
Photopic and Scotopic Light Detection in Patients with Seasonal Affective Disorder and Control Subjects

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Background: *Retinal sensitivity may play a role in the pathogenesis of seasonal affective disorder (SAD) and response to light therapy.*

Methods: *Using a dark adaptation procedure, SAD patients and normal control subjects were tested in the winter and summer, with patients retested after light treatment. The eyes were preadapted to bright light followed by 30 min in darkness, during which subjects detected a dim signal titrated around the detection threshold. Photopic (cone-mediated) and scotopic (rod-mediated) components of the data were identified by nonlinear exponential curve fits to successive threshold estimates.*

Results: *Patients (n = 24) showed significantly lower cone and rod thresholds in the summer than winter, while control subjects (n = 12) showed a similar trend. Relative to the control subjects, however, patients were supersensitive in winter (lower cone final threshold, faster rod recovery). Clinical responders to morning light showed a small summer-like increase in cone sensitivity, whereas nonresponders became subsensitive. In comparison to darker-eyed patients, blue-eyed patients showed a larger summertime increase in cone sensitivity and a similar trend after response to morning light.*

Conclusions: *Heightened retinal sensitivity with increased light exposure, and supersensitivity of patients relative to control subjects in winter, may play roles in the pathogenesis of winter depression and the action of therapeutic light. Biol Psychiatry 1999;46:1642-1648 © 1999 Society of Biological Psychiatry*

Key Words: Seasonal affective disorder, dark adaptation, cones, rods, iris pigmentation, light therapy

Introduction

The antidepressant effect of bright light in winter depression is probably mediated by retinal phototransduction (Wehr et al 1987). The particular photoreceptors

involved have not been identified. Considerable attention has concentrated on scotopic sensitivity, which is mediated by rhodopsin-rich rods. Results have been mixed. Using a dark adaptation paradigm (Krill 1972), Oren et al (1993) found no difference in the scotopic threshold of patients with seasonal affective disorder (SAD) and normal control subjects in winter or summer. Using electroretinography, Lam et al (1992) found lowered b-wave amplitude, indicating subsensitivity in winter among female (but not male) patients compared with control subjects. Similarly, M. Hébert et al (unpublished data, 1999) found higher wintertime response thresholds in subjects with seasonal mood variation than in control subjects. Subsensitivity of the electrooculogram (EOG) has also been reported for SAD patients relative to normal control subjects in winter (Lam et al 1991; Ozaki et al 1993), while both groups appeared subsensitive in summer (Ozaki et al 1995). Both ERG and EOG changes appear to be state dependent, and are normalized after light treatment (Tam et al 1998). A wide range of ophthalmic tests involving both rod and cone function, including higher-order visual evoked potentials, has yielded minimal evidence of abnormality in SAD or change with the seasons in comparison with normal control subjects (Oren et al 1993). It is possible that novel photoreceptors other than the rods and cones transduce the therapeutic light signal, as has been suggested for circadian phototransduction in animals (Freedman et al 1999). Pineal melatonin suppression to bright retinal illumination provides an alternate measure of light sensitivity. During the winter, SAD patients have shown greater melatonin suppression than normal control subjects (supersensitivity), with the opposite result (subsensitivity) in summer (Thompson et al 1990). Earlier, Lewy et al (1985) had shown supersensitivity of suppression in bipolar patients relative to normal control subjects. Whether differences in pineal melatonin secretory activity reflect abnormal retinal response to light is unclear.

Two contrasting ocular hypotheses have been proposed to account for the emergence of depression in winter and the response to treatment with bright light. Remé et al (1990) suggested that in the dark months of the year patients might fail to show a compensatory increase in

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photoreceptor renewal and thus, light sensitivity, increasing their vulnerability to depression. In contrast, Beersma (1990) suggested that patients might show retinal supersensitivity in winter, such that evening room light functions as an extension of daylight, fostering depressogenic circadian phase delays (Lewy et al 1987).

The present study examined cone and rod sensitivity as subjects detected a dim light signal during dark adaptation following a bright light bleach of the visual pigments. Patients with SAD and normal control subjects were compared in winter and summer, and patients were compared before and after morning or evening bright light therapy. We reasoned that if bright light transduction is mediated by the cones—while rods are saturated—patients would show elevated cone thresholds in winter, with increased retinal sensitivity in the summer and after morning light therapy. The study also offered an opportunity to reconsider previous negative results—no seasonal change in retinal sensitivity in SAD patients, and no difference relative to normal control subjects—using a similar procedure (Oren et al 1993).

