Intrinsically Photosensitive Retinal Ganglion Cell Function, Sleep Efficiency and Depression in Advanced Age-Related Macular Degeneration

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Purpose. Melanopsin expressing intrinsically photosensitive retinal ganglion cells (ipRGC) input to multiple brain regions including those for pupil control, circadian rhythms, sleep and mood regulation. Here we measured ipRGC function and its relationship to sleep quality and depression in patients with advanced AMD.

Methods. The melanopsin-mediated post-illumination pupil response (PIPR) was measured in 53 patients with advanced AMD (age 78.8 ± 8.8 years) and in 20 healthy controls (age 72.5 ± 3.3 years). Sleep quality and efficiency was assessed using the Pittsburgh Sleep Quality Index (PSQI). Risk of depression was determined using the Center for Epidemiologic Studies Depression questionnaire.

Results. The group with AMD showed significantly reduced pupil constrictions ($P = 0.039$); PIPR amplitudes ($P = 0.003$); global sleep scores ($P = 0.01$); and higher levels of depression ($P < 0.001$) than the control group. There was a significant correlation between the PIPR amplitude and global sleep score in the AMD group ($P = 0.01$). The amplitude of PIPR significantly correlated with sleep efficiency ($P = 0.008$; regression, $P = 0.01$, $R^2 = 0.13$), but not sleep quality ($P = 0.23$) in the AMD group. There was no correlation between PIPR and depression scores.

Conclusions. Intrinsically photosensitive RGC dysfunction in advanced AMD contributes to the observed reduction in sleep efficiency. The correlation between the melanopsin-mediated PIPR and sleep may indicate reduced photic input to the suprachiasmatic nucleus and ventrolateral preoptic area due to ipRGC dysfunction in AMD.

Keywords: intrinsically photosensitive retinal ganglion cells (ipRGCs), pupil light reflex, post-illumination pupil response, sleep, depression

Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) are dysfunctional in various retinal and optic nerve diseases,[1–4] including AMD.[5,6] Non-image forming functions of these cells include signaling irradiance information for synchronizing the circadian body clock to the solar day,[7] thus mediating photoentrainment through projections to the suprachiasmatic nucleus (SCN)[8,9] and sleep induction through activation of the ventrolateral preoptic area.[10,11] Intrinsically photosensitive RGC dysfunction could therefore alter sleep-wake cycles and affect sleep quality. Intrinsically photosensitive RGCs also signal to the olivary pretectal nucleus (OPN) for mediation of the pupil light reflex (PLR)[12,13] and in particular the post-illumination pupil response (PIPR),[12–15] which is an emerging method for the direct assessment of ipRGC function in healthy and diseased eyes and in persons with chronobiological disorders.[4–6,12–14,16–18] Two recent studies observed that sleep duration was altered in advanced AMD patients; sleep duration decreased in wet AMD and increased in dry AMD,[19,20] but the effect of aberrant ipRGC signaling in AMD[5,6] as a contributing factor was not evaluated. Supporting evidence for an association between ipRGC dysfunction and sleep disorders is provided in primary open angle glaucoma patients,[1,3] where there is also decreased sleep quality.[16,17]

Intrinsically photosensitive RGCs project to brain areas implicated in mood regulation[21] and patients with seasonal affective disorder (SAD) have a dysfunctional melanopsin-mediated PIPR,[22] indicative of a role of aberrant ipRGC signaling in the presence of SAD. In mouse models, depression-related behavior in wild-type mice is observed in response to an altered light and dark cycle but not in ipRGC-deficient mice,[21] demonstrating the ability of light signaling via ipRGCs to influence mood. Given that the melanopsin-mediated PIPR is affected in early and late AMD,[5,6] and the prevalence of depression in AMD patients is as high as 39%,[23–26] with its origin likely to be multifactorial,[27] we determined the role that ipRGC dysfunction in AMD patients has in depression. Based on this evidence, the study aim is to investigate whether ipRGC

dysfunction in AMD is correlated with sleep and mood disorders in patients with advanced stages of this condition. Here we measure melanopsin function using the post-illumination pupil response, and sleep and mood with validated questionnaires to assess nonvisual behavioral disorders in the AMD patients.

