ARCHIVAL REPORT

Abnormal Hypothalamic Response to Light in Seasonal Affective Disorder

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Background: Vulnerability to the reduction in natural light associated with fall/winter is generally accepted as the main trigger of seasonal affective disorder (SAD), whereas light therapy is a treatment of choice of the disorder. However, the relationship between exposure to light and mood regulation remains unclear. As compared with green light, blue light was shown to acutely modulate emotion brain processing in healthy individuals. Here, we investigated the impact of light on emotion brain processing in patients with SAD and healthy control subjects and its relationship with retinal light sensitivity.

Methods: Fourteen symptomatic untreated patients with SAD (34.5 ± 8.2 years; 9 women) and 16 healthy control subjects (32.3 ± 7.7 years; 11 women) performed an auditory emotional task in functional magnetic resonance imaging during the fall/winter season, while being exposed to alternating blue and green monochromatic light. Scotopic and photopic retinal light sensitivities were then evaluated with electroretinography.

Results: Blue light enhanced responses to auditory emotional stimuli in the posterior hypothalamus in patients with SAD, whereas green light decreased these responses. These effects of blue and green light were not observed in healthy control subjects, despite similar retinal sensitivity in SAD and control subjects.

Conclusions: These results point to the posterior hypothalamus as the neurobiological substrate involved in specific aspects of SAD, including a distinctive response to light and altered emotional responses.

W inter seasonal affective disorder (SAD) is a recurrent major depressive disorder occurring in fall/winter with full remission in spring/summer (1–4). Patients with SAD tend to report typical depression complaints such as decreased mood and motivation but also atypical symptoms such as hypersomnia and fatigue, and hyperphagia (particularly for carbohydrates) associated with weight gain, which implies alteration in sleep/wake regulation (5,6) and possibly in metabolism (7). Despite substantial research efforts, the pathophysiology of the disorder is not established. Vulnerability to day-length shortening associated with fall/winter is generally accepted as the main triggering factor of the disorder. Indeed, SAD prevalence varies with latitude (to reach up to 3% in Canada and possibly even up to 10% at higher latitude [2,4]), and light therapy is a treatment of choice for the disorder, with symptom improvements observed within a few weeks of daily (generally morning) light exposures (8). However, the mechanism linking exposure to light and mood regulation is still largely unknown.

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Retinal light sensitivity was recently reported to be abnormal in patients with SAD during the depressive episode, with normalization of retinal function after 4 weeks of light therapy in winter (9). Light also regulates circadian rhythms (10) and acutely affects many processes other than vision, such as melatonin secretion, alertness, sleep, performance, and cognition (11–14). These effects of light are mediated by a photoreception system, which recruits intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin (15,16), in addition to rods and cones (17). These melanopsin ipRGCs present a maximal sensitivity to blue light (460–480 nm) and confer a shorter wavelength maximal sensitivity to nonvisual responses to light, as compared with the photopic visual system, which is maximally sensitive to green light (at around 550 nm) (17).

Seasonal changes in the spectral composition of light occur, with relatively less blue light in winter (18), and recent data showed that blue light therapy is effective to treat SAD (19–22). In addition, blue light therapy requires light levels significantly lower than the recommended 10,000 lux of white light, suggesting that nonclassic photoreception and melanopsin-expressing ipRGCs contribute to the therapeutic effects of light exposure. Functional magnetic resonance imaging (fMRI) studies in healthy individuals showed that exposure to blue monochromatic light, as compared with green monochromatic light, exerts an acute influence on cerebral activations associated with the processing of auditory emotional stimuli, notably in the hypothalamus and amygdala (23). Because these brain areas—involved in emotional processing—are also implicated in mood regulation and mood disorders (23), this acute effect of light could also be involved in the long-term regulation of mood by light, possibly through melanopsin-based photoreception. Winter depression in SAD could thus be caused by some abnormal influence of light (or lack of light) on brain responses to emotionally relevant signals.

Here, we studied the acute impact of light on auditory emotional processing in SAD and investigated the role of classical and non-

classical photoreception in the disorder. We measured retinal light sensitivity and examined the effect of blue and green light exposures on the brain responses to neutral and emotional auditory stimuli in untreated symptomatic patients with SAD and healthy control subjects in fall/winter. We hypothesized that, during the symptomatic episode of SAD, the impact of light exposure on auditory emotional processing would be abnormal, in key brain areas for emotion regulation, such as the amygdala and hypothalamus. We also hypothesized that retinal dysfunction in SAD, which alters the light signal reaching the brain, would be related to the influence of light on these emotional responses.