Based on clinical impressions, D.F. Klein (personal communication) has hypothesized that blue-eyed, light-skinned patients of northern European descent might be more vulnerable than others to SAD. The prevalence of SAD in Scandinavian populations typified by such pigmentation (Pálsson 1978) has been high in some countries (Dam et al 1998; Saarijärvi et al 1999) but not others (Magnússon and Stefánsson 1993). Among patients in New York, approximately one third of whites have been blue-eyed. Interestingly, they show lower depression scores and can be classified by discriminant analysis as less fatigued than their darker-eyed counterparts (N. Goel et al, unpublished data, 1999). Reduced ocular pigmentation in blue-eyed people causes hypersensitivity to bright light (van den Berg et al 1991). They may also respond at lower light levels to artificial dawn simulation used to treat winter depression and delayed sleep-phase syndrome (Terman 1997). Although group assignments in the present study were not based on eye color, we sought to examine this potential factor of retinal sensitivity in SAD.

Methods and Materials

Subjects

The study included 31 patients with SAD (22 women and 9 men, ages 18 to 63 years; mean \pm SD, 37.8 ± 11.0) who had been recruited into light treatment protocols (Terman et al 1990). All received DSM-III-R diagnoses of mood disorder with seasonal pattern (major depressive disorder, $n = 22$; bipolar disorder NOS, $n = 7$; depressive disorder NOS, $n = 2$) with no other Axis I diagnosis. They received general medical examinations and were found to be in good health and without psychotropic or

photosensitizing medication. Complete ophthalmologic examinations (Gallin et al 1995) verified normal ocular status in all patients.

A group of 15 normal control subjects included 8 women and 7 men, ages 23 to 50 years (31.3 ± 7.9), recruited from New York State Psychiatric Institute staff, and screened by the Seasonal Assessment Pattern Questionnaire (SPAQ; Rosenthal et al 1984). All reported good health, normal ocular status, no history of depression, and were medication-free. The SPAQ global seasonality score ranged from 0 to 6 points in control subjects (2.6 ± 1.8); by comparison, patients scored 12 to 23 points (17.4 ± 2.7). All subjects signed an informed consent.

Schedule of Testing and Group Classification

Both patients and normal control subjects received dark adaptation tests during the winter (between December and February) and 4 to 6 months later, in the late spring or summer. The patients were assessed at baseline, while depressed (at least 2 weeks after episode onset), and after 10 to 14 days of light therapy (10,000 lux, 30 min/day, in the early morning or evening; Terman et al 1990). With baseline scores of 20 or more, treatment responders attained score reductions of 50% or more on the Structured Interview for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH–SAD; Williams et al 1994), with a final score of 8 or lower. At the time of the summer tests, depressive symptoms were in remission. Because of attrition, several subjects were not tested at all time points. To maximize available data, groups were reconstituted, depending on the comparison, and normal control subjects were matched with patients for age (± 2 years) and gender.

Dark Adaptometry

Testing was performed between 10 AM and 3 PM using a Goldmann/Weekers dark adaptometer, following a standard protocol (Krill 1972). Subjects sat in a darkroom facing the apparatus, with head position stabilized by a chin rest. They were preadapted for 5 min with 3500 lux white light (the “bleach”) presented in a homogeneous full surround (ganzfeld). Both eyes were exposed without dilation. During the 30 min dark adaptation period, subjects orally reported the presence (yes) or absence (no) of a dim white circular target of 7° visual angle, which flashed 0.75 sec every 1.5 sec. They were instructed to fixate on a dim red spot 18° above the target; such displacement allows the target to stimulate a retinal region containing both cones and rods. Initial target intensity was 3.6×10^{-6} w/cm², or 6.0 log units on the relative intensity scale used to specify momentary thresholds. This signal was easily detectable shortly after the bleach. Every 30 sec, the experimenter gradually adjusted the target intensity upward or downward according to its momentary visibility. The subject received a warning signal 2 sec before each trial. Upon reporting “yes” as target intensity increased from below threshold, the progression was reversed until the subject reported “no.” Responses were registered by punching a pinhole on a drum chart with graphical coordinates indicating the current intensity.

