

## Clinical implications of photophobia in progressive supranuclear palsy

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### ABSTRACT

**Objective:** To determine the impact of photophobia on persons with Progressive Supranuclear Palsy (pwPSP) by determining the functional impact of light sensitivity using methods established in migraine research.

**Methods:** All 60 participants (pwPSP = 15, persons with Parkinson Disease (pwPD) = 15, Older adults = 30) completed a series of questionnaires designed to assess the impact of photophobia on activities of daily living. Group comparisons were controlled for multiple comparisons using a false discovery rate of 0.05.

**Results:** Most (14/15) pwPSP participants noted that bright light hurt their eyes, and this proportion was significantly greater than pwPD (6/15;  $p = 0.03$ , corrected). PSP participants reported statistically significantly more severe light sensitivity on a subjective 0–100 scale ( $p = 0.003$ , corrected), and noted reduced time spent in both indoor and outdoor activities. Some PSP participants ( $n = 3$ ) noted that they needed to wear sunglasses indoors, but most noted a reluctance to leave their house during the day due to photophobia. PwPSP indicated that they require more help from others to complete daily tasks that require them to be outside during daylight hours.

**Conclusions:** Overall, we note a significant debility due to photophobia in PSP, and this impacts outdoor more than indoor activities. The functional disability in PSP caused by photophobia appears to cause a substantive reduction in quality of life. Future studies could consider incorporating specific metrics to evaluate measurable differences with photophobia onset and worsening severity.

### 1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder with clinical features that include postural instability with frequent falls, bulbar palsy, truncal rigidity, progressive cognitive impairment and changes to eye movements, primarily in the form of vertical supranuclear palsy. Photophobia, which is described by patients as an acute sensitivity to light that can be painful in nature, has also been noted as a frequent symptom in PSP. Several studies have noted its presence in PSP cohorts [1], with varying estimates on prevalence. While photophobia is also encountered in other neurodegenerative disorders, it is more common in PSP [2].

Data regarding the degree to which photophobia affects quality of life in PSP patients remains scarce. To date, no studies have examined

patient-reported impacts on daily living from light sensitivity, especially how this may impact participation in indoor and outdoor activities. The objective of this study was to determine the impact of photophobia on persons with PSP (pwPSP) as compared to persons with Parkinson Disease (pwPD). PD was chosen as a control group as it is a neurodegenerative condition that results in a similar progression but does not have a strongly known association with photophobia. To accomplish this, we administered well established assessments of photophobia to cohorts of PwPSP and PwPD which were developed using current literature on photophobia in neurodegenerative disease [1,3] and migraine headaches [4]. This study will show that pwPSP are significantly more likely to report severe photophobia as well as increased limitations to performing outdoor daily activities compared to PwPD.

#### Methods

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Of the 60 participants (N = 30, pwPSP = 15, pwPD = 15), all completed a questionnaire designed to assess how photophobia impacts activities of daily living. These questions were adapted from prior validated surveys assessing the prevalence of photophobia in migraine headaches [1], given the lack of previous studies assessing this symptom specifically in neuro-degenerative disorders. If participants had difficulty communicating, the caregiver would respond. Participants had medical record documentation of a history of PSP or PD. For demographic information, subjects were asked their age, gender, diagnosis, and date of diagnosis (Table 1).

Surveys were collected through REDCap, a secure online web application used to design surveys and store data [5]. Participants were first asked “does bright light hurt your eyes?”, then asked to indicate this symptom has worsened since disease diagnosis. Severity of symptoms were rated on a scale of 0 (not severe) to 100 (the most severe you can imagine). Participants were also asked if they feel “an uncomfortable sense of glare or dazzle in their eyes from bright lights,” and “if flickering lights, glare, specific colors, or high contrast striped patterns bother them or their eyes.” Finally, participants were asked questions surrounding ways they have modified their home and habits, both inside and outside. These questions are outlined in Table 2.

To determine which group has more severe light sensitivity, a one-sided Wilcoxon test was used. Frequency tables with p-values from two-sided fisher exact tests were used to find how many people in each group, PSP or PD, indicated having the symptom. False discovery rate (FDR)-adjusted [6] p-values were reported. A threshold of  $p < 0.05$  was considered statistically significant.