Methods

Participants

Seventy three participants (41 female, 32 male) were recruited from the Queensland Eye Institute (QEI), Queensland University of Technology (QUT) eye clinic, and local optometry practices. Table 1 provides a summary of the participants' clinical characteristics. Forty six of these participants had advanced neovascular AMD (choroidal neovascularization [CNV]; AREDS grade 4)[28] and were under treatment with antivascular endothelial growth factor (Lucentis; Genentech, San Francisco, CA, USA, or Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA). Seven participants had advanced geographic atrophy (GA; AREDS grade 4) and 20 participants served as healthy controls. The age range of the healthy controls is lower than that of the AMD patients (Table 1), however, this age difference was not statistically significant. All participants underwent an ophthalmic examination that included visual acuity, ophthalmoscopy, intraocular pressure measurement and optical coherence topography (OCT, Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Although 36 participants had intraocular lens (IOL) implants, all participants had normal iris musculature postsurgery and cataract removal surgery does not adversely affect circadian rhythm or sleep,[29] with no difference in blue light transmission between blue-blocking and neutral IOLs.[29,30] Those participants without IOLs (AMD, $n = 21$; control, $n = 16$) had crystalline lens opacities less than grade 2 (LOCS III),[31] thus limiting the effect of blue light attenuation by the aging lens.[32] Clinical trials show that an average of 5.6 anti-VEGF injections is administered over 12 months in patients suffering from neovascular AMD.[33–35] This is in accordance with the treatment frequency in our cohort of 5.8 injections per year; therefore, the number of injections administered was grouped in increments of six for comparison of the treatment effect within a 12-month period (Table 1). Five out of 53 AMD patients were taking antidepressant medication (Zoloft; Pfizer, Inc., New York, NY, USA; Lumin; Alphapharm Pty Limited, Millers Point NSW, Australia; or Lexam; Aspen Pharma Pty Ltd, St. Leonards NSW, Australia) that could affect the pupil response; this was considered in the statistical analysis. There was no history of ocular disease or medication affecting the pupil in the control participants. The patients with AMD had no ocular disease other than AMD. Written informed consent was obtained from all participants and the study was conducted in accordance with the requirements of the Queensland University of Technology Human Research Ethics Committee and the tenets of the Declaration of Helsinki.

Assessment of Sleep and Depression

Sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire,[36] a self-assessed screening tool that has been used to determine sleep disturbances in glaucoma[37,38] and to determine sleep quality prior to measurement of the circadian response of ipRGCs.[8] The questionnaire is primarily designed to measure sleep based on a global score. Presence and risk of depression was determined using the Center for Epidemiologic Studies Depression Scale (CES-D),[39] a self-report test designed to measure symptoms associated with depression. The 20-item CES-D questionnaire comprises six scales reflecting the major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. These symptoms have been used in previously validated scales and the CES-D has high test-retest reliability and internal consistency.[39] The Seasonal Pattern Assessment Questionnaire (SPAQ)[40] was used to screen for the presence of seasonal affective disorder (SAD) and provided insight into factors such as social activity, weight, appetite, and energy that may influence mood. While the SPAQ has high specificity, it has low sensitivity and was therefore used for screening rather than as a diagnostic instrument.[41]

Table 1. Summary of AMD Patient and Control Participant Distribution Based on Their Clinical Characteristics

Characteristics	CNV Group	GA Group	Control Group
Participants, *n*	46	7	20
Age, y	78.4 ± 8.7	80.7 ± 9.7	72.5 ± 3.3
Sex, M/F	16/30	4/3	12/8
IOL, *n*	28	4	4
VA (Snellen), *n*			
6/6–6/12	22	0	20
6/15–6/36	17	4	0
6/48–CF	7	3	0
Number of injections, *n*			
0–6	11	–	–
7–12	6	–	–
13–18	6	–	–
19–24	8	–	–
25–30	5	–	–
31–36	6	–	–
37–50	4	–	–

CF, counting fingers; VA, visual acuity.

