

Evidence of a Biological Effect of Light Therapy on the Retina of Patients with Seasonal Affective Disorder

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Background: Retinal sensitivity anomalies have been reported in patients affected by seasonal affective disorder (SAD). We used the electroretinogram (ERG) to assess seasonal change in retinal function in patients with SAD and healthy participants, as well as in patients following 4 weeks of light therapy.

Methods: ERG assessments were obtained in 22 SAD patients (2 men, 20 women, mean age 31 ± 9 years) in the fall/winter season before and after 2 and 4 weeks of light therapy and in summertime. Matched healthy participants (2 men, 14 women; mean age 29 ± 8 years) were evaluated once in the fall/winter and once in summer. The 29-item Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version was administered. Standard ERG parameters were derived from the photopic and scotopic luminance response functions. Salivary melatonin concentration during ERG was assessed in both groups but during fall/winter assessments only.

Results: A significantly lower cone ERG maximal amplitude and lower rod sensitivity was found in SAD patients before light therapy compared with healthy participants. Following 4 weeks of light therapy, a normalization of cone and rod ERG function occurred. ERG parameters in the summer and melatonin concentrations in fall/winter were not significantly different between groups.

Conclusions: Depressed patients with SAD demonstrate ERG changes in the winter compared with healthy comparison subjects with lower rod retinal sensitivity and lower cone maximal amplitude. These changes normalized following 4 weeks of light therapy and during the summer, suggesting that ERG changes are state markers for SAD.

Key Words: Cone, electroretinography, light therapy, melatonin, rod, seasonal affective disorder

Seasonal affective disorder (SAD) is a term used to describe a subtype of major depressive disorder characterized by recurrent depressive episodes in the fall/winter, summer remission of symptoms, and good response to bright light therapy (LT) (1). Because circadian effects of light are mediated through the retina, it was initially considered that the retina itself could play a central role in the pathogenesis of SAD and the response to LT. Several studies have examined retinal function in SAD using various electrophysiological or psychophysical techniques. For example, a rod sensitivity anomaly was observed in patients with SAD using electroretinography (ERG) (2,3), whereas another ERG study showed normalization of rod function in summer in subjects with subsyndromal SAD (S-SAD) (4). In contrast, studies using dark adaptometry (DAT) found subjective rod light sensitivity to be similar between patients with SAD and healthy subjects in both seasons (5,6), whereas cone sensitivity was higher in patients in winter (compared with healthy subjects) with a seasonal increase in sensitivity in summer (6). In studies with electrooculography (EOG), a measure of integrated retinal epithelium and photoreceptor function, lower EOG activity was found in patients with SAD in winter (7,8), although this

was attributed in a subsequent seasonal study to a winter increase in the EOG response in the healthy subjects (9).

Because the techniques just described differ in specificity of retinal function assessment, it is difficult to reach consensus on whether cone function, rod function, or both are altered in patients with SAD. In addition, there is limited information on the effects of LT on retinal function. Nonetheless, these studies suggest that the pathophysiology of SAD may involve the retina. Considering that the retina originates from the primitive forebrain, it should not be surprising that similar neural dysfunction could be present in both the central nervous system (CNS) and the retina. In fact, many studies have implicated dysfunction in central neurotransmitters such as serotonin and dopamine in the pathophysiology of SAD (10). These neurotransmitters have also been shown (mostly in animal studies) to have effects on ERG responses. This study was intended to clarify the understanding about retinal function in patients with SAD by assessing both cone and rod ERGs in summer and winter seasons, as well as following 4 weeks of LT during the fall/winter depressive state. In addition, melatonin was assessed during the ERG, because phase-delayed melatonin rhythms and higher daytime melatonin levels have been reported in some SAD studies (11–14), and it has been shown to negatively affect cone functioning (15).

Methods and Materials

Participants

Twenty-two patients (2 men, 20 women; age range: 21–49 years, mean age 31 ± 9 years) with SAD and 16 healthy participants (2 men, 14 women; age range: 20–43 years; mean 29 ± 8 years) were recruited by media advertising in Quebec City, Canada (latitude $46^{\circ}48'N$). This study was approved by the institutional ethics committee at Centre de recherche Université Laval Robert-Giffard (CRULRG), and participants provided informed consent and received compensation. The two groups were matched for age and sex, as much as possible.