Methods and Materials

More details can be found in Supplement 1.

Subjects

Patients with SAD and control subjects were recruited in the Montreal area (approximate latitude 45°30′N). They were between 18 and 45 years of age (Table 1 for complete characteristics) and gave written informed consent. The study was approved by the institutional Regroupement Neuroimagerie/Québec Ethics Committee.

Patients. Candidates had to present a Global Seasonality Score ≥ 9 on the Seasonal Pattern Assessment Questionnaire (24), perceive seasonal changes as at least a "moderate" problem, and present a score ≥11 on the Beck Depression Inventory II (25). A psychologist then determined the presence of SAD symptoms on the basis of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version (SIGHSAD) (total score ≥25; atypical item score ≥9) (26). The psychologist also excluded bipolarity (with the Mood Disorder Questionnaire [27]) or other psychiatric or medical disorders (with a semistructured interview). Sixteen patients completed the protocol, but two were excluded for technical reasons. All patients participating in the experiment were studied in the absence of any treatment (light therapy or drugs).

Control Subjects. Control subjects were matched with patients for gender, laterality, and age (±2 years except for one female and one male pair, for which the difference was 4 and 6 years, respectively). Control subjects presented a Global Seasonality Score <8, with "no problem" with seasonal changes, and a semistructured interview established the absence of a medical or psychiatric disorder. No sleep disturbances were reported as determined by the Pittsburgh Sleep Quality Index Questionnaire (28) (score ≤5).

Table 1. Subjects Characteristics

	SAD	Control Subjects	p
Number of Subjects	14	16	
Age (≥18; ≤45 yrs)	34.5 ± 8.17	32.25 ± 7.66	.74
Body Mass Index (≤27)	24.01 ± 3.28	23.02 ± 2.43	.30
Gender (Male/Female)	5/9	5/11	.8[a]
Seasonality Score (24)	14.07 ± 3.08	3 ± 2.69	<.001
Depression Level Score (25)	24 ± 10.54	1.38 ± 1.45	<.001
SIGHSAD Total Score (≥25) (26)	31.88 ± 5.91	n/a	
SIGHSAD Atypical Items Only (≥9) (26)	15.64 ± 4.22	n/a	
Anxiety Level (29)	11.65 ± 9.6	1.81 ± 2.6	<.001
Sleep Disturbance (28)	7.64 ± 3.15	2.56 ± 1.5	<.001
Daytime Propensity to Fall Asleep (62)	14.15 ± 4.28	6.5 ± 4.78	.001
Chronotype (63)	53.93 ± 11.69	50.44 ± 10.26	.4
Laterality (left/right)	1/13	1/15	.92[a]
Education, yrs	15.63 ± 3.12	15.76 ± 2.34	.81
Women Using Oral Contraceptive	2/9	4/11	.49[a]
Women in Luteal Phase	2/9	3/11	.70[a]
Ethnicity (Afro-American/Caucasian)	1/13	1/15	.92[a]
Born Outside Quebec[b]	4	5	.87[a]
Born Outside Quebec in a "Southern" Country (>5° south away from Montréal)	1	1	.92[a]
Smoking Habits (smoking/nonsmoking)	4/10	1/15	.10[a]
Date of Experiment (dd/mm/yy) (from 21/11/08 to 07/02/09)	22/12/08 ± 27d	22/12/08 ± 29d	.94
Sleep Time Before Experiment	22:54h ± 0:46h	23:40h ± 1:09h	.073
Wake Time Before Experiment	07:30h ± 0:58h	07:22h ± 1:00h	.74
Sleep Duration Before Experiment	8.6 ± .76	7.89 ± .54	.006
Subjective Sleepiness Immediately Before fMRI Experiment (64)	5.36 ± 1.78	3.25 ± 1.15	.006
Stimuli Volume in fMRI (arbitrary units)	675 ± 435.3	628.1 ± 401.2	.76
First 40-sec Light Exposure in fMRI: Blue/Green	7/7	8/8	1[a]

Values are mean ± SD. None of the characteristics of the subjects showing a significant difference between seasonal affective disorder (SAD) and control subjects alone explained the reported differences in functional magnetic resonance imaging (fMRI) activations, as indicated by regression analyses in SPM5. Therefore the present result cannot be attributed to a single clinical symptom such as levels of depression or anxiety, seasonality, or sleep/wake disturbances.

SIGHSAD, Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version.

[a]p values computed with χ² test, otherwise with unpaired t test.
[b]See Results in Supplement 1 for more details on the place of birth aspect.