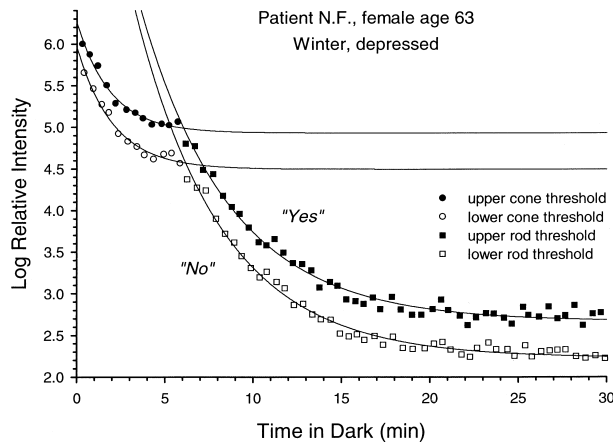


Figure 1. Visual detection threshold judgments during dark adaptation for a patient with winter depression. A 5-min bright light bleach was terminated at 0 min. Symbols: target light intensities at the time of positive detection (yes) and loss of detection (no) as the stimulus intensity was varied upward and downward every 30 sec. Smooth curves: best-fitting nonlinear exponential functions for photopic (cone) and scotopic (rod) segments of successive threshold estimates. Data were further reduced by averaging the upper and lower curves for each subject.

RAW DATA REDUCTION AND SUMMARY. Punched chart data were digitized (SigmaScan, SPSS, Chicago). As illustrated for one case in Figure 1, each test session produced two dark adaptation curves, for upper (yes) and lower (no) thresholds. After about 5 min, the initial decelerating limb of the curve (which reflects cone-mediated photopic adaptation) was superseded abruptly by a more rapid downward progression (which reflects rod-mediated scotopic adaptation). The cone-rod breakpoint was identified by iterative curve fits (SigmaPlot, SPSS) using a nonlinear exponential decay function, $y = a + b \exp^{-cx}$, until the best fits were found for cone and rod components ($r^2 \geq .97$). The rod curves were extrapolated into the time range preceding the breakpoint (which occurred between 4 and 7 min across individuals) and the cone curves were extrapolated past the breakpoint to 30 min. The upper and lower curves were averaged and refit to derive each subject's mean dark adaptation function separately for cones and rods ($r^2 \geq .99$).

Data Analysis and Statistics

The parameter a of the mean exponential fit curve estimates the final dark-adapted threshold; parameter b , the range of adaptation (initial to final threshold); and parameter c , adaptation rate. These parameters are mathematically interdependent, or constrained by the procedure, or both. For example, with higher final cone thresholds (a), the range of adaptation is smaller (b), since the initial threshold ($a + b$) was defined at 6.0 log units. There was a high correlation between the final threshold and range of adaptation for combined data including patients and control subjects across both seasons ($r = -.90, n = 72, p < .0001$). Similarly, adaptation rate was faster with lower final cone thresholds ($r = .59, p < .0001$). In the case of rods, the initial

threshold was not directly measurable, given greater cone sensitivity immediately following the bleach. Although the estimated initial rod threshold was moderately negatively correlated with the final rod threshold ($r = -.34, p < .004$), adaptation rate was unrelated to the final threshold ($r = -.09, NS$).

An omnibus analysis focused on between- and within-group comparisons of the final cone and rod thresholds using multivariate analyses of variance (MANOVA) that could also detect differences in adaptation rate. This approach was selected over repeated-measures analysis of successive data points in the dark adaptation curves (cf. Oren et al 1991) for two reasons: 1) the degrees of freedom in extended time series inflate the opportunity to find false positive effects even using conventional correction factors; and 2) the data are summarized by a unifying equation with parameters that reflect biologic events. We used Wilks' lambda to detect parameter differences within the MANOVAs, and a criterion α level of .05 to identify all effects. Differences in detection threshold were expressed in log units relative intensity, with effect size defined as the standardized difference between means ($d = 0.3$, small; 0.5, medium; 0.8, large; Cohen 1988).

Results

Seasonal Variation in Dark Adaptation

WITHIN-GROUP COMPARISONS OF PATIENTS AND NORMAL CONTROL SUBJECTS. As illustrated in Figure 2, winter baseline samples differed from summer samples in a paired group of 24 patients (Wilks' lambda = 0.069; $F_{4, 20} = 4.81; p = .007$). Cone final thresholds were significantly lower in summer (-0.29 log units; $F_{1, 23} = 7.22; p = .01$). Rod final thresholds were also lower, but the difference was small (-0.10 log units; $F_{1, 23} = 7.29; p = .01$). The recovery rate of cones and rods showed no significant change. There were no significant seasonal effects in 12 normal control subjects, although in the summer, the mean cone threshold decreased by 0.22 log units ($d = 0.44$). Power analysis (for a level of 0.8) indicated that an adequate test of this difference would require a sample size of 23, similar to that of the patients.