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All participants received a formal ophthalmologic examination, and none reported past or present use of medications (except contraceptive pill), substance abuse, or medical condition. Pregnant or breast-feeding women and nightshift workers were excluded.

Mood Assessments

Patients were selected if they met DSM-IV criteria for major depressive disorder with a seasonal pattern as determined by a clinical interview with a board-certified psychiatrist. They were also assessed with the Seasonal Pattern Assessment Questionnaire (SPAQ) (16), a French version of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version (SIGH-SAD) (17), and the Beck Depression Inventory—II scale (BDI-II) (18). To ensure consistency, the French version of the SIGH-SAD was professionally translated back to English and compared with the original. The entry criteria for patients included a SIGH-SAD score of ≥ 21 on the full 29 items and a score ≥ 10 on the 8-item atypical subscale, a Global Seasonality Score (GSS) score of ≥ 11 and perceiving seasonal changes as at least a “moderate” problem on the SPAQ, and a BDI-II score of ≥ 13 . Healthy participants were selected with no history of psychiatric disorder, a score of ≤ 11 on the 29-item SIGH-SAD, a GSS of ≤ 9 on the SPAQ with “no problem” with seasonal changes, and BDI-II score of ≤ 8 . During LT, mood ratings (SIGH-SAD) were assessed weekly by a psychologist.

Materials

All participants were studied between July 2004 and June 2006, in the fall/winter season between September and December (with the exception of two participants tested in January) and in summer between May and August. Light therapy was self-administered at home using a commercial fluorescent lamp (light temperature 3000 Kelvin; SADelite provided by Northern Light Technologies, Montreal, Canada). Patients were told to sit at a table or a desk in front of the lamp at a distance of about 50 cm, receiving an illuminance of approximately 5000 lux at eye level, while reading the newspaper or having breakfast. Daily sessions of 30 min were performed in the morning (before 10 AM) for 4 consecutive weeks.

Methods

Photopic and scotopic ERGs were conducted in all participants at 11:00 AM in both seasons. In summer, symptom remission was confirmed with SIGH-SAD and BDI-II before ERG assessment. In the winter, patients also had ERGs conducted after 2 and 4 weeks of LT. All participants were instructed to maintain a regular sleep/wake schedule during the 3 days before ERG and to fill out a sleep diary in which wake times, bedtimes, and the timing of LT (patient group only) were reported. SIGH-SAD was repeated just before the first ERG.

Electrophysiologic Assessment. We took the opportunity in this study to test in the first 12 participants the effect on the ERG when one eye was not dilated; for the remaining 26, both eyes were dilated (these data are reported in a separate publication). We selected only the dilated eye for ERG analysis, and when both eyes were dilated, we averaged the ERG results. To dilate the eye(s), a drop of anaesthetic proparacaine hydrochloride (Alcaine [Alcon Canada, Mississauga, Ontario, Canada]) .5% was applied followed by a drop of tropicamide (Mydracyl [Alcon Canada]) 1%. Recordings were obtained with Dawson, Trick, Litzkow electrodes (Shieldex 33/9 Thread; Statex, Bremen, Germany) secured deeply into the conjunctival sac, a technique

known to yield highly reproducible ERG responses (19). Ground and reference electrodes (Grass Technologies [Astro-Med, Inc., Brossard, Quebec, Canada] gold cup electrodes filled with EC2 electrode cream) were pasted on the forehead and external canthi respectively, as previously described (20,21).

Flash stimulations were administered with a Ganzfeld (Color Dome, Espion system; Diagnosys, Lowell, Massachusetts) to achieve full-field retinal stimulation. Participants were first dark adapted for 30 min before a series of green light flashes (Color Dome green LED, peak 510 nm) of increasing intensities (range: -4.25 to -1.00 log cd/m².s; stimuli intervals: 1.5–5.0 sec) were presented to generate a scotopic luminance response function. Participants were then light adapted for 15 min to a background light (25.5 cd/m²) to prevent the light adaptation effect (22,23). A series of white light flashes (Color Dome) of increasing intensities (range: -1.12 to 1.375 log cd/m².s; stimuli interval: 1.5 sec) were presented to generate a photopic luminance response function. For each intensity, at least 10 responses or more were averaged to achieve an optimal signal-to-noise ratio.