All showed normal scores on the 21-item Beck Anxiety Inventory (29) and Beck Depression Inventory II (25) (scores <11).

Participants. All participants were moderate alcohol consumers (<7 alcohol unit/week) and were not taking medication. They were asked to refrain from alcohol-containing beverages for at least 36 hours before the experiment. Smokers were included, but smoking was not allowed for the duration of the laboratory experimentations. None had worked on night shifts during the preceding year or traveled across more than one time zone during the last 2 months. All subjects had been living in the province of Quebec for at least 3 years. Women were not pregnant or breast-feeding and were more than 1 year postpartum. Absence of ophthalmic disorder (e.g., glaucoma, color blindness) was assessed by an optometrist (standard examination). Participants completed additional questionnaires, but the scores of these questionnaires were not used as inclusion criteria (Table 1).

At least 1 week before the experiment, participants were familiarized with the magnetic resonance environment during a short MRI session during which a structural image of the brain was acquired. Volunteers were asked to follow a regular sleep schedule based on their preferred sleep times and durations during the 5 days preceding the experimentation. Compliance was verified with sleep logs and actigraphy (Actiwatch-L; MiniMitter/Respironics, Bend, Oregon).

Experimental Protocol

Participants arrived at the laboratory 2 hours after habitual wake time and were maintained in dim light (<5 lux) for 1.5 hours (Figure 1A). One drop of tropicamide 1% was administered in each eye 20 min before entering the scanner to inhibit pupillary constriction. During the fMRI session (12 min), subjects performed an emotional auditory task while being exposed to alternating 40-sec periods of blue (480 nm) and green (550 nm) monochromatic lights (full width
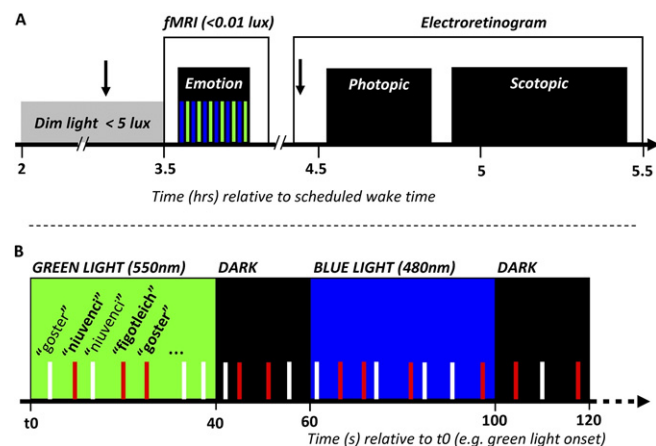
Figure 1. Experimental design. **(A)** General protocol. Arrow: pupil dilator administration. Time relative to scheduled wake time (hours). Subject performed an emotional task in functional magnetic resonance imaging (fMRI) (see **B** for details) before photopic and scotopic electroretinograms were recorded. **(B)** Detailed fMRI procedures. Time (seconds) relative to t0, a time point arbitrarily chosen as a green light onset of the session. The task consisted of a gender discrimination of auditory vocalizations while exposed to alternating blue (480 nm) and green (550 nm) monochromatic light (counterbalanced order). Light exposures lasted 40 sec and were separated by 15–25-sec periods of darkness. Anger (red bars) and neutral (white bars) prosody vocalizations of the three pseudo-word type ("goster," "niuvenci," or "figotleich") were pseudorandomly and evenly administered throughout each light condition across the entire session (interstimuli interval: 3–11 sec; mean: 4.8 sec).

at half maximum [FWHM]: 10 nm), separated by 15–25-sec periods of darkness (30) (order blue and green light was counter-balanced across subject within each group). The fMRI session was followed by photopic and scotopic electroretinogram (ERG) recordings characterizing cone and rod photoreception, respectively.

Technical Issue. In accordance with our previous studies (31,32) and work of others (e.g., [12,13]), we set the photon densities of both monochromatic lights used in fMRI at an equal level, so that comparisons between blue and green exposures could reveal non-classic modulation of brain responses. The irradiance used (10^{13} photon/cm²/sec) was intermediate between the two irradiances of our prior investigation of the impact of light on emotion processing (30) and had successfully been used in another study on the impact of light on auditory working memory (32). A technical problem, however, accidentally set blue and green light irradiance levels at 1.1×10^{13} and $.9 \times 10^{13}$ photons/cm²/sec, respectively (which corresponds to 1.5 and 20 lux, respectively). This affected all data acquisitions and prevented direct comparisons between blue and green exposures but did not compromise comparisons between patients and control subjects for blue and green light separately.

