Received: 12 December 2022 | Accepted: 6 April 2023

DOI: 10.1111/ene.15829

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Neural correlates of photophobia in prodromal and mild dementia with Lewy bodies

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Funding information
Projet Hospitalier de Recherche Clinique (PHRC) inter-régional (IDRCB 2012-A00992-41)

Abstract

Background and objectives: Photophobia is a sensory disturbance provoked by light. Little is known about the association between photophobia and dementia with Lewy bodies (DLB). In this study, we aimed to identify the frequency and the neural basis of photophobia in prodromal and mild DLB.

Methods: One hundred and thirteen DLB patients, 53 Alzheimer's disease (AD) patients, 20 AD and DLB patients, 31 patients with other neurocognitive diseases (including prodromal and mild demented patients), and 31 healthy elderly controls were included in this case–control study. Photophobia was systematically looked for and compared between groups. Among a selection of 77 DLB patients, we used voxel-based morphometry (VBM) to compare those with and those without photophobia (gray matter volume; SPM12, XjView, and Matlab R2021b software).

Results: The frequency of photophobia was higher in the DLB group (47.3%) than in the other groups ($p = 0.002$). The photophobia questionnaire score was higher in the DLB group than in the AD group ($p = 0.001$). Comparison between DLB patients with and those without photophobia showed decreased gray matter in the photophobia subgroup, in the right precentral cortex, in the eyelid motor region of Penfield's homunculus ($p = 0.007$, family-wise error [FWE] corrected).

Conclusions: Photophobia is a quite frequent symptom of prodromal and mild DLB. The neural basis of photophobia in DLB involves the right precentral cortex, which could have a role in the decrease of cerebral excitability, but also the motricity of the eyelids.

KEYWORDS
Alzheimer's disease, dementia with Lewy bodies, Lewy body disease, photophobia, voxel-based morphometry

INTRODUCTION

Dementia with Lewy bodies (DLB) is a frequent neurocognitive disease with key features such as hallucinations, cognitive and alertness fluctuations, rapid eye movement (REM) sleep behavior disorder (RBD), and parkinsonism [1]. In addition to these key characteristics, other symptoms have been described, such as depression and anxiety at the behavioral level and constipation and

orthostatic hypotension at the neurovegetative level [2]. Recently, in the MEMENTO cohort study, we described new symptoms in the prodromal stage of DLB, such as rhinorrhea, sicca syndrome, and photophobia [3]; in this cohort, photophobia was present in 36.3% of patients.

Photophobia is a sensory disturbance provoked by light, and known since 1856 to be associated with the nervous system and in particular the trigeminal nerve [4]. Photophobia was first associated with ophthalmological diseases, such as lesions of the cornea, and subsequently with neurologic and neurogeriatric conditions, such as migraine [5], blepharospasm [6], and progressive supranuclear palsy (PSP) [7]. Photophobia, present in 43%–100% of PSP patients [8], appears to cause a reduction in quality of life, with an impact on outdoor activities [9]. Photophobia has been very rarely studied in other neurocognitive diseases. In a study of six patients with Alzheimer's disease and six with Parkinson's disease, photophobia was described in all patients [10]. In a larger study of 525 PD patients, the proportion of photophobia is not precisely described but visual symptoms present in 63 patients (12%) included photophobia [11]. The neural basis of photophobia is unclear. Recently, activation of the posterior thalamus by optogenetic techniques in mice has induced photophobic behavior [12]. The thalamus has already been described as affected in DLB both functionally [13, 14] and structurally [15, 16], and in particular in the pulvinar [17].

We hypothesized that DLB patients could have photophobia frequently and that it could be related to thalamic atrophy. Thus, our goal was to clarify the frequency of photophobia in DLB compared to other neurocognitive diseases, such as Alzheimer's disease (AD), and to better understand the neural basis of photophobia using voxel-based morphometry (VBM).