Melatonin Assessment. We assessed salivary melatonin, a technique yielding concentrations that are correlated to those observed in plasma (24). Saliva samples were collected with salivettes (Sarstedt, Newton, North Carolina) just before the photopic ERG in winter and, in patients, again after 4 weeks of LT. Each saliva sample was frozen immediately after collection. Melatonin concentrations were determined by direct saliva melatonin enzyme-linked immunosorbent assay (ELISA) with an American Laboratory Products Company kit (Windham, New Hampshire). Assays were performed by a person highly trained with the technique (A.S.). All samples collected from the same participant were assayed on the same plate.

Statistical Analysis

Summary data are reported as mean \pm SD. Analysis of the ERG (see example of waveform at Figure 1) included the amplitude and implicit time of the a-wave and the b-wave. By convention, the a-wave amplitude was measured from baseline to trough of response and the b-wave from the trough of the a-wave to the peak of the response. The implicit time, a measure of response latency, was calculated from the flash onset to the trough of the a-wave (a-wave implicit time) and peak of the b-wave (b-wave implicit time). The b-wave

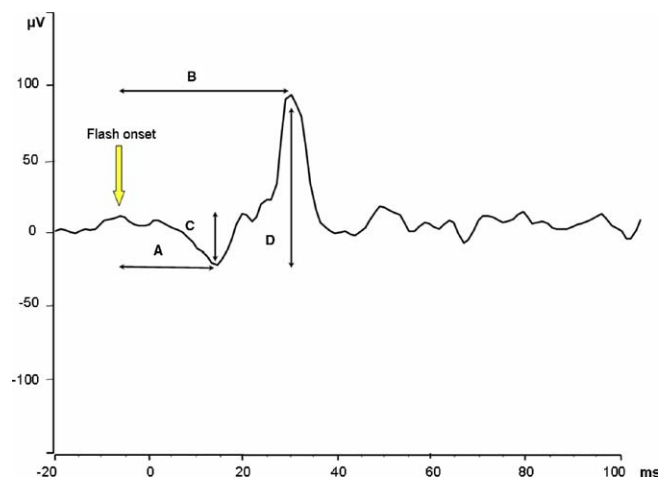


Figure 1. Electretinogram (ERG) wave characteristics: (A) a-wave implicit time, (B) b-wave implicit time, (C) a-wave amplitude, and (D) b-wave amplitude. Amplitude is presented in microvolts and implicit time in milliseconds.

Table 1. Clinical Characteristics of Patients with Seasonal Affective Disorder and Healthy Participants over the Course of the Study

Scores	Patients (n = 22)						Control Subjects (n = 16)	
	Baseline Autumn/Winter	LT Week 1	LT Week 2	LT Week 3	LT Week 4	Summer	Autumn/Winter	Summer
BDI-II	18.9 (15.9–21.9)	10.9 (8.1–13.8)		4.4 (3.1–5.8)		1.82 (.57–3.06)	1.8 (1.0–2.6)	1.4 (.31–2.4)
SIGH-SAD								
21-item	15.6 (14.3–16.9)	7.1 (5.4–8.7)	4.3 (3.2–5.4)	3.0 (2.2–3.8)	2.9 (2.0–3.9)	2.4 (1.4–3.4)	.9 (.3–1.5)	.9 (.3–1.6)
8-item	11.5 (1.1–12.9)	5.9 (4.1–7.7)	3.0 (1.9–4.1)	2.5 (1.6–3.4)	2.1 (1.4–2.7)	1.3 (.7–2.0)	1.1 (.30–2.0)	.6 (.0–1.4)
Total	27.05 (24.9–29.2)	13.0 (9.7–16.2)	7.2 (5.3–9.1)	5.5 (4.1–6.9)	4.9 (3.51–6.3)	3.7 (2.4–5.0)	1.9 (.6–3.2)	1.56 (.3–2.8)
SPAQ GSS	14.3 (12.8–15.7)						3.8 (2.7–5.0)	

Means are presented with their respective 95% confidence limit.