fMRI Task. Acoustic stimuli consisted of three meaningless words ("goster," "niuvenci," "figotleich") pronounced by professional actors (half women) with two different modalities, anger and neutral prosody, as validated by extensive behavioral assessments (33) and in previous experiments (30,34,35). Note that negative and positive emotions are mediated through common (but not completely identical) pathways (36), but our experience is that negative emotion elicits more robust responses, less influenced by individual valence perception (37). Stimuli were presented to the subject via headphones from an audio player. The task of the subject was to press one of two buttons on a keypad (with their right hand) upon discriminating the gender of the speaker pronouncing the pseudo-word. The goal of the study to measure brain responses to emotional words was hidden from the subjects. Stimuli were matched in term of duration (750 msec) and mean acoustic energy. Anger and neutral prosodies were evenly assigned to each light condition (blue, green, darkness).

fMRI Acquisitions. The fMRI data were acquired with a 3-T magnetic resonance scanner (TIM-TRIO, Siemens, Erlangen, Germany). Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence (32 axial slices; voxel size: $3.4 \times 3.4 \times 3$ mm³ with 30% of gap; matrix size $64 \times 64 \times 32$; repetition time = 2180 msec; echo time = 40 msec; flip angle = 90°). Structural brain images consisted of a T1-weighted 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (repetition time = 7.92 msec, echo time = 2.4 msec, time of inversion = 910 msec, flip angle = 15°, field of view = 256×224 mm², matrix size = 256×224, voxel size = $1 \times 1 \times 1$ mm³).

ERG Acquisitions. The ERG recordings were undertaken 4.5 hours after habitual wake time, after the fMRI session. One drop of tropicamide 1% was administered in each eye again 15 min before the first ERG. Recordings were obtained with DTL electrodes (Shieldex 33/9 Thread, Bremen, Germany) placed deep in the conjunctival sac, with reference electrodes placed on the canthi and ground on the forehead (38). Flash stimulations were administered with a Ganzfeld Dome (ColorDome, Diagnosys, Lowell, Massachusetts) to achieve full field retinal stimulation. Participants were first adapted to a background light (25.5 cd/m²) for 15 min before being administered a series of white light flashes of increasing intensity (range: −1.12–1.375 log cd/m²/sec; stimuli interval: 1–5 sec) to generate a photopic luminance response. Participants were then dark-adapted for 30 min (0 lux) before being presented with a series of light flashes (480 nm broadband blue light to better stimulate rods,

which present peak sensitivity at around 505 nm) of increasing intensity (range: -4.25 to -1.00 log cd/m^2/sec; stimuli intervals: 1.5-sec low-intensity; 5-sec high-intensity), to generate a scotopic luminance response.

Data Analysis

Behavior. Behavioral data were analyzed with Statistica 6.1 (StatSoft France, Maisons-Alfort, France). Mixed analyses of variance with group as the between-subjects factor (SAD, control subjects) and prosody (neutral, anger) as the within-subject factor were used to compare reaction times and accuracy on the fMRI task.

fMRI. Brain functional volumes were analyzed with Statistical Parametric Mapping software (SPM5, http://www.fil.ion.ucl.ac.uk/spm). They were realigned, coregistered, spatially normalized (Montreal Neurological Institute space; standard SPM5 parameters), and smoothed (FWHM: 8 mm). The analysis was conducted in two steps, accounting for individual-level fixed effects and group-level random effects, respectively. Changes in regional brain responses were estimated with a general linear model in which emotional and neutral stimuli in each light condition; blue and green light onset and offset were modeled with stick functions ("events") convolved with a canonical hemodynamic response function. A parametric modulation was added to each regressor to track any linear change of the amplitude of brain responses across time. Regressors derived from the realignment of functional volumes were considered as covariates of no interest. High-pass filtering was implemented in the matrix design with a cutoff period of 256 sec to remove low-frequency drifts from the time series. Serial correlations in the fMRI signal were estimated with an autoregressive (order 1) plus white noise model and a restricted maximum likelihood algorithm.