Pupillometry

To assess ipRGC function, we measured the melanopsin-mediated PIPR using customized paradigms developed in our laboratory,[1,5,6,42,43] with high irradiance stimuli designed for use with a pupillographer (RAPDx; Konan Medical USA, Inc., Irvine, CA, USA). Intrinsically photosensitive RGCs produce a sustained pupil constriction after offset of short wavelength light known as the PIPR,[12–14] which is absent with presentation of long-wavelength stimuli that have low melanopsin excitation. Intrinsically photosensitive RGCs also receive extrinsic signals from rods and cones,[44–46] which can be measured by the initial pupil constriction amplitude.[47] Monocular red and blue light stimuli were presented in Newtonian view on a liquid crystal display with a 40-Hz frame rate, with a central physical barrier creating two optical channels for recording binocular pupil responses under infrared illumination. The screen was viewed at infinity through a pair of 50-mm objective lenses to produce a 25° field of view in each eye. Monochromatic stimuli included a 10-second pulse of blue light (short wavelength, $\lambda_{max} = 448$ nm, corneal irradiance: 14.5 log quanta.cm^{-2}.s^{-1}, luminance: 1.3 log cd.m^{-2}) and red light (long wavelength, $\lambda_{max} = 604$ nm, corneal irradiance: 14.4 log quanta.cm^{-2}.s^{-1}, luminance: 1.0 log cd.m^{-2}). The spectral outputs of the LED stimuli were measured with a spectroradiometer (StellarNet, Tampa, FL, USA) and irradiance and luminance was measured with a radiometer (ILT1700 Research Radiometer; International Light Technologies, Peabody, MA, USA). A target (green cross) was

used for patient fixation. A display screen mounted on the side of the pupillographer (Konan Medical USA, Inc.) allowed the examiner to monitor patient fixation during testing.

Procedure

Where AMD was present in both eyes, the worse eye was dilated with 1% tropicamide (Alcon Laboratories, NSW, Australia), and the preferential eye was dilated in healthy controls. The consensual PLR was measured. Participants were adapted to the dim room illumination (<1 lux) for 10 minutes prior to testing. The pupil testing started with an additional 10 seconds dark adaptation before recording. Baseline pupil diameter was then measured during 5 seconds of fixation prior to onset of the 10-second stimulus and the post-stimulus response was recorded for 40 seconds. This resulted in a 55-second interstimulus interval between the long and short wavelengths stimulus. Questionnaires were administered while the patients' eye was dilating. All testing occurred between 8 AM and 4 PM to minimize the effect of circadian variation on the PIPR amplitude.[8,48]

Data Analysis

The Pittsburgh Sleep Quality Index comprises seven components that are each scored on a Likert scale from 0 to 3 and then summed to provide a global score, with higher scores indicating poorer sleep quality.[36] While global scores provide an indication of overall sleep quality, factor analysis has since shown that a multiple factor model is statistically favored over a global score[49,50]; therefore, we scored and analyzed the PSQI using sleep quality and sleep efficiency components.[50] Sleep quality included scores from the subjective sleep quality, sleep latency, and sleep disturbance components, while sleep efficiency included scores from sleep duration and calculated sleep efficiency components (time in bed versus time asleep). Sleep factor scores were calculated by multiplying the component score by the factor loading given by Magee et al.[50] and summing them.

The Center for Epidemiologic Studies Depression questionnaire is also scored on a Likert scale from 0 to 3, with higher scores indicating more depression symptoms, weighted by frequency of occurrence during the past week.[39] A cutoff score of 16 helps in identifying people at risk for clinical depression. Using continuous scoring criteria as described by Radloff,[39] patients were identified as having no clinically significant depression symptoms, subthreshold depression symptoms, possible or probable major depressive symptoms, or having met major depressive episode criteria. Where depressive symptoms were a concern, the treating ophthalmologist for the AMD patients was informed, and control participants were advised to see a general practitioner. The Seasonal Pattern Assessment Questionnaire measures seasonal variations in six items (mood, appetite, weight, sleep, energy, and socializing) by scoring each item on a 5-point scale ranging from 0 (no change) to 4 (marked change). The global score (range 0–24) was calculated by adding the individual item scores and a score ≥11 identified the presence of SAD.[51]

Pupil analysis included identification and extraction of blink artefacts during analysis of pupil recordings by a customized software algorithm with linear interpolation.[43] The data were fitted with linear and exponential models[6,8] and analyzed according to our established protocols.[43] To control for individual differences in resting pupil diameter, all data are reported as a percentage of the resting baseline pupil diameter (average pupil diameter during a 5-second prestimulus period)[42,43]; a larger percentage value indicates smaller constriction amplitude. The PIPR was quantified at 6 seconds after light stimulus offset.[52] Initial pupil constriction was defined as the minimum pupil diameter within 3 seconds after stimulus onset.[53,54] The short wavelength stimulus with high melanopsin excitation (609.8 α-opic lux) served to measure the intrinsic ipRGC response. The long wavelength stimulus with low melanopsin excitation (9.7 α-opic lux) was presented as the control and to account for autonomic pupillary reactivity and is not reported.