BDI-II, Beck Depression Inventory—II scale; LT, light therapy; SIGH-SAD, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version; SPAQ GSS, Seasonal Pattern Assessment Questionnaire, Global Seasonality Score.

amplitudes were then plotted against flash intensities to generate the photopic and scotopic luminance-response functions respectively. A luminance response function allows the detection of the saturating response of the photoreceptors (Vmax) as well as the intensity necessary to generate half the saturating response (log K), which is interpreted as retinal sensitivity. Both parameters were derived according to reported methods (21,25,26). More precisely, the log K parameter was calculated with the Origin 7.0 software after performing a sigmoidal curve fitting on all points that preceded Vmax (OriginLab, Northampton, Massachusetts).

Repeated-measures analysis of variance (ANOVA) was used to assess the effects of LT (baseline and after 2 and 4 weeks) on depression ratings (21- and 8-item SIGH-SAD) and on all the ERG parameters for both the photopic and scotopic ERGs.

Two-way ANOVAs with repeated measures were used for group and season comparisons. Significant interactions were followed by specific contrast analyses for which alpha was set at .025 to correct for multiple comparisons. All analyses were conducted using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, Illinois).

Results

Table 1 presents the clinical data (SIGH-SAD, BDI-II, and SPAQ) of both groups. Age was not significantly different between groups (unpaired *t* test, *p* > .05). Both the 21-item and 8-item SIGH-SAD scores improved during LT [*F*(4,84) =

111.23 *p* < .0001 and *F*(4,84) = 60.40 *p* < .0001, respectively] with improvement observed between baseline and Week 2 (*p* < .01 and *p* < .001, respectively) but not between Week 2 and Week 4.

Using strict criteria (27) to define “remission” (29-item SIGH-SAD score of ≤ 8) and “response” (decrease of ≥ 50% from the baseline score), we observed that all patients responded to LT, whereas 81% achieved remission after 4 weeks (see Figure 2).

Melatonin Concentration During ERG

Because of technical issues, melatonin was extracted in 53 of the 60 saliva samples. Those not extracted included three samples obtained at baseline and two at posttreatment in the patient group, and two samples in the healthy participant group. The mean melatonin concentrations in patients at baseline (2.3 ± 2.2 pg/mL) and after 4 weeks of LT (2.0 ± 1.5 pg/mL) were not significantly different (paired *t* test; *p* > .05) than those observed in healthy subjects (2.6 ± 1.5 pg/mL). One outlier in the patient group showed a higher melatonin concentration before LT than the others (10.8 pg/mL; see Figure 3).

Photopic ERG

Cone luminance response functions are reproduced in Figure 4A. A season-by-group interaction [*F*(1,36) = 17.72; *p* < .0001] was observed, with Vmax being 13% lower in patients (*p* = .001) in winter but not different in summer (*p* > .05). An effect of weeks of treatment [*F*(2,42) = 33.87 *p* < .0001] was observed with improvement in Vmax amplitude observed between baseline and Week 4 and between Week 2 and 4 (*p* < .001).

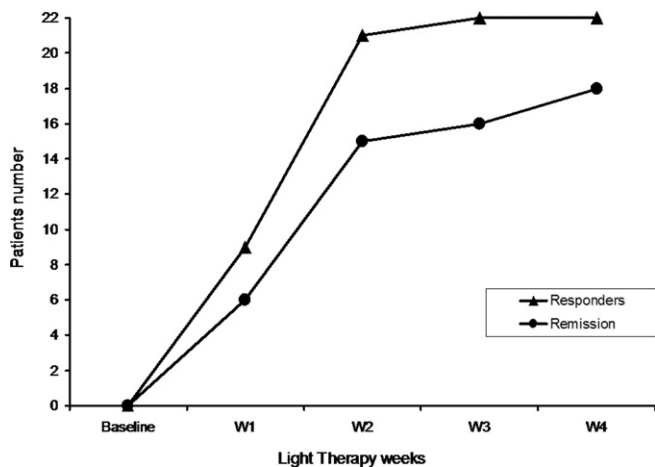


Figure 2. Number of responders and remitters among patients with seasonal affective disorder (n = 22) during the 4-week light therapy treatment.

