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Atypical pattern of rod electroretinogram modulation by recent light history: A possible biomarker of seasonal affective disorder

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ABSTRACT

Our goal was to challenge both normal controls and patients with seasonal affective disorders (SAD) to various light histories and then measure their retinal response modulation using the electroretinogram (ERG) in both winter and summer. In winter and summer, 11 normal controls and 12 SAD patients were exposed to three different light conditions for 1 h (10,000, 100 and 5 lux) followed by an ERG. Groups showed similar ERG amplitudes in the 100 lux condition. Compared with the 100-lux condition, in controls, the ERG response was significantly increased in the 5-lux condition; in SAD, it was significantly decreased in the 10,000-lux condition. This pattern was present in both seasons. This is the first time a retinal response modulation anomaly has been observed in SAD patients in both the depressed and euthymic states. Retinal response modulation may represent an interesting biomarker of the disease for future research.

1. Introduction

In patients with seasonal affective disorder (SAD), a mood lowering is observed during fall and winter, with remission usually occurring in spring and summer, when the photoperiod increases (Rosenthal et al., 1984). Although SAD patients are less exposed to natural light in winter, their pattern of light exposure is not different from the one observed in the healthy population (Guillemette et al., 1998; Hébert et al., 1998). However, a defect in retinal light sensitivity has been hypothesized to explain the vulnerability of SAD patients to seasonal light changes (Beersma, 1990; Remé et al., 1990). We and others have demonstrated in fact a rod sensitivity anomaly in SAD patients as measured with the electroretinogram technique (ERG) (Lam et al., 1992; Hébert et al., 2002; Hébert et al., 2004). The ERG is a bio-potential recorded at the surface of the eye, which allows the functional assessment of various retinal cells such as rods (night; scotopic vision) and cones (day; photopic vision), but also ON-bipolar cells (Heynen et al., 1985; Stockton et al., 1989; Lei and Perlman, 1999). Many aspects could influence the ERG response, one of which appears to be the light history (Gagné et al., 2007). In the latter study, we exposed participants for 60 min (on different days) to three light conditions prior to cone and rod ERG assessment. It was found that rods were particularly sensitive to prior light exposure, with increased rod ERG maximal amplitude observed after being exposed to 5 lux for 1 h, when compared with 100 lux or 10,000 lux exposures, the two latter conditions yielding similar rod maximal response. No difference was found on cone response.

Knowing that SAD patients demonstrate a rod retinal sensitivity anomaly (observed only during the depressive episode), we aimed to challenge these patients with the above light history protocol in order to detect if the rod adaptation mechanism would be altered. Moreover, due to the recent discovery of a cone ERG anomaly in SAD patients (Lavoie et al., 2009), cone function was also assessed during the light history protocol with the ERG. Since in Lavoie et al. (2009) the rod and cone anomalies in SAD patients were observed to normalize in summer or after successful treatment with light therapy, our protocol was therefore applied in the same patients during both the depressed and remitted states, which corresponded to the winter and summer seasons, respectively. Our goal was to see how patients with SAD would adapt to this light history challenge and, if anomalies were present, at when they would be detected, that is, only during winter (state marker) or during both seasons (trait marker).

2. Method

2.1. Subjects

Twelve SAD subjects (11 females and 1 male) aged between 20 and 36 years old (mean 27, SD 4.9) and 11 healthy controls (10 females and 1 male) aged between 20 and 36 years old (mean 26.6, SD 4.68) were recruited on the campus of the University Laval using email solicitation. All participants signed a consent form approved by the institutional ethics committee (Centre de Recherche de l'Université Laval Robert-Giffard). The participants were also matched for age and gender as much as possible. They all reported to be in good physical health and did not take any medication at the time of the study, except for oral contraceptives in women. There was no extreme chronotype based on a French adaptation of the Morningness-Eveningness Chronotype Questionnaire (Horne and Ostberg, 1976) as the evening chronotype could impact the

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ERG response when performed in the morning (Rufiange et al., 2002). Exclusion criteria included the following: irregular menstrual cycle, pregnancy and attempt to get pregnant, breastfeeding, use of light therapy in the last 3 months, night work and travel of more than two time zones 1 month before the study.