This study was reviewed and approved by the Vanderbilt University Human Research Protection Program Institutional Review Board. Written informed consent was obtained from all participants or guardians of participants in the study.

1.1. Data availability

Data will be made available at the request of other investigators.

2. Results

A total of 30 participants were included: 15 PwPSP (Males = 5, Females = 10, Average Age = 71) and 15 PwPD (Male = 8, Females = 7, Average Age = 65.4).

Table 2 indicates that 14/15 (93%) PwPSP noted that bright light hurt their eyes, whereas only 6/15 (40%) of PwPD (FDR adjusted  $p = 0.03$ ) noted the same. PwPSP reported more severe light sensitivity on a subjective 0–100 scale (average severity of 64, standard deviation of 26) than PwPD (average severity of 33, standard deviation of 26) to a statistically significant degree ( $p = 0.003$ ). The photophobia severity scores for each cohort are compared in Fig. 1. No correlation was noted with photophobia severity and patient age ( $r = 0.34$ ) or disease duration ( $r = 0.35$ ). Participants were also asked if they feel an uncomfortable sense of glare or dazzle in their eyes from bright lights – 13/15 (87%) of PwPSP indicated yes, while only noted by 8/15 (53%) of PwPD (FDR adjusted  $p = 0.11$ ). There was no significant difference in the effect of flickering lights, glare, specific colors, or high contrast striped patterns – 6/15

Table 1 Demographics of Participants.

Demographics	PSP	PD
Total Number	15	15
Number of Females (%)	10 (67)	7 (47)
Average Age	71 years (Range 63–80, SD = 6.2)	65.4 years (Range 59–81, SD = 5.6)
Average Disease Duration	2.2 years (Range = 1–5, SD = 1.4)	7.3 years (Range = 2–11, SD = 3.7)

Table 2 Presence of photophobia.

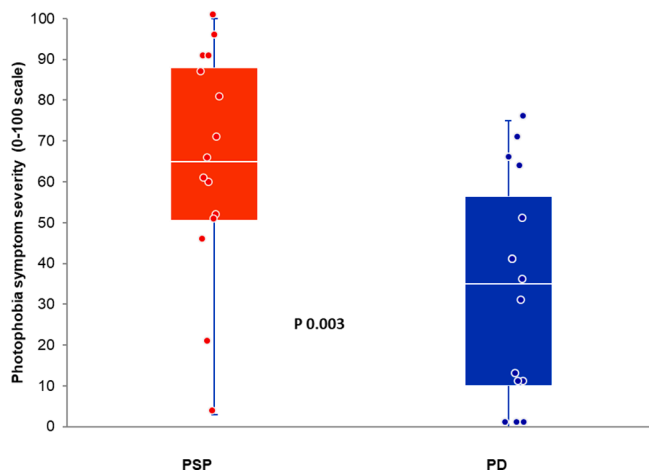
	PSP (%) (n = 15)	PD (%) (n = 15)	Fisher p-value	FDR adjusted p-values
<i>Presence of Photophobia</i>				
Does bright light hurt your eyes?	14 (93)	6 (40)	0.005	0.03
Do you feel an uncomfortable sense of glare or dazzle in your eyes from bright light?	13 (87)	8 (53)	0.04	0.11
Do flickering lights, glare, specific colors, or high contrast striped patterns bother you or your eyes?	6 (40)	5 (33)	0.71	0.77
<i>Indoor Activities</i>				
Do you turn off the lights or use curtains to create darker conditions?	9 (60)	4 (27)	0.14	0.23
Have you modified your home (closed blinds, lowered the brightness on screens, etc.)?	7 (47)	2 (13)	0.11	0.23
Have you found yourself less able to watch television or look at an electronic screen or monitor?	3 (20)	3 (20)	1.0	1.0
Do you have to wear sunglasses when inside?	3 (20)	0 (0)	0.22	0.32
<i>Outdoor Activities</i>				
Do you feel less willing to leave the house during the day?	6 (40)	1 (7)	0.08	0.21
Do you have to wear sunglasses when outside during the day?	13 (87)	6 (40)	0.02	0.09
Do you feel more limited in being able to pursue outdoor activities?	8 (53)	3 (20)	0.13	0.23
Do you feel more restricted to your home overall, especially during daylight hours?	2 (13)	0 (0)	0.48	0.63
Do you overall have to have more help from others to achieve daily tasks that require you to be outside during the daylight?	8 (53)	0 (0)	0.002	0.03

(40%) of PwPSP experienced pain with those stimuli compared to 5/15 (33%) of PwPD (FDR adjusted  $p = 0.77$ ). Of note, 2 individuals participating in this study had previously been diagnosed with strabismus and diplopia, and one with meibomian gland dysfunction – no other patients had previously existing ophthalmologic conditions.