PARTICIPANTS AND METHODS

Study design and participants

AlphaLewyMA is a longitudinal study, whose aim is to search for biomarkers of DLB, taking place in the tertiary memory clinic named "Centre Mémoire de Ressources et de Recherche" (CM2R) of Strasbourg and Colmar, France [18]. All patients enrolled in the AlphaLewyMA study had been referred to experienced neurologists and geriatricians of the CM2R for cognitive or behavioral complaints by their specialist, their local memory clinic, or their general practitioner. Healthy elderly controls (HC) were recruited among friends and relatives of the patients or via the listing of controls of the local clinical investigation center. Patients and HC underwent the following: a standardized screening protocol including medical history, various questionnaires including one on photophobia, physical and neurological examinations, neuropsychological tests including Mini-Mental State Examination (MMSE), brain MRI, and blood and cerebrospinal fluid (CSF) collection. Features of parkinsonism were evaluated using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III): akinesia, rigidity, and tremor at rest (rated from 0 for no symptoms to 4 for severe symptoms). Fluctuations were assessed with the Mayo Clinic fluctuations scale [19]. The Parkinson's disease-associated psychotic symptoms questionnaire was used to evaluate the presence of hallucinations [20]. RBD was evaluated using a sleep questionnaire on RBD from the publication by Gjerstad et al. [21], simplified into two questions for the patient and the caregiver: one concerning movements during sleep, the second concerning vivid dreams and nightmares. Photophobia was assessed with a three-level questionnaire (0 = normal sensitivity to light, 1 = occasional photophobia or with only certain types of light, 2 = permanent photophobia or with all types of light). Data were collected at three time points, each year during the 2-year follow-up. We considered photophobia to be present when patients responded positively to the questionnaire about photophobia at least once out of the three visits. A systematic questioning on new health problems is carried out every year, including ophthalmic diseases, with the aim to avoid bias about photophobia due to eye diseases.

Patients with prodromal DLB or DLB dementia were selected according to McKeith's criteria [1, 22]. Patients with prodromal AD or AD dementia were selected according to Dubois' criteria [23]. Patients were considered to have DLB and AD if they met both the Dubois criteria and the McKeith criteria concurrently. For example, a patient with memory storage disorders, a CSF in favor of AD, and two of the four clinical criteria for DLB was considered to have both DLB and AD. A total of 247 participants were included in this study: 110 DLB patients (DLB group), 57 AD patients (AD group), 19 DLB and AD patients (DLB + AD group), 30 diseased control patients (DC group), and 31 HC (HC group). The DC group consisted of patients originally included in the study with cognitive disorders as found in AD and DLB who, after a follow-up in the study, were found to have neither AD nor DLB. The DC group had various diagnoses, defined according to international criteria. All participants provided written informed consent for the study in accordance with the Declaration of Helsinki, and the study was approved by the Ethics Committee of East France (IV).

Neuroimaging study

We used VBM to investigate the neuroanatomical correlates of photophobia in 77 of the 110 DLB patients. These 77 patients were selected because they had participated in all three visits during the 2 years. Presence of photophobia at any time point was scored 1 and its absence was scored 0, using the photophobia questionnaire (see earlier). Each of these patients had undergone a high-resolution anatomical MRI scan at inclusion. T1-weighted three-dimensional anatomical images were obtained using a 3 T MRI scanner (Verio 32-channel Tim Siemens scanner; Siemens) using a volumetric magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (FOV = 256 × 256 mm^2, image matrix = 256 × 256, slice thickness = 1 mm, repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°). VBM analyses included image preprocessing and statistical analyses. These steps were carried

out using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/) running on Matlab R2021b (MathWorks). Anatomical MR images were spatially preprocessed using standard procedures [24]. All T1-weighted structural images were first segmented, bias-corrected, and spatially normalized to the Montreal Neurological Institute (MNI) space using an extension of the unified segmentation procedure that includes six classes of tissue. The DARTEL registration toolbox was then used to build a study-specific template and to bring into alignment all the segmentation images. The VBM analysis was done on modulated gray matter (GM) images; that is, the GM value in each voxel was multiplied by the Jacobian determinant derived from the spatial normalization. This procedure preserves the total amount of GM from the original images. These modulated GM images were smoothed with a Gaussian kernel (FWHM, 8 mm). Analyses compared DLB with photophobia and DLB without photophobia in terms of GM volume (SPM12 and XjView), including age and total intracranial volume as covariates, and thresholded at $p<0.05$ corrected (family-wise error, FWE).