PATIENTS VERSUS NORMAL CONTROL SUBJECTS.

To control for possible influences of age and gender on dark adaptation thresholds and recovery rates, subsets of patients and normal control subjects were matched for comparisons in winter ($n = 12$ pairs) and summer ($n = 10$ pairs). As illustrated in Figure 2, the groups differed only in the winter (Wilks' lambda = 0.34; $F_{4, 8} = 3.88; p = .05$). The final cone threshold in patients was significantly lower (-0.37 log units; $F_{1, 11} = 6.39; p = .03$), and rod recovery rate was faster ($\Delta c = 0.04; F_{1, 11} = 12.28; p = .005$). In summer, both the cone and rod curves for the two groups nearly superposed.

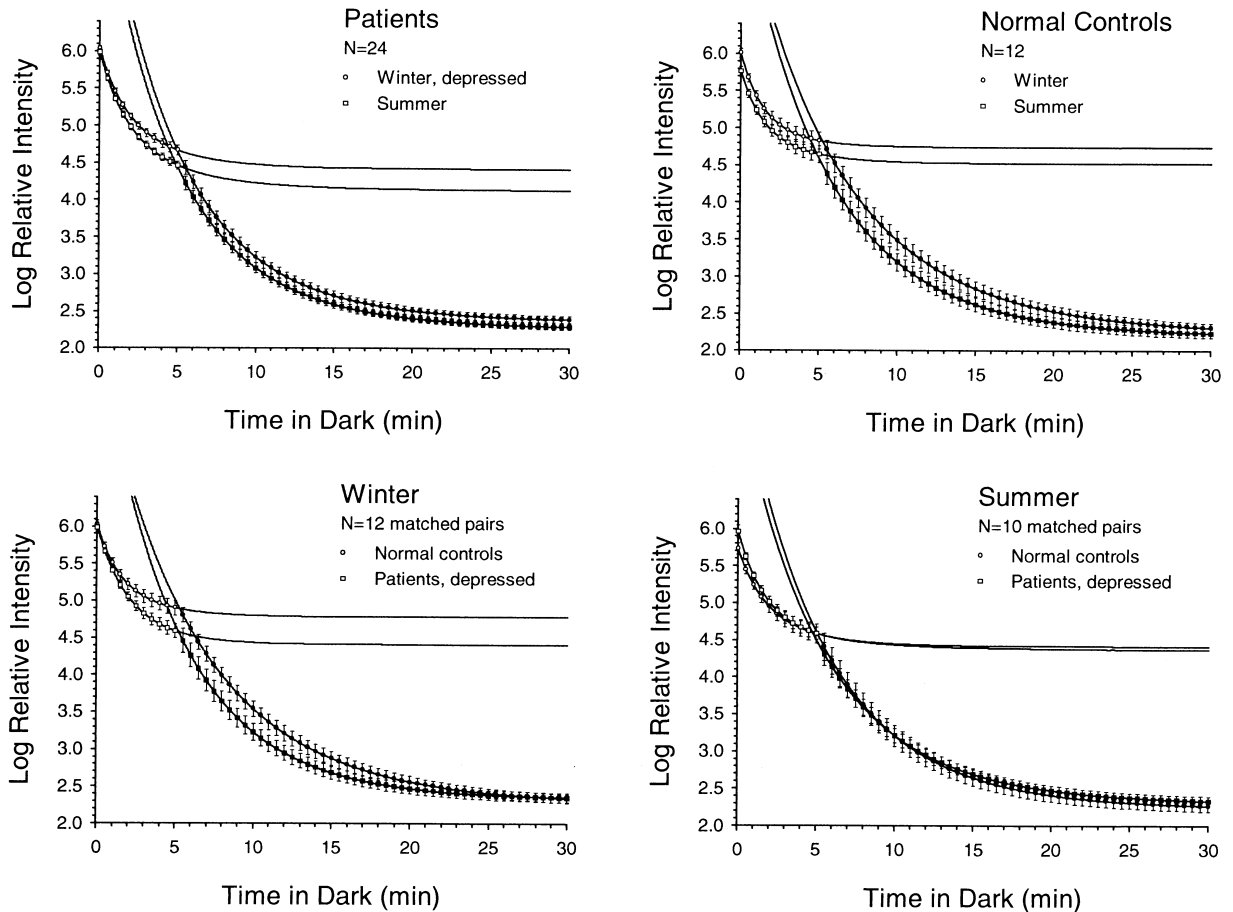


Figure 2. Group mean dark adaptation functions for patients and normal control subjects. *Upper panels*: separate seasonal comparisons for patients and control subjects. *Lower panels*: age- and sex-matched comparisons of patients and control subjects in winter and summer. Symbols (mean \pm SEM) are superimposed on the fitted curves at 30-sec intervals spanning the time range of cone-based (open symbols, 0.5 to 5 min) and rod-based (filled symbols, 5.5 to 30 min) observations. Curves were extrapolated over the entire interval according to the parameters of the nonlinear exponential declines.