The summary statistic images resulting from the contrasts of interest were further smoothed (FWHM: 6 mm) and entered in the random effects analyses. This second level analyses consisted of two-sample t test on independent measures with unequal variance, which constituted maps of the t statistics thresholded at $p_{uncorrected} = .001$. One-sample t tests were also computed to identify whether the observed effect was significant in each population separately. Statistical inferences were performed after correction for multiple comparisons at a threshold of $p_{corrected} = .05$. Corrections for multiple comparisons were computed on the entire brain volume (Family Wise Error) or on small spherical volumes around a priori locations of activation (10 mm radius), which were expected in structures involved in the processing of emotional auditory stimuli (34,35), in arousal regulation (39,40), in the impact of light on nonvisual brain function (30–32,41), or in brain areas to which the melanopsin-expressing ipRGC project (42,43). Multiple regression analyses were carried out with questionnaire scores (Table 1) with standard SPM5 procedure.

ERG. One control subject did not complete the photopic and scotopic ERG assessment, because of technical problems, and photopic ERG data of another control subject were accidentally not recorded. Log K, which is the intensity necessary to reach half of the saturating amplitude of the ERG b-wave and constitutes a measure of retinal sensitivity (9,38), was computed for scotopic and photopic data of all the other subjects with sigmoidal curve fitting (Prism 4, GraphPad, La Jolla, California). Two-sample t tests compared scotopic and photopic LogK.

Results

Demographic Data

As expected, patients with SAD presented high SIGHSAD scores and were significantly more seasonal, anxious, and depressed than
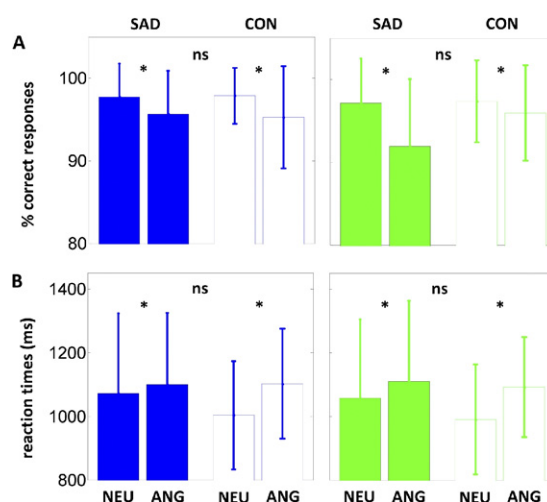
Figure 2. Behavioral results of the functional magnetic resonance imaging (fMRI) task. **(A)** Accuracy (mean ± SD); **(B)** reaction times (mean ± SD). *Significant differences ($p \leq .05$); nonsignificant difference ($p > .05$). ANG, anger prosody; CON, control subjects; NEU, neutral prosody; SAD, seasonal affective disorder patient.

control subjects (Table 1). SAD patients reported feeling sleepier than control subjects during the day in general and presented significantly more sleep disturbances. Sleep duration and subjective sleepiness immediately before the experiment were also significantly higher in SAD patients. By contrast, possible confounds such as age, body mass index, education level, and chronotype did not differ significantly between groups. Wake time before the experiment and the date of the experiment were also similar in both groups.

Performance of the fMRI Task

Accuracy in the gender discrimination task was high ($> 90\%$) in both light conditions but tended to be higher for neutral than anger prosody [mean ± SD; blue: neutral (97.8 ± 3.6%) > anger (95.4 ± 5.7%), $F(1,28) = 3.94, p = .057$; green: neutral (97.3 ± 5.1%) > anger (94.1 ± 7.1%), $F(1,28) = 3.36; p = .077$] (Figure 2A). In both light conditions, reaction times were significantly slower for anger than neutral prosody [mean ± SD; blue: neutral (1034 ± 211 msec) < anger (1101 ± 195 msec), $F(1,28) = 7.22, p = .012$; green: neutral (1022 ± 210 msec) < anger (1101 ± 204 msec), $F(1,28) = 9.63, p = .004$] (Figure 2B). Critically, accuracy and reaction times did not differ between patients and control subjects [$F(1,28) < 2.5, p > .12$] with no group × prosody interactions [$F(1,28) < 2.2, p > .14$].

These results indicate that the emotional content of the stimuli was equally well perceived by patients and control subjects, preventing behavior bias in the fMRI analyses comparing both groups.

