

Research report

Dose-response relationship for light intensity and ocular and electroencephalographic correlates of human alertness

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Abstract

Light can elicit both circadian and acute physiological responses in humans. In a dose response protocol men and women were exposed to illuminances ranging from 3 to 9100 lux for 6.5 h during the early biological night after they had been exposed to < 3 lux for several hours. Light exerted an acute alerting response as assessed by a reduction in the incidence of slow-eye movements, a reduction of EEG activity in the theta–alpha frequencies (power density in the 5–9 Hz range) as well as a reduction in self-reported sleepiness. This alerting response was positively correlated with the degree of melatonin suppression by light. In accordance with the dose response function for circadian resetting and melatonin suppression, the responses of all three indices of alertness to variations in illuminance were consistent with a logistic dose response curve. Half of the maximum alerting response to bright light of 9100 lux was obtained with room light of ~ 100 lux. This sensitivity to light indicates that variations in illuminance within the range of typical, ambient, room light (90–180 lux) can have a significant impact on subjective alertness and its electrophysiologic concomitants in humans during the early biological night. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

The human circadian timing system is sensitive to ocular light exposure. Light is capable of resetting the human circadian pacemaker and synchronizing (entraining) endogenous circadian rhythms to the 24-h day. The effects of light depend on the circadian phase at which light is administered. Light administered after the nadir of core body temperature can advance the phase of circadian rhythms whereas light given before the temperature nadir can induce delays (for a review see [9]). Dose response studies have demonstrated a non-linear relationship between light intensity (illuminance) and phase shifts of the circadian pacemaker

[3,40]. The dose response function to a single episode of light in the delay region can be characterized by a logistic function with a high sensitivity such that half of the maximal resetting response achieved in response to bright light (9100 lux) is obtained with just 1% of this light (dim room light of ~ 100 lux; see [40]).

In addition to its effect on the timing of circadian rhythms, light has been shown to exert direct effects on a number of physiologic variables in humans. Plasma melatonin and core body temperature are frequently used dependent variables in research on direct, non-circadian effects of light. Light exposure can result in melatonin suppression and elevation of core body temperature [2,4,5,12,23,29,31]. The direct effects of light — as well as the circadian effects — appear to be mediated by the eyes. Thus acute elevation of body temperature and suppression of melatonin are not observed when the eyes are covered [10,12], or light is administered to the skin in the popliteal region [18,25]. The photoreceptor(s) mediating these effects have not

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been identified, but recent data indicate that retinal non-rod and non-cone photoreceptors might form the basis of this non-image forming photoreceptive pathway mediating both the circadian and direct effects of light in rodents [15,27].

It has been reported that the direct effects of light are not limited to physiologic variables but also include neurobehavioral performance measures such as alertness and reaction times [2,7,8,39]. The dose response characteristics of these effects of light have not been established. Furthermore, the positive effects of bright light on neurobehavioral performance remain controversial because such effects were not observed in a number of studies [11,14,20,22]. These conflicting results may be related to the range of light intensities investigated, the phase of the endogenous circadian cycle of light sensitivity at which these effects were assessed as well as the sensitivity of the dependent measures employed in these studies. Recent data indicate that quantification of slow eye movements (SEMS) as well as quantitative EEG analysis can yield sensitive indicators of changes in alertness and neurobehavioral performance capability during baseline conditions as well as during conditions of sleep loss and circadian phase misalignment [6,28]. Under these conditions decrements in neurobehavioral performance are associated with a higher incidence of SEMS as well as an increase in EEG activity in the theta range, especially when recorded from frontal areas of the cortex [6].

To further investigate the direct effects of light we exposed subjects to a broad range of light intensities (3–9100 lux) during the early biological night and quantified SEMS and the EEG during wakefulness.

2. Methods

2.1. Subjects selection

Potential volunteers were recruited via poster and newspaper advertisement in the Greater Boston area. After passing a telephone screening interview, potential subjects gave informed consent and completed the following screening questionnaires: the Beck Depression Inventory-II, the Horne-Östberg Morningness-Eveningness Questionnaire, and a questionnaire covering sleep habits and physical health. Subjects showing no evidence of psychopathology or symptoms of a sleep disorder on these screening instruments were scheduled for a physical examination, routine blood and urine chemistries, and a 12-lead electrocardiogram. They also received a screening interview with a licensed psychologist to rule out personal or familial history of major psychopathology and to determine their comprehension of and ability to comply with the investigational procedures. Finally, potential volunteers were interviewed by

an investigator, and written informed consent was obtained for the protocol, which was approved by the Brigham and Women's Hospital's Human Research Committee.