Next, participants were asked questions about their symptoms of photophobia and resulting limitations in both indoor and outdoor situations. The questionnaire specified this by instructing participants to consider only the effects of the symptoms in questions 1–3 (see Table 2) when answering the subsequent questions.

Although a higher percentage of PwPSP reported turning off the lights while indoors (60% PSP, 27% PD) or modifying their home environment to decrease light (47% PSP, 13% PD), the difference did not reach statistical significance with this population size. Additionally, 3 PwPSP (20%) indicated that they needed to wear sunglasses indoors while no PwPD reported a similar behavior. No differences were noted with the ability to look at televisions or other electronic devices, with 20% of patients in both cohorts noting limitation due to light sensitivity.

Participants were also asked to indicate how light sensitivity has affected outdoor activities. 40% (6/15) PwPSP indicated that they felt less willing to leave their house during the day while 7% (1/15) of PwPD had marked the same (FDR adjusted  $p = 0.2$ ). PwPSP also indicated that they require more help from others to complete daily tasks that require them to be outside during daylight hours (53%) compared to PwPD (0%) (FDR adjusted  $p = 0.02$ ). Furthermore, while it did not reach the level of statistical significance, it is important to note that an overwhelming majority of PwPSP (87%, 13/15) remarked they had to wear their



**Fig. 1.** Boxplots display the distribution of photophobia symptom severity, on a scale of 0 (not severe) to 100 (the most severe you can imagine), among patients with progressive supranuclear palsy (PSP,  $n = 15$ ) and Parkinson disease (PD,  $n = 15$ ). The circles represent individual data points within the PSP and PD cohorts. The horizontal white line represents the median (PSP = 65, PD = 35) with the 1st-3rd quartiles being inside the colored boxes and the full range of the data within the blue lines. Overall, participants with PSP experienced more severe light sensitivity compared to PD patients ( $p = 0.003$ ). PSP = Progressive Supranuclear Palsy, PD = Parkinson Disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sunglasses when outside during the day, while less than half of PwPD indicated the same (40%, 6/15, FDR adjusted  $p = 0.09$ ). Overall, there was more significant debility from photophobia reported by PSP patients than PD patients when performing outdoor activities rather than indoor ones.

Lastly, participants were asked if severity of photophobia has worsened since their diagnosis. 58% of PwPSP and 43% of PwPD answered in the affirmative, however there was no significant difference in the binomial test for either group (PwPSP = 0.3, PwPD = 1).

### 3. Discussion

The findings in this study demonstrate that photophobia is reported at a significantly higher frequency and to a greater degree of severity by PSP patients as opposed to PD patients. This increased light sensitivity also appears to translate to greater limitation with pursuing outdoor activities of daily living. PwPSP report that they feel less willing to leave the house during the day (40% for PSP and 6% for PD), must wear sunglasses when outside during the day (87% for PSP and 40% for PD), feel more limited in being able to pursue outdoor activities (53% for PSP and 20% for PD), and overall have to have more help from others to achieve daily tasks that require them to be outside in the daylight (53% for PSP, 0% for PD). These results emphasize the functional disability – particularly with outdoor activities – in PSP, which may lead to a reduced quality of life. There was no statistically significant difference in reported limitation with indoor activities between PSP and PD patients.