fMRI Results

The clinical manifestation of a mood disorder (i.e., the depressive episode) alters normal brain function (23). Therefore, before investigating how blue and green light modulate brain responses to neutral or angry prosody stimuli, we assessed whether brain responsiveness to all stimuli differed between patients and control subjects (i.e., irrespective of the light and prosody conditions). We found that, as compared with control subjects, patients with SAD presented increased responses to all auditory stimuli in a dorsoposterior area of the thalamus compatible with the dorsal pulvinar and a dorsal area of brainstem located next to superior cerebellar peduncle and encompassing several nuclei of the ascending arousing system (Figure 3, Table 2). Multiple regression analyses showed
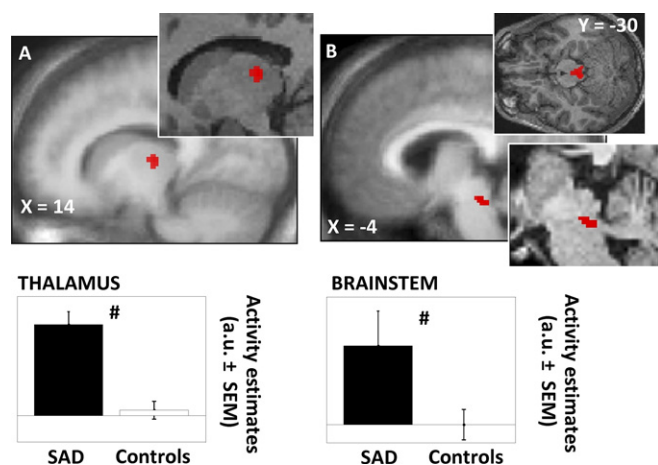
Figure 3. Significant differences between patients with seasonal affective disorder (SAD) and healthy control subjects (Controls) in the brain responses to all auditory stimulus types (irrespective of light and prosody condition). **(A)** Thalamus (dorsal and posterior); **(B)** brainstem (median-posterior, next to superior cerebellar peduncle). Results are overlaid over the mean structural image of all subjects. Insets: enlargements in representative subjects. Graphs: activity estimates (arbitrary unit [a.u.] ± SEM) of the brain responses to all auditory stimulus types. #$p_{corrected} \leq .05$ (group difference).

Figure 4. Significant differences between patients with SAD and Controls in the impact of blue and green light exposure on the brain responses to auditory emotional stimuli. Results are overlaid over the mean structural image of all subjects. Inset: enlargement in a representative subject. Graphs: change in activity estimates (a.u. ± SEM) between the light condition (blue, green) and the darkness condition for the processing of auditory emotional stimuli. *$p_{corrected} \leq .05$ (in SAD patients taken in isolation); ~$p_{corrected} = .07$ (in SAD patients taken in isolation); nonsignificant difference $p_{uncorrected} > .1$ (in control subjects taken in isolation); #$p_{corrected} \leq .05$ (group difference). B, brainstem; CP, corpus collusum; F, fornix; MB, mammillary bodies; OT, optic tract; SC, superior colliculus; T, thalamus; 3V, third ventricle; other abbreviations as in Figures 1 and 3.

that the group differences in thalamic and brainstem responsiveness were not related to single characteristic of subjects that differed between SAD and control participants (cf. Table 1).

Brain responses to auditory stimuli under blue or green light exposures were compared with brain responses in darkness to take into account the global difference in brain responsiveness and allow for group comparisons. Analyses revealed that, as compared

with darkness, blue light exposure increased responses to angry prosody stimuli in the posterior hypothalamus, dorsolateral to mammillary bodies, in patients with SAD (Figure 4, Table 2). In contrast, under green light exposure, responses to these emotional stimuli were decreased in a slightly more ventral hypothalamic area

Table 2. fMRI Results

Brain Areas	Side	X Y Z	Z Score	p
All Stimuli Types (irrespective of the light and prosody conditions)				
SAD > Control Subjects				
Thalamus[a]	R	14 −18 4	3.61	.010
Brainstem[a]	L	−2 −28 −22	3.58	.011
Control Subjects > SAD				
No significant voxel				
Anger Prosody Stimuli				
[Blue > Dark] × [SAD > Control Subjects]				
Hypothalamus[bc]	L	−2 −2 −12	3.21	.027
[Blue > Dark] × [Control Subjects > SAD]				
No significant voxel				
[Green > Dark] × [SAD > Control Subjects]				
No significant voxel				
[Green > Dark] × [Control Subjects > SAD]				
Hypothalamus[cd]	L	−4 −2 −18	3.13	.032

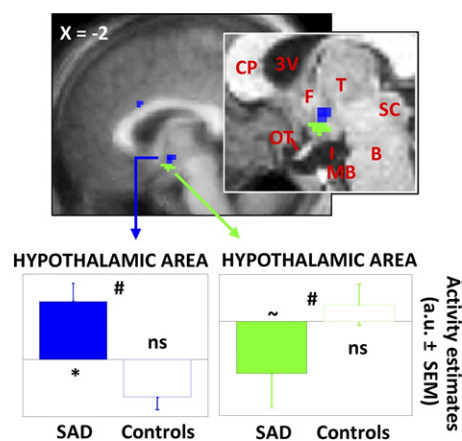XYZ: relative coordinates (mm) in Montreal Neurological Institute space.

fMRI, functional magnetic resonance imaging; L, left; R, right; SAD, seasonal affective disorder.