2.2. Subjects

Twenty-three healthy young male ($n = 22$) and female ($n = 1$) volunteers, aged 18–44 years (mean: 27.8 years; S.D.: ± 8.91), participated in a 9 day protocol (for screening procedures and protocol details, see [40]). Subjects were informed that the purpose of the experiment was to investigate the effects of light on the biological clock. Prior to the study, subjects had to keep a regular sleep–wake cycle for at least 2 weeks. Subjects were required to telephone the laboratory immediately prior to their scheduled bedtimes and immediately after their scheduled waketimes to document adherence to an 8-h sleep episode, with bedtimes and waketimes fixed at their reported habitual times. Adherence to a regular schedule during the week immediately prior to admission was verified by wrist actigraphy (Mini Motionlogger, AMI, Ardsley, NY); only subjects who maintained the regular schedule as instructed were admitted to the laboratory for the study. The timing of the experimental light exposure was based on an on-line core temperature assessment. This on-line measurement was misestimated in two subjects who were excluded from further analyses (see below). In another subject, data on self-reported sleepiness were not valid. There was therefore an $n = 20$ for self reported sleepiness. Due to technical difficulties, EOG data were available only in 17 subjects and EEG data only in 16 subjects.

2.3. Protocol and light exposure episode

Following 3 scheduled days and nights in the laboratory during which subjects slept at their habitual times, the subjects underwent a constant routine (CR) of ~ 50 h to assess their circadian phase based on the rhythm of core body temperature (CBT). Subjects were kept awake during the CR in a semi-recumbent position in dim light (< 10 lux at eye level). Caloric and fluid demands were met by hourly snacks. After on-line assessment of the subject's initial phase of CBT, their bedtime times were scheduled to start 4.5 h after the CBT minimum (~ 2300 – 0530). After one recovery sleep episode of 8 h, subjects were exposed to a 6.5-h light pulse centered 3.5 h before their expected CBT minimum, therefore ending 0.25 h before their expected CBT minimum. Each subject was randomly assigned to a single illuminance, ranging from 3 to 9100 lux. The light levels during the 4.75 h before and after light exposure was ~ 3 lux. Subjects were required to remain seated for the duration of the 6.5-h light exposure, alternating their gaze between a fixed spot on the wall

and free gaze every 6 min. No photophobic behavior (e.g. closing one's eyes, reading) was allowed during any portion of the experimental light exposure. A technician was constantly present with the subject and enforced adherence to the stringently timed procedures of the light treatment protocol. The next day, subjects awoke into a second constant routine of ~30 h duration to assess the effects of the experimental light pulse on the phase of the circadian pacemaker. Subjects were allotted a final 8-h sleep episode and were discharged upon awakening on day 9. During the baseline days, illuminance in the horizontal angle of gaze was <150 lux during wake periods and <0.03 lux during sleep periods.

2.4. Assessment of subjective and objective alertness

At 30 min intervals beginning 30 min after scheduled awakening, subjects were instructed to take computerized tests of alertness/sleepiness (Karolinska Sleepiness Scale or KSS). In addition, at 1-h intervals, starting 1 h after scheduled waketime, the Karolinska Drowsiness Test (KDT) [16] was performed, during which the subjects were instructed to relax and fixate on a 5 cm black dot, attached to a computer screen 1 m away for 4 min.