PATIENTS WITH BLUE OR DARKER EYES. A post-hoc exploratory analysis focused on the potential role of eye color as a factor influencing cone and rod final thresholds. Blue-eyed patients showed a significant seasonal change ($n = 7$; Wilks' lambda = 0.16; $F_{2, 5} = 12.84$; $p = .01$) located to a large summertime reduction in the cone final threshold (-0.57 log units; $F_{1, 6} = 14.14$; $p = .009$) nearly twice as great as that of the total sample (-0.29 log units), while the rod final threshold remained constant (-0.07 log units, NS). Darker-eyed patients also showed a seasonal change ($n = 17$; Wilks' lambda = 0.66; $F_{2, 15} = 3.82$; $p = .05$), however, it was located to a small summertime reduction in the rod final threshold (-0.11 log units; $F_{1, 16} = 6.05$; $p = .03$) similar in magnitude to that seen in the total sample (-0.10 log units), while the decrease in the cone final threshold (-0.17 log units) was not significant. The number of blue-eyed normal control subjects ($n = 3$) was inadequate for a statistical comparison.

Effect of Bright Light Therapy On Dark Adaptation

Twenty-one patients given morning light and 10 given evening light were drawn from two treatment protocols (Terman et al 1990), in which 22 were responders and 9 were nonresponders. Several nonresponders refused to return for posttreatment dark adaptation tests, limiting that sample (see Figure 3) and hindering statistical evaluation. Nonetheless, an ANOVA of cone final thresholds showed a trend toward an interaction between treatment time, treatment response, and eye color ($F_{2, 22} = 2.93$; $p = .07$), as further delineated in Figure 3. The difference between responders and nonresponders was significant for the larger subgroup of patients given morning light ($F_{1, 19} = 4.25$; $p = .05$), an effect located to a threshold increase in nonresponders ($+0.30$ log units; $F_{1, 5} = 22.62$; $p = .004$), whereas responders showed a nonsignificant decrease (-0.13 log units). Under morning light, every blue-eyed patient (5/21, 16.4% of the total)

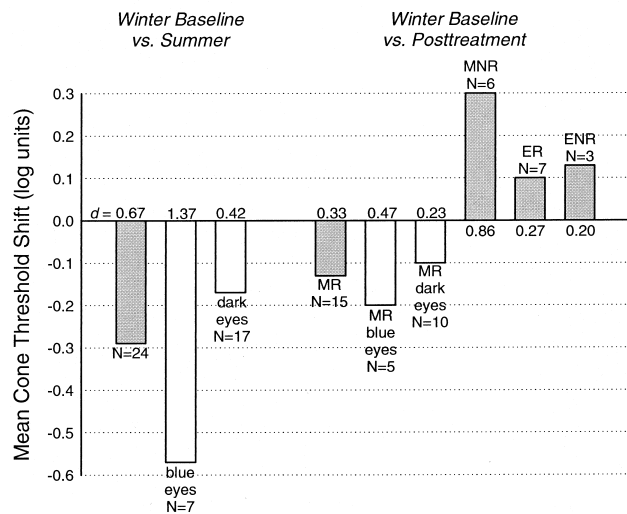


Figure 3. Summertime and posttreatment changes in the mean cone final threshold in patients relative to the winter baseline. *Filled bars*: primary group comparisons. *Open bars*: subgroups of blue- and darker-eyed patients. *d*, effect size of changes; MR, responders to morning light treatment; MNR, morning light nonresponders; ER, evening light responders; ENR, evening light nonresponders.

was a responder, but a larger sample would be needed to demonstrate a significant therapeutic advantage over patients with darker eyes ($\chi^2_1 = 2.63$; $p = .10$).