[a]The same two significant clusters of voxel are obtained in the thalamus and brainstem if the analyses only included: 1) all stimuli in darkness; 2) all stimuli under green light exposure; 3) all stimuli under blue light exposure; 4) emotional stimuli under blue or green light exposure; 5) neutral stimuli under blue or green light exposure (i.e., these differences between groups are observed for every stimuli subgroup).

[b]Clusters not affected by an exclusive mask ($p = .05$) of the (Neutral × [Blue > Dark] × [SAD > Control Subjects]) contrast, indicating that the light condition effect was specific to the emotional (angry prosody) stimuli.

[c]Because of the difference in irradiance level between blue and green light (see technical issue in Methods and Materials), the contrast computing the interaction between blue and green light conditions [(Blue > Green)] × [SAD > Control Subjects] is not valid. However, if this contrast is nevertheless computed, it shows a single significant difference in the hypothalamus (−2 0 −18 mm; Z = 3.73; $p_{svc} = .006$) which further strengthens the results obtained for each light condition separately.

[d]Clusters not affected by an exclusive mask (p = .05) of the (Neutral × [Green > Dark] × [SAD > Control Subjects]) contrast, indicating that the light condition effect was specific to the emotional (angry prosody) stimuli.

in patients with SAD. Importantly, these effects of blue and green light were not observed in control subjects and were significantly different between patients and control subjects. Again, multiple regression analyses showed that these results were not significantly related to single characteristics of subjects that differed between groups (cf. Table 1). Finally, no impact of light wavelength on the processing of neutral auditory stimuli was found in either group, demonstrating the specificity of the effects for emotional stimuli and for the patients with SAD.

ERG Results

Scotopic and photopic light sensitivity, as indicated by LogK, did not differ between patients and control subjects [mean $\pm$ SD; Photopic LogK: patients (.108 $\pm$ .093), control subjects (.108 $\pm$ .102), $t(26) = .008$, $p = .99$; Scotopic LogK: patients ($-2.72 \pm .12$), control subjects ($-2.75 \pm .11$), $t(27) = .66$, $p = .51$].

Discussion

These results demonstrate that exposure to light has an acute impact on emotional brain processing in untreated symptomatic patients with SAD in fall/winter and that this impact depends on light spectral composition; blue light increased and green light decreased responses to auditory emotional stimuli in the posterior hypothalamus, as compared with healthy control subjects. This study also reveals that, in the context of our protocol, SAD patients presented increased thalamic and brainstem responsiveness to vocal stimuli, regardless of their emotional content and of the light condition.

Compared with control subjects, patients showed higher thalamic activation to auditory stimuli in the dorsal pulvinar and in regions of the brainstem compatible with the locus coeruleus and dorsal raphe nucleus (although fMRI spatial resolution does not allow identification of specific brainstem nuclei). The locus coeruleus and dorsal raphe nucleus are implicated in reward regulation and depression (44) and constitute an important source of norepinephrine and serotonin, respectively. Interestingly, serotonin levels seem to be influenced by season and bright sunlight (45), and altered serotonin receptor functions have been described in SAD (2,3,46). Animal data also showed that complete light deprivation reduced noradrenergic projections from the locus coeruleus to the prefrontal cortex (47), which is essential for cognition (48). In addition, metabolic and serotoninergic dysfunction in the pulvinar has been related to depression (49). Therefore, the differential responsiveness to vocal stimuli could constitute a marker of a general increased sensitivity in SAD during the fall/winter depressive episode, speculatively related to serotonin and norepinephrine functions.

Emotional processing was affected by blue and green light in a single area of the brain—taking into account baseline differences between groups (i.e., responses under blue or green light were compared with darkness)—pointing to light-induced variation in hypothalamic reactivity specific to SAD, at least during the fall/winter symptomatic episode. These effects were not observed with neutral stimuli, showing their specificity for the processing of emotional stimuli. In other words, they were not caused by an overall change in brain reactivity throughout the 40-sec light exposure. We showed that, in healthy individuals and as compared with green light, blue light exposure increased the functional connectivity between the amygdala, temporal cortex voice-sensitive area, and a hypothalamic area located in the vicinity of the present significant hypothalamic cluster (30). Dysfunction in hypothalamus-related functions is typically observed in SAD, as indicated by changes in sleep, feeding, metabolism, and motivation (2,3,5–7). One plausible

implication of our findings is that exposure to light participates in the long-term normalization of these hypothalamic functions and leads to remission. However, on the basis of our protocol, we cannot determine whether it is the case or whether these abnormal hypothalamic responses to light constitute a trait-marker triggering the disorder when light availability declines or a state-marker secondary to other phenomenon.