2.5. EEG and eye movement recording and analysis

The EEG derived from Fz-Cz, Cz-Pz and Pz-Oz and the EOG was recorded in 18 subjects. All signals were digitized on-line (12 bit AD converter, 0.122 μ V/bit; storage sampling rate at 128 Hz for the EEG and 64 Hz for the EOG), digitally low-pass filtered at 35 Hz (4th order Bessel type anti-aliasing filters, total 24 dB/Octave) and high-pass filtered using a time constant of 0.3 s (Vitaport-2 digital recorder, TEMEC Instruments B.V., Kerkrade, The Netherlands). The raw signals were stored on-line on a Flash RAM Card (SanDisk, USA) and downloaded off-line to an Apple Macintosh hard drive. The EEG signals during the 4-min KDT were visually inspected for eye blinks, SEMS and small body movements. Two-s epochs containing muscle artifact, eye blinks or SEMS and micro-sleeps were marked as artifact and stored in a separate artifact channel (Vitaport Paperless Sleep Scoring Software). Artifact free 2-s epochs were subjected off-line to spectral analysis using a fast Fourier transform (FFT, 10% cosine window) resulting in a 0.5 Hz resolution. Before calculating the FFT, the EEG signals were pre-whitened in order to gain resolution in the amplitude of high frequency EEG components. All EOG recordings during the light exposure were inspected visually and 30-s epochs were scored for the presence or absence of SEMS (for details see [6]).

2.6. Melatonin collection and assay

Blood samples were collected twice an hour throughout the protocol, beginning on baseline day 2, from an indwelling intravenous forearm catheter for analysis of melatonin. Immediately after collection, each whole blood sample was placed in a Vacutainer tube with EDTA, centrifuged at 2°C for 10 min at 2200–2800 rpm, and the separated plasma was placed in an aliquot tube and frozen at –25°C. Blood samples were later assayed for plasma melatonin concentration (assay sensitivity of 2.5 pg/ml; intra-assay and interassay percent coefficients of variation, 8 and 13%, respectively; DiagnosTech, Osceola WI). Post hoc inspection of the circadian melatonin phase revealed that the timing of the experimental light exposure based on an on-line core temperature assessment was misestimated in two subjects who were excluded from further analyses. In the remaining 21 subjects, light was calculated to have been centered on average 1.96 ± 0.95 (S.D.) h before the fitted maximum of the plasma melatonin rhythm [40].

2.7. Core body temperature

Core body temperature was collected continuously throughout the study using a rectal thermistor (YSI, Yellow Springs, OH) with data stored at one minute intervals.

2.8. Statistics

The statistical package SAS[®] (SAS[®] Institute, Cary, NC, Version 6.12) was used. To evaluate whether light had an effect on the subjective rating of alertness, the occurrence of SEMS, plasma melatonin and core body temperature, the time course of these variables during light exposure was analyzed. Furthermore, subjects exposed to light levels within the lowest 33rd percentile were assigned to a low level light group ($N=6$ for subjective sleepiness, $N=5$ for EEG and EOG measures), and subjects exposed to levels within the highest 33rd percentile to a high light level group ($N=7$ for subjective sleepiness, $N=6$ for EEG and EOG measures). In addition, subjects exposed to light levels between the low and high 33rd percentile were assigned to a middle level light group ($N=7$ for subjective sleepiness, $N=6$ for EEG and $N=5$ for EOG measures). The geometric mean of illuminance in these three groups were 23, 230 and 3190 lux for the low, middle and high intensity group, respectively.

To construct a dose response curve for the alerting effect of light, a four parameter logistic model was fitted to the data (for references see [40]). The four parameter logistic model

$$\left[f(x) = \frac{a-d}{1+(x/b)^c} + d \right]$$

fits well responses to data that have a sigmoidal relationship with increasing stimulus strength. In this logistic model, the a term represents the estimated response of the system to 0 lux of light, the b term represents the lux value at which 50% of the maximal effect is observed, the d term represents the asymptotic maximal responsiveness of the system, and the c term is a measure of the steepness of the rising portion of the curve. Data were fit with a nonlinear least squares-fitting analysis based upon the Levenberg–Marquardt method. Residual analysis revealed a normal distribution of the data and there was no multicollinearity between the estimated parameters (all correlation coefficients < 0.5). Together with the adjusted r^2 value (see Table 1), an estimate of the goodness of fit, this indicates an appropriate fit to the chosen regression model.

For time course analyses, repeated measures ANOVAs (rANOVA) were used with the repeated fac-

tor *time* and the factor *group*. All P values derived from rANOVAs were based on Huynh–Feldt's (H–F) corrected degrees of freedom, but the original degrees of freedom are reported. When the F-ratio proved significant, post-hoc comparisons using Duncan's multiple range test were performed. EEG power density for each frequency bin in the range of 1–32 Hz was standardized to the sum of total EEG power density in the range of 1.0–32 Hz for each subject separately (log ratio).