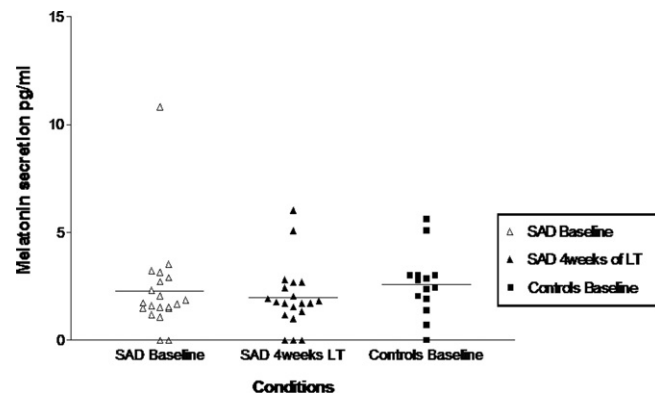


Figure 3. Salivary melatonin concentration in patients with seasonal affective disorder (SAD) (n = 22) at baseline and after 4 weeks of light therapy (LT) and in healthy participants (n = 16) for the fall/winter testing period only. No melatonin data were acquired in summer.

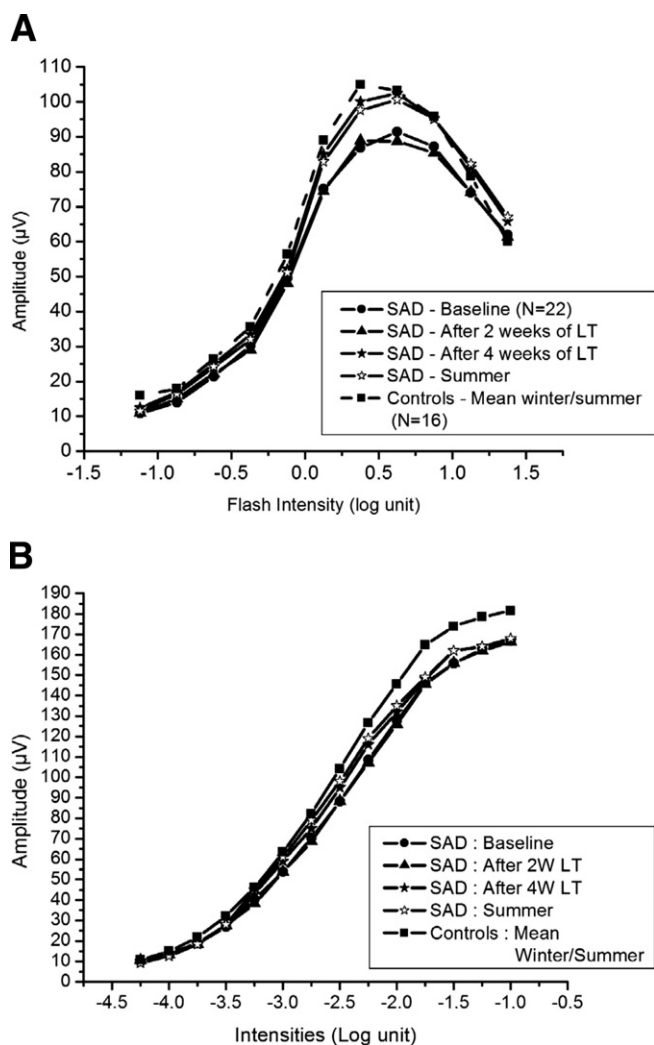


Figure 4. (A) Mean photopic electroretinogram (ERG) luminance response function (LRF) in healthy participants ($n = 16$) and patients with seasonal affective disorder (SAD; $n = 22$). In patients, LRF is presented at baseline and after 2 and 4 weeks of light therapy (LT) in fall/winter and once in summertime. In healthy participants, summer and fall/winter LRF were averaged together because they were not different. (B) Mean scotopic ERG LRF in healthy participants and in patients with seasonal affective disorder.

B-wave implicit time at Vmax changed marginally during treatment [$F(2,42) = 3.059$; $p = .06$], but a season-by-group interaction [$F(1,36) = 4.295$; $p < .05$] was observed with implicit time being 7% longer in patients during the depressive episode only ($p < .0001$). A significant change in b-wave implicit time was observed between seasons in patients ($p < .0001$), with normalization of this parameter in summer.