2.1.1. SAD patients

SAD patients underwent the following tests and showed scores above 13 for the French version of the Beck Depression Inventory II (BDI-II) (Beck et al., 1996); 11 for the Global Seasonality Score (GSS) of the French adaptation of the Seasonal Pattern Assessment Questionnaire (SPAQ) (Rosenthal and Wehr, 1984), along with considering that their seasonal changes represented at least a "moderate" problem; 22 for the 29-item Structured Clinical Interview Guide for the Ham-D, SAD version (SIGH-SAD), along with a score of 8 or more for the 8-item atypical symptoms. A clinical interview with a psychologist was also conducted to exclude any comorbidity, using the Structured Clinical Interview for DSM-IV (SCID). The BDI-II and the SIGH-SAD were repeated during the summer to monitor the remission of symptoms prior to retesting (see table 1). It should be noted that the need to meet the DSM-IV criteria for major depression with a seasonal pattern specifier, has recently been criticized (Rosenthal, 2009). In fact, most of our patients did not meet the criteria for major depression. However, all patients were remitted in summer in the absence of medication, which reassures us of the validity of our diagnosis made using the above widely used questionnaires.

2.1.2. Healthy controls

None of the subjects was either S-SAD or SAD according to the BDI-II (score of ≤8), SIGH-SAD (score of ≤11) and SPAQ (GSS of ≤9). S-SAD is a moderate type of SAD in which subjects show significant mood variations across seasons (GSS of >9 but less than 11) but that represent only a mild or moderate problem to them (Kasper et al., 1989).

2.3. Protocol

Prior to the cone and rod ERG assessments, all participants were randomly exposed to three light conditions for 60 min (5 lux, 100 lux and 10,000 lux) on different days (within a 1-week period) during fall/winter (November and February) and spring/summer (May and August). The 100-lux condition represents the equivalent of normal indoor lighting; 10,000 lux is the standard level recommended for light therapy; and 5 lux, represents a very dim environment, which requires the use of both rods and cones to generate the so-called "mesopic vision". On their way to the laboratory, all participants were instructed to wear dark sunglasses (cutting off 88% of the light) to reduce natural sunlight exposure that could interfere with the laboratory controlled light conditions.

2.4. Light exposures

We followed the same light and ERG protocols as per Gagné et al., (2007). In brief, light exposure began upon arrival to the laboratory. All participants were instructed to play computer games in order to maintain constant eye gaze. Light exposure conditions were measured with an International IL-1700 radiometer. For the 10,000-lux exposure, three Canadian Standard Association safety approved phototherapy lamps (Northern Light Technologies, SADelite model) using two fluorescent tubes (Philips, color temperature of 3000 kelvin and ranging from 420 to 700 nm) were installed around the computer screen (sides and top). For the 5-lux exposure, only the computer screen was turned on, providing the required intensity. In the 100-lux condition, standard room lights were turned on along with one SADelite lamp (top of the computer screen). Controlled light exposure always occurred between 9 h and 14 h, since this time frame does not impact the ERG parameters (Marcus et al., 2004).

2.5. Electroretinogram recordings

After each light condition, a full-field cone and rod ERG was performed. Recordings were obtained simultaneously in both non-dilated eyes with DTL electrodes (Shieldex 33/9 Thread, Statex, Bremen, Germany) deeply secured into the conjunctival sac. This electrode type has been shown to allow reproducible results (Hébert et al., 1995). Moreover, with performance being equivalent to corneal electrode type, these are now preferred by a majority of users (Beeler et al., 2007). Ground and reference electrodes (Grass gold cup electrodes filled with Grass EC2 electrode cream) were pasted on the forehead and external canthi.

For the photopic cone ERG, participants were light-adapted for 10 min to a white light background set at 80 cd/m^2 (about 300 lux) provided by a Ganzfeld Color dome (Espion, Diagnosys LLC, Littleton, MA). A cone luminance-response function (LRF) was achieved using 18 white flash intensities ranging from 0.076 to 3200 cd.s/m^2. For the scotopic rod ERG, participants were dark-adapted for 30 min and green flashes were then provided by the Ganzfeld Color dome in order to better stimulate the rods. Then a LRF was obtained using 15 flash intensities ranging from 0.000178 to 1 cd.s/m^2.

Table 1
Scores obtained from the questionnaires administered to SAD subjects and controls in winter and in summer.