3. Results

3.1. Illuminance dependent effects on alertness, plasma melatonin and core body temperature

Fig. 1 illustrates the time course of alertness and SEMS in a subject exposed to a light level (3 lux) within the first 33rd percentile of the illuminance range, in a subject within the second 33rd percentile (106 lux) and

Table 1
Results of a two-way ANOVA for repeated measures with the factor group, the factor time, and the interaction factor group \times time for subjective alertness, plasma metabolism and core body temperature during the light exposure episode

Variable	Group	Time	Group \times Time
Subjective alertness	$F_{1,11} = 10$; $P < 0.009$	$F_{6,66} = 3.4$; $P < 0.02$	$F_{6,66} = 4.5$; $P < 0.004$
Plasma melatonin	$F_{1,11} = 98.1$; $P < 0.0001$	$F_{6,66} = 6.8$; $P < 0.01$	$F_{6,66} = 6.5$; $P < 0.001$
Core body temperature	$F_{1,11} = 1.5$; n.s.	$F_{6,66} = 29.6$; $P < 0.0001$	$F_{6,66} = 1.1$; n.s.

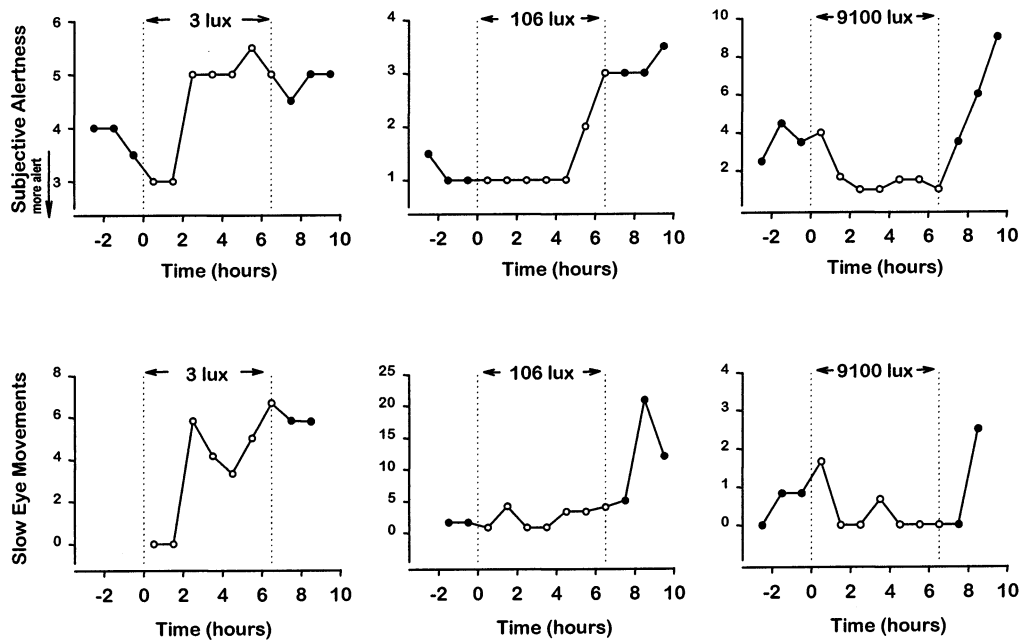


Fig. 1. Time course of subjective sleepiness and the incidence of slow eye movements (SEMS) for three individuals exposed to either 3, 106 or 9100 lux. Subjective alertness was assessed on the 9-point Karolinska Sleepiness Scale (1 = very alert; 9 = very sleepy, fighting sleep). Values for the incidence of SEMS represent the percentage of 5-min intervals containing at least one SEM. Stippled vertical lines delineate the duration of light exposure (6.5 h). Open symbols represent data points during light exposure; closed symbols represent values obtained outside the time window of light exposure.