Figure 3 compares the directional change of cone final thresholds and their effect sizes across the seasons and light treatment conditions. The effect size of the summertime threshold decrease was greatly magnified for blue-eyed patients. In winter, morning light responders also showed a threshold decrease after 10 to 14 days of treatment. Although the effect size was small and the change fell short of significance, it was markedly magnified in blue-eyed patients (-0.20 log units, $d = 0.47$), as we also observed in summer. Power analysis indicated that an adequate test of the threshold decrease in blue-eyed patients would require approximately doubling the sample size (from 5 to 9). By contrast, patients receiving evening light showed small threshold elevations, and morning light nonresponders became markedly subsensitive ($+0.30$ log units, $d = 0.84$). These latter groups included too few blue-eyed patients ($n = 0$ to 2) to permit differentiation by eye color.

Discussion

Our study mathematically isolated photopic (cone-mediated) and scotopic (rod-mediated) segments of the dark adaptation function based on detection of a stimulus target in a retinal region containing both receptor types. Patients were distinguished by a significant summertime decrease

in both cone and rod final thresholds, which were mirrored by trends in normal control subjects. In particular, the magnitude of the cone shift in patients (approximately 0.3 log units) was large in comparison to diurnal variation in photopic sensitivity assessed by dark adaptation tests in young male adults (approximately 0.1 log units; O'Keefe and Baker 1987).

Our results replicate a dark adaptation study in which the final scotopic threshold did not differ between SAD patients and normal control subjects in winter (Oren et al 1993). The data are not consistent, however, with an early finding of increased scotopic thresholds in 3 normal observers who experienced extended daylight exposure in the summer (Sweeney et al 1960). Given far larger sample sizes in Oren's study and ours, we must question the generality of that finding, or attribute it to the intense outdoor exposure conditions.

Contrary to the prediction that patients with SAD would show retinal subsensitivity in winter relative to normal control subjects (Remé et al 1990), final photopic thresholds and scotopic recovery rate in this study both indicated supersensitivity. Several other studies have indicated scotopic (but not photopic) subsensitivity. For example, the scotopic ERG is subsensitive in SAD patients and subsyndromal individuals relative to normal control subjects in winter (Lam et al 1993). The photopic ERG has yet to be tested in patients with SAD. Cones and rods may respond differently to ambient light intensity. In contrast to rods, bright light stimulates synthesis of cone photoreceptor pigments, enhancing sensitivity (for review, see Remé et al 1991).

Our finding of greater wintertime cone sensitivity in patients relative to normal control subjects supports Beerma's (1990) hypothesis that patients falsely perceive evening room light as a summer-like extension of the photoperiod. Contrary to prediction, however, we did not find diminished sensitivity after successful light therapy. Prior to treatment, supersensitivity to evening light could contribute to depressogenic circadian phase delays (Lewy et al 1987). Morning light therapy would counteract the phase delays induced by evening light exposure. On the other hand, evening light therapy would exacerbate the "summer night" effect, and thus, be countertherapeutic. Indeed, evening light is generally less effective than morning light for treatment of winter depression (Lewy et al 1998; Terman et al 1998), but it is not without positive effect relative to placebo (Terman et al 1998).

Patients who showed a therapeutic response to morning light treatment also showed a small posttreatment decrease in the cone final threshold in the direction of the summertime state, in contrast with nonresponders, who showed a large threshold increase. The magnitude of the threshold shift in responders, however, fell far short of the summer-

time state. Thirty min exposure to artificial light for 10 to 14 days may constitute a lower cumulative dose than extended summertime exposure to natural morning light, and, thus, produce a smaller effect. Light exposure may result in reduced melatonin availability in the retina (i.e., loss of the physiologic "dark signal"). Morning light therapy curtails melatonin availability by direct suppression of pineal secretory activity (Terman et al 1988) and by circadian phase advances that shift the nocturnal episode earlier (Lewy et al 1987; Terman et al 1988). Both factors may contribute to the antidepressant effect. Additionally, at the retinal level, there is an antagonistic interaction between melatonin and dopamine activity, and cone sensitivity may be enhanced by light-elicited dopamine synthesis (reviews: Oren 1991, Remé et al 1991).

Even with significant threshold differences relative to control subjects, this study does not demonstrate that light stimulation of the cones or rods mediates the antidepressant effect or that the state of these receptors in winter is involved in the pathogenesis of SAD. Other photoreceptors may be involved in the retina (as has been indicated for circadian phototransduction; Freedman et al 1999), or even the skin or vasculature (Oren and Terman 1998). Cone sensitivity in particular appears vulnerable to seasonal variation and changes after light treatment, however, and its potential role in SAD merits further investigation.