No treatment or group effect was found on the Vmax a-wave amplitude and implicit time nor log K (retinal sensitivity).

Scotopic ERG

Rod luminance response functions are reproduced in Figure 4B.

At Vmax, no interaction in terms of group and season [$F(1,36) = .004$; $p > .05$] or weeks of treatment [$F(2,42) = .455$; $p > .05$] was observed. A change in log K was observed between weeks of treatment [$F(2,42) = 5.057$; $p < .05$] with retinal sensitivity improving significantly between baseline and Week 4 ($p < .05$). A season-by-group interaction was also observed [$F(1,36) =$

21.572; $p < .0001$] with rod retinal sensitivity in winter being significantly lower by .13 log in patients at baseline when compared with the healthy participants ($p < .05$). A seasonal variation in log K was seen in patients ($p < .0001$), with lower retinal sensitivity observed in fall/winter baseline. Of interest, at baseline, 63% of patients demonstrated a log K value that was at least 1 SD (SD = .08 log unit) below the mean of healthy participants (see Figure 5). Following 4 weeks of LT, the 1 SD difference was still present in 40% of patients, whereas in summer only, 18% of the sample fell below the 1 SD criterion. Various covariables tested, such as SIGH-SAD and SPAQ scores, age, eye color, and date of recording, could not explain this result.

In patients, an effect of weeks of treatment was observed on Vmax b-wave implicit time [$F(2,42) = 4.888$; $p < .05$] but only between baseline (68.5 msec) and Week 4 (72.9 msec; $p < .05$). However, no significant season-by-group interaction was observed [$F(1,36) = 1.328$; $p > .05$]. No treatment effect or season-by-group effect was found on Vmax a-wave amplitude and implicit time.

Discussion

These results replicate previous ERG studies showing a rod sensitivity anomaly in patients with SAD. In addition, we report that cone ERG responses are affected in SAD and, similar to the rod system, demonstrate a seasonal variation with normalization of both rod and cone ERG function in summer. However, another important finding is that both systems also normalized after 4 weeks of LT, which to our knowledge represents the first demonstration of a biological effect of LT on retinal function. Given that all patients responded to LT, we cannot determine whether the normalization of ERG responses after LT is necessary for clinical response and whether there are differences between responders and nonresponders to LT. In this study, we observed a relatively high remission rate (81%) after 4 weeks of treatment with 5000 lux for 30 min in the morning. Although we cannot exclude a placebo response, the inclusion of patients with high scores on the 8-item atypical subscale may have contributed to the high response rate because atypical symptoms have been found to predict good response to LT (27). Another limitation of the study was that the patient sample included only two men, so we cannot examine whether there is a sex difference in the results.

Although consistent with previous reports, the decrease in rod sensitivity of .13 log unit in patients with SAD compared with healthy participants was not as marked as that reported in two previous ERG studies in SAD (.21 log unit) and S-SAD (.18 log unit) (3,4). One possible explanation is that our patient sample was tested mostly in the fall, whereas in the other ERG studies, more than half the patients were tested later in winter when they may have been depressed for a longer time. We also found a significantly shorter rod b-wave implicit time in patients (at baseline, but not after 4 weeks of LT), which is in agreement with the only other ERG study in which this measure was reported (2). However, the implication of any link between faster response peak time and lower sensitivity remains unclear.

Using a similar analysis as per the S-SAD study (3), we also found that at baseline, almost two thirds of patients had a rod light sensitivity that was at least 1 SD below the mean of the healthy subjects. Following 4 weeks of LT and despite marked improvement in mood in all patients, this difference was still present in 40% of patients. It is possible that the dose (5000 lux