Statistical analysis

The Statistical Package for Social Sciences software (SPSS v. 27.0.0.0, http://www-01.ibm.com/software/analytics/spss/) was used for further statistical evaluation as required. Where appropriate, differences in demographic and clinical data were assessed using parametric (ANOVA, *t*-tests) and nonparametric tests (Kruskall–Wallis H, Mann–Whitney U). Post-hoc analyses employed Tukey and Mann–Whitney U for ANOVA and Kruskall–Wallis tests, respectively. For categorical measures, χ^2 tests were applied. For each test statistic, a probability (*p*) value of <0.05 was regarded as significant.

RESULTS

Clinical results

A detailed description of the five groups is given in Table 1. The five groups were comparable in terms of educational level, gender, and handedness. The DC and HC groups were younger than the AD and DLB + AD groups; only the HC group was younger than the DLB group ($F=6.653$, $p<0.001$). The DC and HC groups had higher MMSE scores than the AD and DLB + AD groups; only the HC group had a higher MMSE score than the DLB group ($F=61.781$, $p<0.001$). The DLB and DLB + AD groups had higher rigidity UPDRS-III scores than the AD and HC groups ($F=51.150$, $p<0.001$). The DLB and DLB + AD groups had higher akinesia UPDRS-III scores than the AD and HC groups, and the DLB group had a higher score than the DC group ($F=54.148$, $p<0.001$). The DLB groups had a higher tremor UPDRS-III scores than the AD group ($F=9.876$, $p<0.043$). The Parkinson's disease-associated psychotic symptoms questionnaire score was higher in the DLB group when compared to the AD and HC groups and was higher in the DC group when compared to the AD group ($H=42.335$, $p<0.001$). The Mayo Clinic Fluctuations Scale score was higher in the DLB group than in the AD, HC, and DC groups. The RBD sleep questionnaire score was higher in the DLB group compared to the AD group but not when compared to the other groups ($H=22.780$, $p<0.001$). The number of prodromal DLB was 77, prodromal AD 29, and prodromal DLB + AD 5. ^{123}I-FP-CIT SPECT (single-photon emission computed tomography) (dopamine transporter [DAT] scan) was conducted in 45 prodromal and mild DLB patients and we found dopamine transporter loss in 31 patients.

The frequency of photophobia was higher in the DLB group (47.3%) than in the other groups (AD group, 19.3%; DLB + AD group 15.8%; DC group 30.0%; and HC group 35.5%; $p=0.002$). The photophobia questionnaire score was higher in the DLB group than in the AD group ($p=0.001$) but was not higher than in the DLB + AD group ($p=0.060$), the DC group, and the HC group (Table 1). We determined the reliability of our questionnaire by applying Cronbach's alpha for the 3 years: the alpha was 0.741. The diagnosis of patient in the DC group with photophobia status is given in Table S1. During the 2-year follow-up, in the DLB group 7 patients had ophthalmic disease: 3 patients had no photophobia (2 cataract surgeries and 1 retinal detachment), 4 patients had photophobia (1 ectropion, 2 age-related macular degeneration [AMD], and 1 chronic glaucoma); in the AD group 5 patients had ophthalmic disease: 3 without photophobia (1 AMD, 1 chronic conjunctivitis, 1 chronic glaucoma) and 2 with photophobia (1 bilateral blindness, 1 chronic uveitis); in the DLB + AD groups no patient developed eye disease; in the HC group 3 patients had ophthalmic disease all with photophobia (1 angle closure glaucoma, 1 AMD, 1 unilateral blindness); and in the DC group 1 patient with photophobia developed an ophthalmic sarcoidosis and 1 without photophobia had bilateral AMD. No keratitis, iritis, blepharitis, or blepharospasm was noted whatever the group during the 2-year follow-up.

Neuroimaging results

Of the 77 DLB patients with brain MRI, 44% had photophobia. Comparison of the DLB subgroup with photophobia and the DLB subgroup without photophobia showed decreased GM in the subgroup with photophobia, in the right precentral cortex (Brodmann area 9), in the eyelid motor region of Penfield's homunculus ($p=0.007$, FWE-corrected, $T=5.34$, $k=90$ for the peak level, and $p=0.006$, FWE-corrected for the cluster level). No other area was found with this correction. Figure 1 shows the precise localization of the precentral GM decrease.