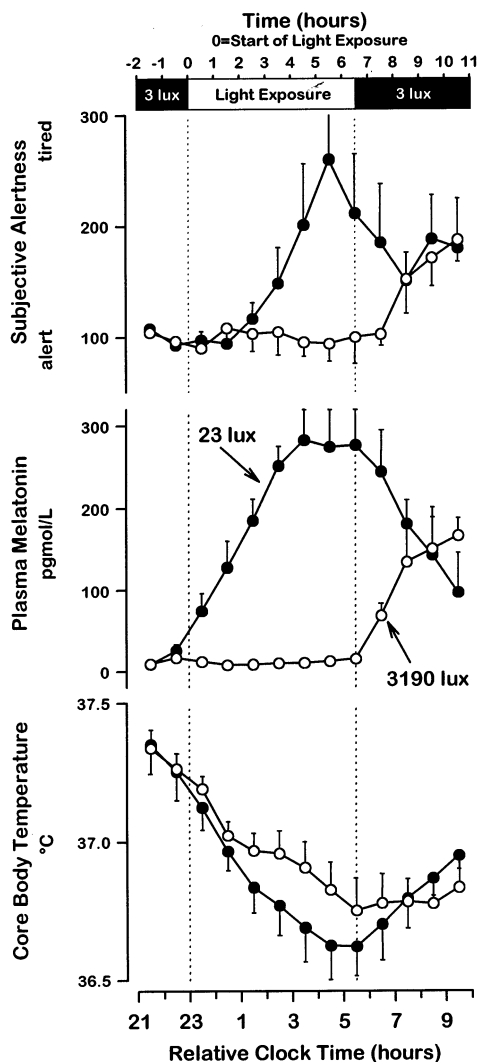


Fig. 2. Time course of subjective alertness, plasma melatonin and core body temperature before, during and following the light exposure episode. Subjects were grouped according to the first (closed symbols) and last 33rd percentile (open symbols) of the range of illuminances. Data represent mean values ± 1 S.E.M. A total of 23 and 3190 lux represent the geometric mean of illuminances in the two groups.

in a subject within the third 33rd percentile (9100 lux). Both the deterioration in subjective alertness and the increase in the number of SEMs were attenuated in the subjects exposed to 106 and 9100 lux. Both measures of alertness rapidly deteriorated upon return to dim light (< 3 lux).

In the high intensity light group, alertness level ratings rose immediately after the start of the light exposure. This did not occur in the low intensity light group (Fig. 2). Compared with the low intensity light group, the time course of alertness in the high intensity light group was significantly different such that subjects rated themselves as significantly less sleepy in the later part of the light exposure episode (factor 'group': $F_{1,11} = 10$, $P < 0.009$, for further statistics see Table 1). Plasma melatonin levels

were significantly lower during the entire 6.5-h light exposure episode in subjects exposed to high illuminances (Fig. 2, factor 'group': $F_{1,11} = 10$, $P < 0.0001$, for further statistics see Table 1). Two hours after the light exposure episode, alertness and plasma melatonin were no longer significantly different between the two groups. Mean core body temperature during the light exposure episode was higher in the high light group. However, none of the factors 'Group' or the interaction 'Group \times Time' reached significant levels (Table 1).

3.2. Illuminance dependent effects on ocular and electroencephalographic correlates of alertness

Illuminance dependent effects on ocular and electroencephalographic correlates of alertness, subjective alertness, the incidence of SEMs and EEG theta–alpha activity during the last 90-min episode of the light exposure was assessed in each subject and then averaged within each of the three light exposure groups (Fig. 3). The geometric mean of illuminance in these groups were 23, 230 and 3190 lux for the low, middle and high intensity group, respectively. Subjective alertness was significantly greater in the mid- and high- illuminance group as compared to the low intensity group. SEMs and EEG theta–alpha activity were significantly lower among subjects exposed to illuminances in the mid- and high-range (Duncan's multiple range test, $P < 0.002$ for each variable). For none of the three indices of alertness were significant differences between the mid- and high-intensity group observed.

3.3. Illuminance dependent effects on the spectral composition of the EEG in the 1.5–20 Hz range

It was investigated whether light elicits effects on EEG frequencies outside the range of 5–9 Hz, by computing the spectral composition of the EEG during wakefulness over the range of 1.5–20.0 Hz. Comparison of the EEG in the low- and high-illuminance group demonstrated that significant effects during the last 90 min of light exposure were limited to the 5–9 Hz range (Fig. 4, $F_{1,9} = 7.6$; $P < 0.02$; $P > 0.05$ for all other frequencies). The effect within the 5–9 Hz range was already present during the first 90-min episode of light exposure but did not reach statistical significance ($P = 0.12$, data not shown).