Importantly, the data showed no performance differences between groups, which ensures that our results are not due to behavioral differences during data acquisition (e.g., differences in task difficulty). Moreover, both populations did not differ for many other possible confounds, such as age, gender, education level, wake time, or dates of experiments (cf. Table 1). As expected, however, SAD patients differed from control subjects for several aspects typically related to their pathology, such as daytime sleepiness, anxiety and depression levels, sleep duration, and seasonality. Although several of these factors are likely to have contributed to our results, none of them was identified by regression analyses as significantly contributing to the results on their own.

The spatial resolution of fMRI does not allow determination of which hypothalamic nucleus was specifically affected by light, but a number of posterior hypothalamic nuclei receive retinal projections directly, or indirectly through the suprachiasmatic nucleus (17,50). Some of them, such as the hypocretin/melanin-concentrating hormone postero-lateral hypothalamus, are involved in the regulation of sleep, wakefulness, motivation and metabolism. Through their numerous projections, hypocretin/melanin-concentrating hormone neurons regulate activity in nuclei of the ascending arousal system of the brainstem, including the locus coeruleus and dorsal raphe nucleus, and in the thalamus (51). Likewise, light of various wavelengths could also affect the processing of emotional stimuli in the paraventricular nucleus of the hypothalamus, which is involved in emotional responses (52) and vegetative regulation (53).

Scotopic (rod-dependent) light sensitivity did not differ between patients and control subjects, which contrasts with our predictions on the basis of previous observations of lower rod sensitivity in SAD (9,54,55). This discrepancy cannot be attributed to the sample of patients, because SIGHSAD scores, depression, and seasonality levels were similar to those reported in previous studies on SAD (e.g., [19,46]), including those investigating retinal sensitivity (9,54). It should be noted, however, that it is the seasonal change in rod retinal sensitivity that has been most reported to be abnormal in SAD, whereas differences between patients and control subjects were not systematically detected in fall/winter (54–56). With regard to cone function, only one study so far reported decreased function in symptomatic patients with SAD in fall/winter (9), a result that was not observed in the current study. Only short-term light history (preceding hours) was closely controlled in the present protocol. We cannot therefore exclude that longer-term light history influenced our ERG results (57). However, there seems to be no indication in the literature for difference in light history between SAD patients and healthy control subjects (58). In spite of this, our results suggest that abnormal rod or cone function cannot account for the altered hypothalamic responses observed in SAD under blue and green light exposures.

The irradiance level we used is compatible with the recruitment of melanopsin-expressing ipRGCs (59), and a polymorphism in the melanopsin gene has been linked to SAD (60). However, all photoreceptors are likely to have contributed (17), especially given the results obtained with green light, and further research is warranted to identify how each photoreceptor participates in the influence of light on emotional brain processing in patients and healthy individ-

uals. Nonetheless, our results support that the wavelength of light is an important factor for light therapy as well as for optimal indoor lighting, particularly for individuals more vulnerable to seasonal light variation, such as SAD patients, but also for an important part of the population, namely subsyndromal SAD sufferers (up to 18% of the North American general population), who experience intermediate seasonal emotional, mood, and vigilance problems that—although bothersome—do not reach clinical significance (61).

The acute impact of light on emotional brain responses might not be related to its long-term impact on mood regulation. However, emotions and mood are intimately related. Mood alteration in mood disorders modify emotional brain responses, whereas emotional responses can greatly influence (subsequent) mood (23). Furthermore, although the impact of light on emotional processing might differ between negative and positive stimuli, common brain pathways respond to emotional stimuli, regardless of emotional valence direction (36), supporting that similar effects of light likely take place for positive emotions.

As a whole, the results provide experimental evidence for a central role of the hypothalamus in the seasonal-light-decline sensitivity present in SAD. Abnormal light responsiveness in the posterior hypothalamus constitutes a neurobiological substrate of SAD during the fall/winter depressive episode that could trigger the disorder or, conversely, lead to remission. Future studies should address these questions and compare symptomatic and asymptomatic states in the same individuals, in fall/winter, before and after light therapy, and spring/summer.

Supplementary material cited in this article is available online.

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