DISCUSSION

This study confirms that photophobia exists in DLB, that it correlates clinically with the presence of hallucinations, and that structurally the difference between DLB with and without photophobia is in the precentral cortex.

TABLE 1 Clinical and demographic features of dementia with Lewy bodies patients, Alzheimer's disease patients, dementia with Lewy bodies and Alzheimer's disease patients, diseased controls, and healthy controls.

Feature		DLB ($N=110$)	AD ($N=57$)	DLB + AD ($N=19$)	DC ($N=30$)	HC ($N=31$)	Statistic test, p	Post-hoc[e]
Age, years[a]		71.4 (9.3)	74.5 (8.4)	74.8 (8.5)	67.3 (9.4)	66.0 (9.0)	$F=6.653$, $p<0.001$*	HC < DLB, AD and DLB + AD DC < AD and DLB + AD
Education[a,b]		11.9 (4.3)	12.0 (3.9)	11.7 (2.9)	12.0 (3.3)	12.7 (2.1)	$H=1.994$, $p=0.737$	
Sex (F/M)		58/52	30/27	9/10	17/13	18/13	$\chi^2=0.711$, $p=0.950$	
Handedness (R/L/A)		94/9/1	49/6/1	18/0	25/3/1	29/2	$\chi^2=4.645$, $p=0.795$	
MMSE score (/30)[a]		25.3 (3.9)	24.1 (3.3)	23.2 (3.9)	27.0 (2.8)	28.8 (1.2)	$H=61.781$, $p<0.001$*	HC > DLB + AD, AD, and DLB DC > DLB + AD, AD
Photophobia, *N* (%)		52 (47.3)	11 (19.3)	3 (15.8)	9 (30.0)	11 (35.5)	$\chi^2=16.912$, $p=0.002$*	
Photophobia questionnaire	0/1/2	58/25/27	46/9/2	16/2/1	21/3/6	20/9/2	$H=19.061$, $p<0.001$*	DLB > AD
Parkinsonism	Rigidity 0/1/2/3/4	36/59/6/1/0	34/4/1/0/0	6/6/1/0/0	16/6/1/1/0	30/1/0/0/0	$H=51.150$, $p<0.001$*	DLB > HC and AD DLB + AD>HC and AD
	Akinesia 0/1/2/3/4	39/52/11/0/0	35/3/0/0/0	7/7/1/0/0	18/3/3/0/0	30/1/0/0/0	$H=54.148$, $p<0.001$*	DLB > HC, AD, and DC DLB + AD>HC and AD
	Tremor 0/1/2/3/4	75/21/0/0/0	35/2/0/0/0	11/4/0/0/0	21/2/0/0/0	27/2/0/0/0	$H=9.876$, $p<0.043$*	DLB > AD
Hallucinations (/10)[a]		1.5 (1.9)	0.3 (0.8)	0.4 (0.7)	1.3 (2.0)	0.1 (0.3)	$H=42.335$, $p<0.001$*	DLB > HC and AD; DC > AD
Fluctuations[c]	0/1/2/3/4	19/34/30/15/6	36/7/5/0/0	6/8/1/2/0	14/7/1/2/1	22/6/1/0/1	$H=61.408$, $p<0.001$*	DLB > AD, HC, and DC
RBD	0/1/2	37/22/28	36/6/2	9/3/4	12/6/2	19/9/1	$H=22.780$, $p<0.001$*	DLB > AD
CSF[a]	Abeta-42	822.7 (291.9)	582.5 (201.6)	598.8 (241.0)	1115.5 (275.8)	–	$F=22.139$, $p<0.001$*	DLB > AD, DLB + AD; DC > AD, DLB + AD, DLB
	P-Tau	44.1 (15.2)	87.3 (30.1)	92.4 (28.7)	44.4 (12.4)	–	$F=52.146$, $p<0.001$*	DLB < AD and DLB + AD; DC < AD and DLB + AD
	Tau	292.1 (185.8)	651.9 (291.5)	622.8.6 (173.1)	287.1 (102.0)	-	$F=34.203$, $p<0.001$*	DLB < AD and DLB + AD; DC < AD and DLB + AD
Hippocampal atrophy[d] 0/1/2/3/4	Left hippocampus	33/19/22/10/4	9/11/14/7/1	1/4/7/3/2	9/6/1/0/0	16/11/2/0/0	$H=30.165$, $p<0.001$*	AD+DLB > HC and DC; AD>HC and DC; DLB > HC
	Right hippocampus	32/11/21/8/6	6/16/13/5/2	0/6/6/1/2	6/4/2/0/0	10/12/3/0/0	$H=20.225$, $p<0.001$*	AD+DLB > HC and DC; AD>HC