Statistical Analysis

Statistical analyses were performed using commercially available statistical software (IBM SPSS, version 21; IBM Corporation, Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test. Independent sample *t*-tests evaluated each variable (presence of IOL, initial constriction, PIPR, sleep quality, sleep efficiency, and level of depression) between the CNV and geographic atrophy patients, as well as between the control group and AMD group. Spearman's correlation coefficient was used to determine the association between the pupil metrics (initial constriction and PIPR) and sleep (global score, sleep quality, and sleep efficiency), as well as between the pupil metrics and depression scores within the AMD group. These analyses were repeated after excluding the five patients who were taking antidepressant medication. The association between visual acuity and number of injections administered with depression and sleep scores was determined using correlation analysis. Where a significant correlation was found, linear regression analyzed the relationship between sleep and depression scores and the pupil metrics. Multiple regression analysis was completed to account for the effect of age, presence of IOL, and treatment frequency. A value of $P < 0.05$ was considered statistically significant.

Results

There was no significant difference between CNV ($n = 46$) and GA ($n = 7$) patients for initial pupil constriction amplitude, PIPR amplitude, depression score, and global sleep score. Therefore, AMD patients with CNV and GA were combined into a single group for additional analyses. There was no significant effect of IOL surgery on all parameters. Multiple regression analysis showed no effect of age ($\beta = 0.14$, $P = 0.07$, $R^2 = 0.05$); IOL ($\beta = -1.8$, $P = 0.13$, $R^2 = 0.03$); and treatment frequency ($\beta = -0.2$, $P = 0.16$, $R^2 = 0.08$) on the PIPR. The mean (± standard deviation) values of all measured variables (pupil parameters, sleep and mood scores) for the AMD group and control group are given in Table 2. The long wavelength stimulus showed a low variability (±3.3%), indicative of a minimal effect of autonomic reactivity. The pupil parameters (pupil constriction and PIPR) for the AMD group were significantly reduced compared to the control group, indicating lesser pupil constriction amplitudes at stimulus onset and at post-illumination. The group with AMD had a higher global sleep score indicating poorer sleep compared to controls. Analysis of the sleep factor components demonstrated sleep efficiency scores were higher in the AMD group. However; the sleep quality score was not significantly different between groups. The group with AMD had a significantly higher level of depression compared to the control group (Table 2). All participants scored less than 4 on the SPAQ index, with the exception of one AMD patient who scored 8 out of a possible 24 and was still below the cutoff for seasonal affective disorder.

Correlation analyses identified a positive association between the PIPR amplitude and global sleep score ($r = 0.34$, $P = 0.01$) for the AMD group (Fig. 1A). As the amplitude of PIPR decreased, indicating a reduced sustained constriction, the

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Table 2. Mean (± SD) Values for the Pupil Parameters, Sleep Component, and Depression Scores for AMD Patients and Healthy Control Participants

Metrics	AMD Participants, $n = 53$	Control Participants, $n = 20$	*P* Value
Initial constriction amplitude (% baseline)	65.7 ± 8.0	61.5 ± 6.9	0.039*
PIPR amplitude (% baseline)	91.2 ± 5.9	87.4 ± 4.0	0.003*
PSQI global Score	6.5 ± 3.2	4.5 ± 2.5	0.013*
Sleep quality score	2.6 ± 1.7	1.9 ± 1.2	0.057
Sleep efficiency score	1.5 ± 1.1	0.8 ± 0.5	0.001*
CES-D score	9.3 ± 9.1	2.9 ± 4.0	< 0.001*

* $P < 0.05$.

global score increased, demonstrating poorer sleep behavior ($F_{1,51} = 6.75$, $P = 0.01$, $R^2 = 0.12$). Correlations between the PIPR amplitude and sleep efficiency and sleep quality factors in the AMD group identified that poorer sleep efficiency was associated with a decrease in PIPR amplitude ($r = 0.36$, $P = 0.01$; regression, $F_{1,51} = 7.55$, $P = 0.01$, $R^2 = 0.13$; Fig. 1C), but no correlation was found between sleep quality and PIPR ($r = 0.17$, $P = 0.23$; Fig. 1E). Initial pupil constriction amplitude did not correlate with the global sleep score ($r = 0.09$, $P = 0.52$); sleep efficiency ($r = 0.12$, $P = 0.41$); or sleep quality ($r = 0.05$, $P = 0.71$) in the AMD group. Sleep scores (CNV and GA groups) did not correlate with visual acuity ($r = -0.04$, $P = 0.77$) or number of injections administered in the CNV group ($r = 0.19$, $P = 0.19$).