The limited number of blue-eyed subjects in our study only allowed comparisons of seasonal threshold shifts in patients and posttreatment shifts by morning light responders. Indeed, differences between patients and normal control subjects might have their origins in iris pigmentation, not clinical status. That no blue-eyed patient failed to respond to light, however, suggests a differential susceptibility to the treatment. Furthermore, threshold shifts were larger than for darker-eyed patients, both seasonally and in response to treatment. Reduced melanin pigment in blue eyes significantly increases light transmittance through the iris and the surrounding eye wall (van den Berg et al 1991). A resulting increase in retinal illuminance might sensitize circadian phototransduction and enhance the operative dose of therapeutic light. Based on the clinical observation that blue-eyed patients appear more sensitive than those with darker eyes to low levels of dawn simulation (Terman 1997), we hypothesize that they would also respond to lower doses of bright morning light. This prediction is strengthened by our recent finding that blue-eyed patients show lower depression scores (N. Goel et al, unpublished data, 1999). It would be interesting to determine the prevalence of SAD relative to eye color in genetically confined populations, such as in Scandinavia where approximately 70% of the population is blue-eyed and only 6% is dark-eyed (Pálsson 1978). Contrary to D.F.

Klein's (personal communication) hypothesis of increased vulnerability for SAD, light iris pigmentation may indeed provide a protective factor.

A limitation of this study was in sample sizes that provided inadequate power to establish probable effects observed as trends with small-to-medium effect size, such as seasonal variation of cone sensitivity in normal control subjects. The arduous dark adaptation procedure discouraged both patients and control subjects from returning for repeated testing, and necessitated reconstituting groups for each 2-point comparison (winter/summer, baseline/post-treatment). A second liability of the study was the omission of artificial pupillary dilation during the dark adaptation tests. Differential rates of spontaneous dilation following the preadaptation bleach, or resting levels themselves, might distinguish patients from normal control subjects and affect threshold estimates otherwise attributed to the photoreceptors. Indeed, altered cholinergic sensitivity in depression may be reflected in pupillary responses to pilocarpine (Sokolski et al 1996). That said, however, pupil size is considered to have only a small effect on dark adaptation (Hood and Finkelstein 1986), and pupil size did not differ after 10 min of darkness in a study of SAD patients and normal control subjects (Oren et al 1993). A third liability of the study was the use of mathematical extrapolation to determine the final cone threshold, given that the rod adaptation curve overshadowed the cone adaptation curve before cone adaptation was complete. Both components, however, were precisely described by distinct exponential components. As an alternative, the final cone threshold could be directly measured during dark adaptation using a cone-sensitive chromatic target within the foveal region (Krill 1972). Other measures of retinal sensitivity, such as the photopic ERG, might provide finer resolution, and offset the inherent variability of psychophysical reports using the dark adaptation paradigm.

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References

- Beersma DGM (1990): Do winter depressives experience summer nights in winter? *Arch Gen Psychiatry* 47:879-880.
- Cohen J (1988): *Statistical Analysis for the Behavioral Sciences*, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates.