Abbreviations: A, ambidextrous; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DC, diseased controls; DLB, dementia with Lewy bodies; F, female; HC, healthy controls; L, left; M, male; MMSE, Mini-Mental State Examination; R, right; RBD, rapid eye movement (REM) sleep behavior disorder; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Mean (SD).

[b] Education: years from primary school.

[c] Scores on the Mayo Fluctuation Scale (/4).

[d] Mean (SD, number of patients tested). According to Scheltens et al., [36].

[e] Tukey post-hoc test for ANOVA (F), Kruskall–Wallis post-hoc test on SPSS (H).

* $p>0.05$.

We showed that photophobia is quite a frequent neurosensory symptom in DLB, since it was present in 47.3% of patients. We had previously demonstrated in the MEMENTO cohort with prodromal DLB patients that the frequency of photophobia was slightly lower at 36.3% [3]. This difference may be explained by the fact that the present study included patients with mild cognitive impairment (MCI) and mild dementia, whereas the previous study included patients with subjective cognitive complaints and MCI, thus overall at an earlier stage. Moreover, photophobia is less common in AD: in the present study, the frequency was 19.3%.

Many studies suggest that photophobia in the context of migraine is characterized by diffuse associative visual cortex abnormalities, possibly linked to thalamic structures [25]. In the same way, the neural basis of visual hallucinations in DLB almost systematically includes the associative visual cortex and frequently includes the cuneus [26, 27]. The main hypothesis is that visual areas are deficient and send false information (bottom-up phenomenon), and the information is not recognized as abnormal because of a deficiency also of the frontal lobe (top-down phenomenon) [27]. Thus the visual system, including the occipital cortex, could be the link between visual hallucinations and photophobia.

However, the comparison of the two DLB subgroups with and without photophobia did not find a difference in the visual cortex but in the right precentral cortex. Several mechanisms could explain photophobia in DLB. The first one would be an impairment of the trigeminovascular system, as described in migraine [28]. The second could be related to a possible blepharospasm secondary to DLB. The third one could be related to the eye directly. Indeed, photophobia is frequently associated with disorders of the eye such as iritis, uveitis, and blepharitis [29]. No such problem was identified in the DLB group, but there was one uveitis in the AD group, and one in the DC group (sarcoidosis) during the 2-year follow-up.

We found a proportion of photophobia of 35.5% in the elderly controls. In young subjects, using a question on gene by light, the proportion is also 35% according to a study on students without migraine [30]. The lower proportion of photophobia in the DLB+AD group may be explained by the greater cognitive impairment (although not significant), or by a lesser awareness of the disorders anosognosia or anososodiaphoria, or by the fact that the association of the two diseases may modify the symptomatology, rather on the side of the disappearance of symptoms that are frequent in the healthy subject than on the side of the appearance of a symptom.

The trigeminovascular system is a complex system with first-order thalamus neurons located in the ventral posteromedial nucleus (VPM) that project to different parts of the cortex, including the primary and secondary sensory cortex and the insula [31, 32]. These projections (the so-called pain matrix) are more likely to play a role in the perception of pain, and particularly the perception of a headache in migraine [32]. Noseda et al. identified, in the posterior thalamus of rats, units of neurons that responded to the stimulation of the dura and were in the majority of cases also photosensitive [28]. The cortical projections of dura/light-sensitive neurons include the somatosensory cortex, the visual cortex, but also the primary and secondary motor cortex [28]. These cortex are part of the precentral cortex. This raises the question of a link between this motor system and the photophobia of DLB patients. Normally, the precentral cortex exhibits 20 Hz oscillatory activity that is essential for setting up proper levels of intracortical and thalamic inhibition [32]. In the context of DLB patients with photophobia, the decreased GM volume in the right precentral cortex could decrease the ability of this precentral cortex to govern cortical excitability and the activity of descending modulatory pathways. These differences between photophobia and non-photophobia have also been found in migraine patients in the premonitory phase: patients with photophobia had hyperactivation of the right precentral cortex [33].