Scores (mean ± SD)	Patients(n = 12)		Controls(n = 11)	
	Winter	Summer	Winter	Summer
SIGH-SAD, 29 items, total score	25.58 ± 2.81	3.25 ± 1.48	2.36 ± 2.38	1.90 ± 2.02
SIGH-SAD 8 items, typical symptoms	15.25 ± 2.13	1 ± 1.41	1.18 ± 1.89	0.9 ± 1.36
BDI-II	26.83 ± 2.13	1.75 ± 2.18	3.2 ± 3.46	2.3 ± 3.62
SPAQ(GSS)	17.16 ± 11.24	N/A	57.27 ± 7.9	N/A
Chronotype	46.92 ± 11.24	N/A	57.27 ± 7.9	N/A

2.6. Statistical analysis

A three-way analysis of variance (ANOVA) with repeated measures was performed to assess the effect of conditions, groups and seasons on ERG parameters, with repeated factors being seasons and conditions. The MIXED procedure of the SAS ® (SAS Institute Inc., Cary, NC) program was used with a repeated statement and the covariance structure minimizing the Akaike criterion. The method of Kenward-Roger was used to calculate the degrees of freedom. When necessary, logarithmic transformation of the dependent variable was used to reach a normal distribution and to satisfy the assumption of homogeneity of variance. Pairwise comparisons were then made using protected the Fisher LSD (least significant difference) test.

A-wave and b-wave amplitudes were measured from the waveform obtained at the Vmax (maximal response) observed on the luminance response function. By convention, the a-wave amplitude is measured from baseline to trough, and the b-wave from the trough of the a-wave to the peak of the b-wave. Therefore, the implicit time of the a- and b-wave corresponds to the time (ms) to reach the trough of the a-wave and the peak of the b-wave respectively. The photopic Vmax was set at the highest amplitude achieved on the LRF, no matter the intensity. However, due to cone intrusion occurring at higher intensities, the pure rod Vmax does not necessarily correspond to the highest amplitude. Therefore, scotopic Vmax was defined as the amplitude reached at a fixed intensity of 0.18 cd.s/m^2. This intensity was observed to yield to the maximal response of the rods with no cone intrusion (detectable by the presence of a clear a-wave on the ERG response). Vmax is also used to define another parameter known as log K which is interpreted as retinal sensitivity. Log K is defined as the intensity necessary to reach half of the saturation amplitude (½ Vmax). To calculate this parameter, we fitted the graph points (up to the LRF Vmax) with a sigmoidal curve fitting program (Origin 7.0 software; OriginLab Corporation, Northhampton, MA).

3. Results

3.1. Photopic cone ERG

The three-way ANOVA revealed a significant effect of condition for the Vmax b-wave ($F_{2,84}$ = 15.80, P<0.0001) and a significant Group × Season interaction for the a-wave amplitude ($F_{1,105}$ = 19.33, P<0.0001). No significant effect was found on implicit times or Log K.

3.1.1. Effect of Condition

Compared with the 100-lux and 10,000-lux conditions, the 5-lux exposure yielded to a significant decrease in Vmax b-wave in both groups (P<0.0001) and that independently of seasons. See Fig.1.

3.1.2. Effect of Group × Season

A-wave amplitude of the SAD patients increased in summer (mean −22.33 μV, SD 5.12) compared with winter (mean −16.0 μV, SD 4.58; P<0.001) but this was not dependent of the condition. In winter, the a-wave amplitude in SAD was significantly lower than that observed in healthy controls (controls: winter, −20.94 μV, SD 4.70 vs. SAD −16.0 μV, SD 4.58; P = 0.0003) but not during summer (mean −20.82 μV, SD 4.45 vs. SAD −22.33 μV, SD 5.12; P = 0.249), suggesting therefore a normalization of the a-wave during the remitted state in summer.

3.2. Scotopic rod ERG

Significant effects of Group ($F_{1,40.1}$ = 4.15, P = 0.048) and condition ($F_{2,20.9}$ = 32.07, P<0.0001) and Group × condition ($F_{2,20.9}$ = 33.69, P<0.0001) were observed for the scotopic Vmax. Significant Group × Season interactions were found for the log K ($F_{1,\ 105}$ = 14.43, P = 0.0002). No significant effect was found for either a-wave amplitude or a- and b- waves implicit times.