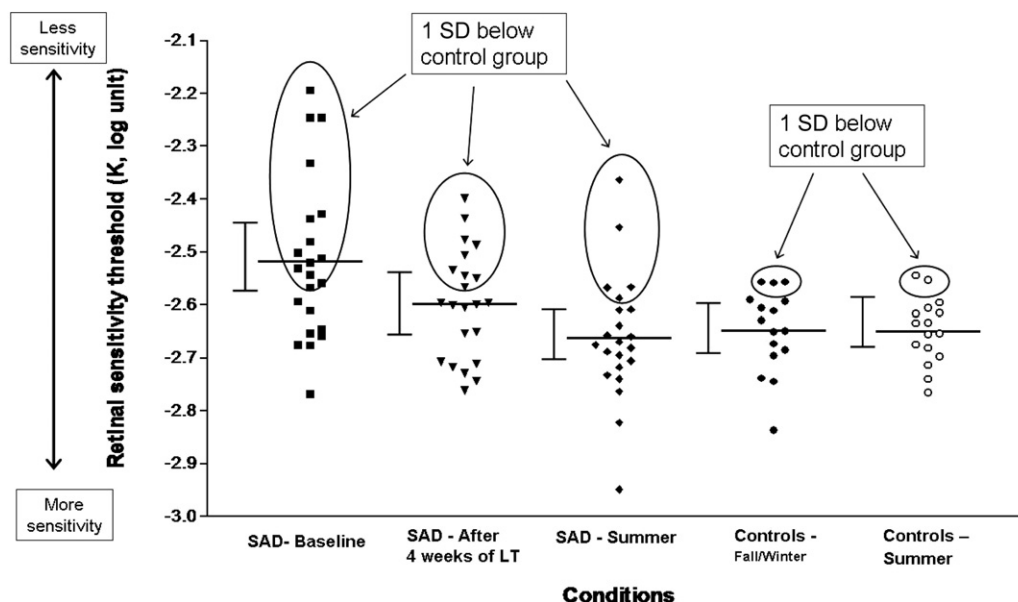


Figure 5. Retinal sensitivity values (log K) in healthy participants ($n = 16$) in fall/winter and summer seasons and in patients with seasonal affective disorder (SAD; $n = 22$) at baseline and after 4 weeks of light therapy (LT) in fall/winter and once in summertime.

for 30 min), duration (4 weeks) of LT (or both) used in this study is not sufficient to correct entirely the rod sensitivity anomaly in all patients; that there is a lag time between clinical and ERG response; or that the relationship between improvement and retinal function in this study is obscured by a placebo effect.

Cone b-wave amplitude can be inversely correlated with melatonin in some studies (28), but we found no difference in salivary melatonin concentration between groups. Only one patient showed high levels of melatonin at baseline, but the corresponding cone ERG was not particularly low. These results suggest that the reduction in cone ERG sensitivity was not due to excess melatonin secretion. The 13% decrease in cone Vmax b-wave amplitude is also not sufficient to classify these patients as having abnormal cone photoreceptor functioning by clinical standards. Moreover, this decrease in cone ERG response may appear to conflict with reports suggesting higher cone sensitivity using DAT (6) and lack of seasonal variation in the EOG ratio in patients with SAD (9). Reconciling these results is not yet possible because these varied techniques measure different retinal processes. Replication of these findings will be important to determine which are more consistently linked to the pathophysiology of SAD.

The physiologic basis for retinal dysfunction in SAD and the underlying mechanism by which LT affects retinal functioning remain poorly understood. Dopamine is a major neurotransmitter in the retina (29,30) that also clearly affects the ERG. Dopamine antagonists increase rod sensitivity in cat retina (31), as does destruction of dopaminergic neurons (32). Therefore, lower rod sensitivity could result from an increase in retinal dopaminergic activity. Of note, this would be consistent with studies showing higher eye-blink rate, low prolactin levels, and deficient heat loss response previously reported in patients with SAD (33–36), all of which have been interpreted as suggestive of an increase in central dopaminergic activity (35,37). However, there is no single neurotransmitter in the retina that can account for both rod and cone dysfunction in SAD, so other retinal neurotransmitters such as serotonin or gamma-aminobutyric acid must also be involved.

In conclusion, reduced ERG cone and rod functioning appears to be a state marker of SAD, with retinal anomalies observed only during the fall/winter depressive episode and with normalization of retinal parameters following successful treatment with LT. These findings may be related to common neurotransmitter dysfunction in the CNS and the retina, although other explanations, such as a circadian phase shift in retinal function cannot be fully discounted. We believe that the retina represents a good model to investigate CNS activity, but additional studies are necessary to clarify the interaction between neurotransmitters in the retina and in the brain and to understand these retinal findings and how they relate to the pathogenesis of SAD.

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