The pathophysiology of photophobia in PSP remains unknown but we can speculate on possibilities using putative mechanisms of photophobia in other conditions. Photophobia itself can be observed in many forms of intracranial pathology such as meningitis, blepharospasm, intracranial hemorrhage, and migraine [3]. The nociceptive trigemino-vascular pathway in migraines is thought to be activated by photic stimulation of melanopsinergic intrinsically-photosensitive retinal ganglion cells (ipRGCs) with axonal projections into the posterior thalamus [7]. IpRGCs are known to be affected by neurodegenerative disorders – prior studies have shown lower melanopsin levels and degeneration of retinal ipRGCs resulting in impairment of the signaling pathway in

Parkinson's disease; this has been viewed as a possible culprit in circadian dysfunction in that condition [8]. It is possible that the heightened degree of photophobia in PSP could be a result of ipRGC dysfunction but to our knowledge, no study has looked at the state of this melanopsinergic pathway in PSP.

Optical coherence tomography has shown distinct changes in retinal morphology in PD and Parkinsonian syndromes (multiple system atrophy, PSP, and corticobasal syndrome) [9]. Interestingly, that study by Albrecht et al. noted reduced thickness of the inner and outer nuclear layers of the retina in PSP but not in PD; in fact they were able to differentiate PSP from PD within their sample of 40 patients with a sensitivity of 96% using these measurements. However, the scope of their study did not include assessment of light sensitivity in their population, so it remains unclear if these retinal changes are correlated with photophobia. Sevim et al. [10] also found further reductions in retinal layer thickness and volume with increasing duration of disease in both PD and PSP, but our results did not show a corresponding correlation between disease duration and severity of photophobia.

To date, there are no proven pharmacological treatments for photophobia, nor are there surgical treatments of any kind for photophobia in PSP. In a small cohort of patients, pupillary constriction through instillation of pilocarpine was shown to be effective at diminishing photophobia [11]. Nerve blockage of the superior cervical ganglion or greater occipital nerve has also proven to be temporarily helpful in relieving photophobia [12]. Sunglasses may also be used to mitigate the effects of photophobia. Overall however, managing photophobia primarily relies on addressing the underlying etiology. Recognizing the conditions in which patients are most light sensitive can be an insightful first step in being able to properly develop treatments that are efficacious and personalized. PSP patients have been shown to struggle with depression and impaired subjective health status [13], which could be exacerbated by the presence of photophobia and could increase caregiver burden as well. However, more work is needed to understand the connection between photophobia and psychiatric comorbidity and quality of life. Inclusion of photophobia in future QoL measures and anticipatory guidance regarding photophobia given at diagnosis are two ways to tangibly improve patient care.

One limitation of this study is the cross-sectional nature of our approach. This could be improved with a longitudinal design in patients with early symptoms suggestive of PSP. Critically, apart from one question where the same responses were observed, every symptom and behavioral change associated with photophobia was reported more often in PSP than PD. Given that our patients were more severe, we suspect earlier detection of photophobia may be important in identifying PSP patients. Another limitation is that we were not able to use a questionnaire or ADL performance evaluation tool that had been specifically validated for use in patients with neurodegenerative disorders. While standard measures of ADL performance do exist in this population, they do not specifically address tasks that may be impaired by photosensitivity, and there is a lack of validated measures for screening for photophobia in neurodegenerative syndromes. We would argue that the results of this study strongly support the evidence regarding the prevalence of photophobia in PSP patients, and justify the creation of such validated metrics of this symptom. Future studies could also incorporate specific quality of life and mental health metrics to see if there are measurable differences with onset and worsening severity of photophobia.

This study illustrates the potentially significant effect that photophobia has on the ability of PSP patients to perform daily tasks, particularly outdoors. This could subsequently lower quality of life in patients with PSP and is deserving of consideration from the research and clinical communities. The pathophysiological mechanism linking PSP and photophobia remains elusive. An improved understanding of this clinical symptom can lead to development of measures for symptomatic management of photophobia particularly outside the home, which will improve the patient's level of functionality and could affect their overall

quality of life.

### Conflict of interest

Authors declare that no conflict of interest.

### CRediT authorship contribution statement

**Deepankar Mohanty:** Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Kaitlyn R. Hay:** Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Writing - review & editing, Visualization, Project administration. **Sean Berkowitz:** Writing - review & editing. **Shriji Patel:** Writing - review & editing. **Ya-Chen Lin:** Formal analysis. **Hakmook Kang:** Formal analysis. **Daniel O. Claassen:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

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### Data Availability

Data will be made available at the request of other investigators.

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