Photophobia can also be considered as an autonomic nervous system symptom as is the case in Parkinson's disease, multiple system atrophy, or PSP [34]. It is then often associated with a pupillomotor dysfunction [8]. We described this autonomic involvement in DLB in a previous article, where we demonstrated that DLB patients also had other early neurovegetative disorders, namely rhinorrhea, sicca syndrome, and constipation [3].

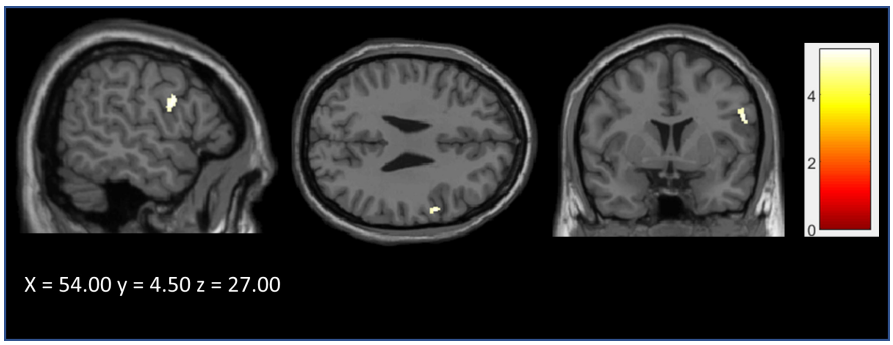

FIGURE 1 Comparison between prodromal and mild dementia with Lewy bodies patients with and without photophobia, showing decreased gray matter concentration in the right precentral cortex in the photophobia subgroup. Sagittal, axial, and coronal views. Family-wise error (FWE) corrected threshold $p < 0.05$, including age and total intracranial volume as nuisance covariates.

The precentral region on the right that we detected as being decreased in GM volume corresponds to the motor activity of the face and particularly the eyes and eyelids according to Penfield's homunculus [35]. Photophobia in DLB could therefore be related to a motor dysfunction of the face. The patients would blink less or less well, which would promote the entry of light into the orbit and therefore result in discomfort.

CONCLUSIONS

This study confirmed the existence of photophobia in almost half of the prodromal and mild DLB patients. The neural basis of photophobia in DLB involves the precentral cortex, which could have a role in the motricity of the eyelids, and the decrease of cerebral excitability. The next step will be to evaluate brain MRI microstructural and functional changes in DLB patients to determine more precisely the brain areas involved in photophobia.

AUTHOR CONTRIBUTIONS

Alice Tisserand: Writing – original draft; software; formal analysis. **Benjamin. Cretin:** Conceptualization; investigation. **Mary Mondino:** Software; formal analysis. **Anne Botzung:** Investigation; project administration. **Lea Sanna:** Project administration; formal analysis; data curation. **Catherine Demuynck:** Investigation; methodology. **Pierre Anthony:** Investigation; methodology. **Candice Muller:** Investigation; methodology. **Olivier Bousiges:** Investigation; methodology. **Nathalie Philippi:** Investigation; methodology; conceptualization. **Frederic Blanc:** Writing –original draft; software; formal analysis; Conceptualization; investigation.

ACKNOWLEDGMENTS

The authors thank the patients, healthy controls, and their relatives for their participation in the study. They also thank Nick Barton for language editing.

CONFLICT OF INTEREST STATEMENT

F.B. was the national coordinator for France for the Eisai Delphia (E2027), Axovant Headway-DLB and Roche Graduate clinical trials; he had received honoraria from Roche, Eisai, and Biogen for oral presentations. The other authors declare that they have no competing interests.

FUNDING INFORMATION

This study was funded by Appel à Projet Interne (API) of the University Hospital of Strasbourg, France Alzheimer, Fondation Université de Strasbourg, and Projet Hospitalier de Recherche Clinique (PHRC) inter-régional (IDRCB 2012-A00992-41).

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tisserand A, Cretin B, Mondino M, et al. Neural correlates of photophobia in prodromal and mild dementia with Lewy bodies. *Eur J Neurol*. 2023;30:2215-2221. doi:10.1111/ene.15829