149 |
| Init | 3.225 | 2 | 0.199 |
| End | 3.181 | 2 | 0.204 |
| ADV | 0.904 | 2 | 0.636 |
| Dilatation (%) | 0.040 | 2 | 0.980 |

*The parameter shows a significant effect between groups. ADV=Average dilation velocity; Re-ADV=Re-ADV; LAT-D=Latency of dilation; Init=Initial diameter; End=End diameter; ACV=Average constriction velocity; MCV=Maximum constriction velocity; ADV=Average dilation velocity; Init=Initial diameter; End=End diameter

Figure 3: Scatter plots of pupil maximum constriction velocity as a function amplitude of pupil constriction for the subject groups

Table 8: The rank order of different pupil light reflex parameters that can discriminate groups
PD group who had a relatively large amplitude of constriction had the slower pupil velocity response. This could indicate a deficit in the parasympathetic motor pathway. The difference in slopes between the groups suggests that measuring the PRL reflexes as a function of light level may help to determine to separate the sensory deficit from any motor deficit.

It may not possible to exclude the motor contribution to the results of constriction latency (LAT-C). Comparisons between FOG and non-FOG PD patient groups regarding this parameter showed FOG PD group had significant LAT compared to non-FOG PD group. The LAT could suggest deficits in either afferent (sensory) or efferent (motor) parasympathetic pathway of ANS. However, constriction latency is not considered as good as MCV to represent the cholinergic (motor) mediated pathway of ANS.[24,34]

Delay in T75% recovery time and slower re-dilation velocity were considered to be strong indicators of motor impairment in the sympathetic pathway of ANS due to adrenergic reduction.[31,34] Unexpectedly, both PD patient groups showed faster recovery time (T75%) and faster re-dilation velocity after pupil constriction (re-ADV) compared to healthy controls, with FOG PD group being faster than non-FOG PD group on these two parameters. Faster T75% and re-ADV that were shown in PD patients could be secondary to less constriction percentages (Con %) that were shown among PD patients compared to healthy controls. That means because both PD patient groups constricted less than healthy controls, then it was expected that their re-dilation recovery time and velocity would be faster. This finding suggests two things. First, both PD patient groups have no obvious motor impairment in the sympathetic pathway of ANS compared to healthy controls. Second, faster T75% and re-ADV in PD patient groups are secondary effects to motor impairment in the parasympathetic pathway of ANS. However, the results of constriction latency (LAT-C) showed that both PD patient groups had significant delay compared to healthy controls. Furthermore, the amount of dilation of non-FOG PD patients was less than the other two groups which still it may not possible to exclude the potential impairment of sympathetic pathway of ANS among PD patients. Similar to our results, it has been found that PD patients had faster but not significant 50% re-dilation recovery time than healthy controls.[49]

Cognitively impaired PD patients have been shown to have more constriction PLR deficits than those patients who have normal cognitive functions (Stergiou et al.). The deficits in the cognitive impaired PD patients were similar to the pupil dysfunction reported in Alzheimer’s disease patients. This suggests that both groups of patients have the same central cholinergic deficit.[14] It has been shown that FOG and FOG severity are associated with frontal cognitive dysfunction and frontal cognitive dysfunction severity, respectively.[10] Cognitive impairment could be due to degeneration of subcortical regions such as locus coeruleus (LC) in the brain stem. This area is known to be affected in PD and Alzheimer’s disease patients.[30]

It is possible that the PLR deficits are due to alterations in the brain stem rather than more centrally or in the peripheral pathways. The LC in the brain stem is one possible site. Pupil size is a good indicator of activity in the LC.[51,52] Rapid changes in the release of acetylcholine (ACh) and adrenaline (NE) occur due to variation activity in LC. The LC activity changes the pupil responses.[53] Since FOG PD patients showed larger impairments on some of sympathetic and parasympathetic PLR parameters, it is possible that adrenergic and cholinergic systems are impaired in FOG PD patients to a greater extent than non-FOG PD patients due to abnormal activities in LC or other autonomic cortical centers.

Although the results confirmed that the PLR was affected in PD, we could not rule out that many of these deficits were due to degraded sensory input from the retina. The general trend in the results was that the deficits reflect a deficit in the parasympathetic pathway, but there are also data suggesting a sympathetic deficit. It is possible that measuring the PRL for different light levels may provide a better understanding of the pupil deficits in PD.

**Conclusion**

Both PD patient groups had pupillary light reflex parameter abnormalities. It was difficult to determine whether the abnormalities were due to impaired sensory input or deficits in the parasympathetic motor input. Nevertheless, the FOG-PD group had larger differences for the parameters that were likely due to sensory impairment, whereas parameters that were likely due to motor deficits were equally affected in both PD groups. There was also evidence that the pupillary sympathetic pathway was affected in PD.

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**Conflicts of interest**

There are no conflicts of interest.

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