For the depression score analysis, 2/53 AMD patients met the criteria for major depression, 2 of the 53 AMD patients had possible major depression and 6 of the 53 AMD patients had symptoms of subthreshold depression. Five AMD patients were taking antidepressant medication; one control participant had subthreshold depression symptoms while all other control participants showed no clinical signs of depression. There was no correlation between PIPR and depression score for the AMD group ($r = 0.23$, $P = 0.1$; Fig. 2A). The patients with AMD ($n = 4$) with major or possible major depression, according to the CES-D scores, did not have significantly reduced PIPR amplitudes compared to the mean PIPR for the AMD group. Exclusion of the patients on antidepressant medication did not affect the average pupil measurements. There was no correlation between depression scores and the initial pupil constriction amplitude ($P > 0.05$). Depression scores did not correlate with visual acuity in the CNV/GA group ($r = 0.03$, $P = 0.85$) or number of injections administered in the CNV group ($r = 0.13$, $P = 0.38$).

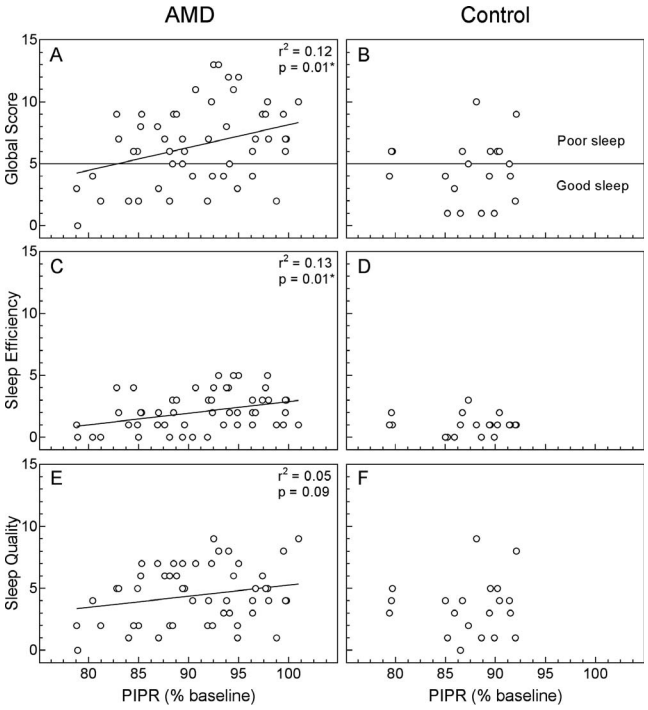

Figure 1. Correlation between PIPR and sleep components. The scatterplot and linear regression lines show the association between the PIPR to a blue light stimulus ($\lambda_{max} = 448$ nm) and sleep components in AMD patients ($n = 53$; **A**, **C**, **E**) and healthy control participants ($n = 20$; **B**, **D**, **F**). The *horizontal line* in the top graphs indicates a cutoff point in the global score to distinguish between "good" and "poor" sleep.

Discussion

This is the first study to investigate the relationship between ipRGC function, sleep behavior, and depression in AMD. We hypothesized that altered ipRGC function in AMD will lead to sleep and mood disturbances due to their projections to corresponding brain areas. Based on previous studies,[17,21] we proposed that aberrant light signaling through dysfunctional ipRGCs will contribute to these behavioral changes. A positive correlation was observed between reduced ipRGC function as measured by the melanopsin-mediated PIPR and poorer sleep efficiency, with ipRGC dysfunction accounting for 13% of the reduced sleep efficiency. There was no relationship between ipRGC function and risk of depression in AMD patients; however, a limitation of this study is that the number of depressed AMD patients was low, hence further studies with a larger cohort are needed.

All three photoreceptor types; rods, cones, and ipRGCs are affected in advanced AMD[5,55] and contribute to the initial pupil constriction during stimulus presentation,[47] whereas ipRGCs and rods contribute to the sustained post-illumination pupil response.[12,15] At least five different ipRGC subtypes (M_1–M_5)[56,57] project to nonimage forming centers in the rodent brain, with the M_1 and M_2 subtypes likely to be homologous to the outer and inner stratifying melanopsin cells found in humans and nonhuman primates.[58–60] A recent mouse study using single M_1 ipRGC axonal tracing and confocal microscopic analysis identified up to five different brain targets that received input from a single M_1 subtype ipRGC, indicating that a single ipRGC can affect brain areas involved in numerous light-mediated behaviors.[61] Therefore, the correlation between poor sleep efficiency and reduced PIPR may be attributed to individual dysfunctional M_1 ipRGCs projecting to both the SCN and OPN.