- Dam H, Jakobsen K, Møllerup E (1998): Prevalence of winter depression in Denmark. *Acta Psychiatr Scand* 97:1-4.
- Freedman MS, Lucas RJ, Soni B, von Schantz M, Muñoz M, David-Gray Z, et al (1999): Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science* 284:502-504.
- Gallin PF, Terman M, Remé CE, Rafferty B, Terman JS, Burde RM (1995): Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. *Am J Ophthalmol* 119:202-210.
- Hood DC, Finkelstein MA (1986): Sensitivity to light. In: Boff K, Kaufman L, Thomas J, editors. *Handbook of Perception in Human Performance*, vol 1. New York: Wiley, pp 1-66.
- Krill AE (1972): Evaluation of night vision: Dark adaptation. In: Krill AE, editor. *Hereditary Retinal and Choroidal Diseases*. Hagerstown, MD: Harper & Row, pp 189-226.
- Lam RW, Beattie CW, Buchanan A, Mador JA (1992): Electroretinography in seasonal affective disorder. *Psychiatry Res* 43:55-63.
- Lam RW, Beattie CW, Buchanan A, Remick RA, Zis AP (1991): Low electrooculographic ratios in patients with seasonal affective disorder. *Am J Psychiatry* 148:1526-1529.
- Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, et al (1998): Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry* 55: 890-896.
- Lewy AJ, Nurnberger JI, Wehr TA, Pack D, Becker LE, Powell RL, et al (1985) Supersensitivity to light: Possible trait marker for manic depressive illness. *Am J Psychiatry* 142: 725-727.
- Lewy AJ, Sack RL, Miller S, Hoban TM (1987): Antidepressant and circadian phase-shifting effects of light. *Science* 235: 352-354.
- Magnússon A, Stefánsson JG (1993): Prevalence of seasonal affective disorder in Iceland. *Arch Gen Psychiatry* 50:941-946.
- O'Keefe LP, Baker HD (1987): Diurnal changes in human psychophysical luminance sensitivity. *Physiol Behav* 41:193-200.
- Oren DA (1991): Retinal melatonin and dopamine in seasonal affective disorder. *J Neural Transm* 83:85-95.
- Oren DA, Joseph-Vanderpool JR, Rosenthal NE (1991): Adaptation to dim light in depressed patients with seasonal affective disorder. *Psychiatry Res* 36:187-193.
- Oren DA, Moul DE, Schwartz PJ, Alexander JR, Yamada EM, Rosenthal NE (1993): An investigation of ophthalmic function in winter seasonal affective disorder. *Depression* 1:29-37.
- Oren DA, Terman M (1998): Tweaking the human circadian clock with light. *Science* 279:333-334.
- Ozaki N, Rosenthal NE, Moul DE, Schwartz PJ, Oren DA (1993): Effects of phototherapy on electrooculographic ratio in winter seasonal affective disorder. *Psychiatry Res* 49:99-107.
- Ozaki N, Rosenthal NE, Myers F, Schwartz PJ, Oren DA (1995): Effects of season on electro-oculographic ratio in winter seasonal affective disorder. *Psychiatry Res* 59:151-155.
- Pálsson J (1978): Some anthropological characteristics of Icelanders analyzed with regard to the problem of ethnogenesis. *J Hum Evol* 7:695-702.
- Remé CE, Terman M, Wirz-Justice A (1990): Are deficient retinal photoreceptor renewal mechanisms involved in the pathogenesis of winter depression? *Arch Gen Psychiatry* 47:878-879.
- Remé CE, Wirz-Justice A, Terman M (1991): The visual input stage of the mammalian circadian pacemaking system. I. Is there a clock in the mammalian eye? *J Biol Rhythms* 6:5-30.
- Rosenthal NE, Bradt GJ, Wehr TA (1984): *Seasonal Pattern Assessment Questionnaire (SPAQ)*. Bethesda, MD: National Institute of Mental Health.
- Saarijärvi S, Lauerma H, Helenius H, Saarijärvi S (1999): Seasonal affective disorders among rural Finns and Lapps. *Acta Psychiatr Scand* 99:95-101.
- Sokolski KN, Demet EM (1996): Increased pupillary sensitivity to pilocarpine in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 20:253-262.
- Sweeney EJ, Kinney JAS, Ryan A (1960): Seasonal changes in scotopic sensitivity. *J Opt Soc Am* 50:237-240.
- Tam EM, Lam RW, Yatham LN, Zis AP (1998): Psychobiological effects of light therapy in seasonal affective disorder. In: Lam RW, editor. *Seasonal Affective Disorder and Beyond: Light Treatment for SAD and Non-SAD Conditions*. Washington, DC: American Psychiatric Press, pp 117-142.
- Terman JS, Terman M, Schlager D, Rafferty B, Rosofsky M, Link MJ, et al (1990): Efficacy of brief, intense light exposure for treatment of winter depression. *Psychopharmacol Bull* 26:3-11.
- Terman M (1997): Light on sleep. In: Schwartz WJ, editor. *Sleep Science: Integrating Basic Research and Clinical Practice*. Basel: Karger, pp 230-251.
- Terman M, Terman JS, Quitkin FM, Cooper TE, Lo ES, Gorman JM, et al (1988): Response of the melatonin cycle to phototherapy for seasonal affective disorder. *J Neural Transm* 72:147-165.
- Terman M, Terman JS, Ross DC (1998): A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry* 55:875-882.
- Thompson C, Stinson D, Smith A (1990): Seasonal affective disorder and season-dependent abnormalities of melatonin suppression by light. *Lancet* 336:703-706.
- van den Berg TJTP, Ijspeert JK, de Waard PWT (1991): Dependence of intraocular straylight on pigmentation and light transmission through the ocular wall. *Vis Res* 31:1361-1367.
- Wehr TA, Skwerer RG, Jacobsen FM, Sack DA, Rosenthal NE (1987): Eye versus skin phototherapy of seasonal affective disorder. *Am J Psychiatry* 144:753-757.
- Williams JBW, Link MJ, Terman M, Rosenthal NE (1994): *Structured Interview Guide for the Hamilton Depression Scale-Seasonal Affective Disorder Version (SIGH-SAD)*, revised ed. New York: New York State Psychiatric Institute.