Poor sleep is a common complaint in the aged population,[62] but there is no evidence for a significant age-related difference in sleep behavior,[63,64] consistent with data from our healthy control group, suggesting that the sleep problems detected in

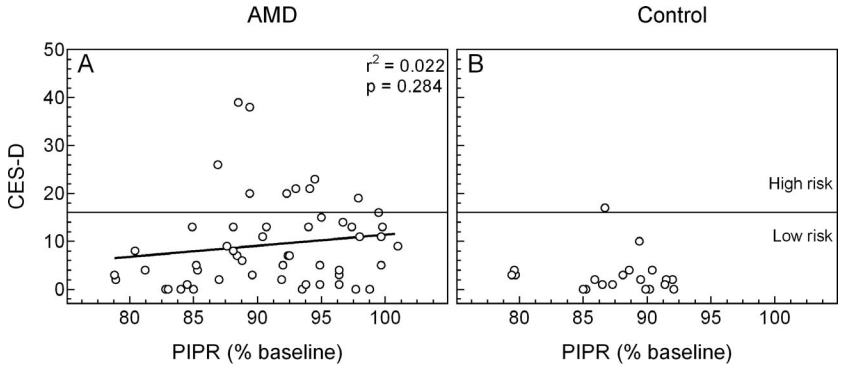

Figure 2. Correlation between PIPR and mood. The scatterplot and linear regression lines show the correlation between the 6s PIPR to a blue light stimulus ($\lambda_{max} = 448$ nm) and depression in AMD patients ($n = 48$; **A**) and healthy control participants ($n = 20$; **B**). The *horizontal line* indicates a cutoff point to identify people at risk for depression (>16) and those with low to no risk for depression (<16).

the AMD group are secondary to comorbidities rather than to aging.[64] Furthermore, ipRGC function is robust to aging,[42,65] with one study showing an enhanced response to high irradiance short wavelength light associated with advancing age.[66] Therefore, it is unlikely that the advanced age of the participants provided the basis for the association between ipRGC dysfunction and poor sleep efficiency in this study. Other contributors to poor sleep behavior in the elderly may include changes relating to time in REM and slow-wave sleep,[67] medical or psychiatric illness,[64] and sleep-related disorders such as restless legs syndrome or sleep apnea,[68,69] although only sleep apnea has been previously associated with AMD.[69] The sleep quality component of the PSQI questionnaire considers these contributing factors as it addresses sleep disturbances and perceived sleep quality; however, these were nonsignificant in our cohort.

Depression in AMD has been attributed to functional disabilities and loss of independence due to impaired vision.[24–26,70,71] Of the AMD patients in this study, 28% had either met criteria for risk of depression or were taking antidepressant medication. However, no correlation between ipRGC function and depression in advanced AMD was found, hence our hypothesis for a causal relationship between the dysfunction of these cells and altered signaling to mood centers could not be evaluated in this sample. Irregular light exposure can influence cognitive and mood functions directly through ipRGCs[21] as demonstrated in patients with SAD who have a reduced PIPR amplitude.[22] Seasonal affective disorder may be caused by an abnormal response to seasonal light changes,[72] with melanopsin gene variants increasing the risk for SAD in 5% of individuals.[73] As the SAD patients had no ocular pathology, the lower PIPR amplitude may be due to irregular light exposure, although this was not measured in that study.[22] Our AMD cohort did not report any symptoms of SAD; therefore, the reduced PIPR amplitude in our study may be due to pathologic ipRGC dysfunction that leads to aberrant inputs to the brain, rather than due to irregular light exposure. It is still unknown which ipRGC subtype(s) project to mood centers in the human brain and whether these projections are affected by AMD. Visual acuity and number of intravitreal injections did not correlate with the depression scores in this study. Visual impairment is a risk factor for depression, but it is not an inevitable consequence of vision loss and depression can occur regardless of the level of vision impairment.[24,74] Further research is needed to determine the cause of the association between AMD and depression.

In conclusion, this study provides the first evidence that ipRGC dysfunction contributes to reduced sleep efficiency in patients with advanced AMD. With subtypes of melanopsin ipRGCs that stratify in different regions of the inner plexiform layer and project differentially to the SCN and OPN, this new knowledge advances insights into ipRGC contributions to AMD and its nonvision-related disorders, allowing a further understanding of this complex condition.

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