3.4. Dose-response relationship for light intensity and subjective alertness, SEMs and EEG theta–alpha activity

Alertness ratings, the incidence of SEMs and EEG theta–alpha activity (5–9 Hz) during the last 90 min of 6.5 h light exposure were plotted against the light intensity to which subjects were exposed (Fig. 5). Fitting the data with a logistic regression equation (see

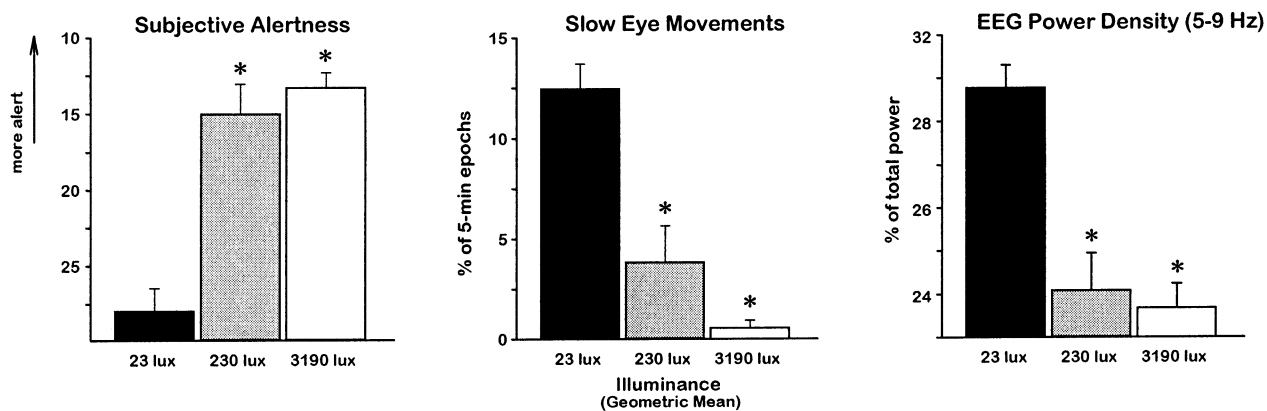


Fig. 3. Illuminance dependent effects on subjective alertness, the incidence of slow eye movements (SEMS) and EEG power density in the theta–alpha range (5–9 Hz). Mean values + 1 S.E.M. Asterisks indicate significant differences between the 23 lux group vs. the 230 lux group and the 23 lux group vs. the 3190 lux group (Duncan's multiple range test $P < 0.003$).

Section 2) revealed a steep dose response function (Table 2) with half of the fitted maximal alerting effect of light estimated to be induced by ~ 100 lux as rated subjectively, by ~ 180 lux as measured by the occurrence of SEMS and by ~ 90 lux as measured by EEG theta–alpha activity.

3.5. Correlations between subjective alertness, SEMS, EEG and melatonin suppression

To investigate the association between alertness, SEMS, EEG theta–alpha activity and melatonin suppression, Pearson Product Moment correlations were computed for each variable separately.

For all indexes of alertness (i.e. subjective ratings, SEMS and EEG theta–alpha activity) high correlations with the degree of melatonin suppression were present (Table 3).

4. Discussion

It is concluded from these data that nighttime exposure to typical room light (90–180 lux) can exert an alerting effect in humans, as assessed by subjective ratings, SEMS, and EEG activity in the theta and alpha range. The magnitude of this alerting response to light is dependent on the intensity of the light stimulus. The illuminance response function can be appropriately described by a logistic regression model, regardless of whether alertness is quantified by subjective ratings or by analysis of the electrooculogram and electroencephalogram. This illuminance response function is similar to that of the dose response function reported for the magnitude of suppression of plasma melatonin concentrations as a function of light intensity, as well as the dose response function reported for the circadian phase resetting effects of light [40]. Thus, whereas for the current

indices of alertness, the half-maximum alerting effect of light was achieved with illuminances between 90 and 180 lux, the half-maximum effects for melatonin suppression and circadian phase resetting were obtained at 50–130 and 80–160, lux respectively. This relatively high sensitivity may explain why in some previous experiments a direct effect of light was not observed as the effects of 'bright light' were compared to 'dim light' conditions that were of sufficient intensity to elicit near maximal effects [14,31].

The characteristic of the dose response functions described for the alerting effects of light may imply that these effects are mediated by the same receptive elements and retinohypothalamic pathways that mediate

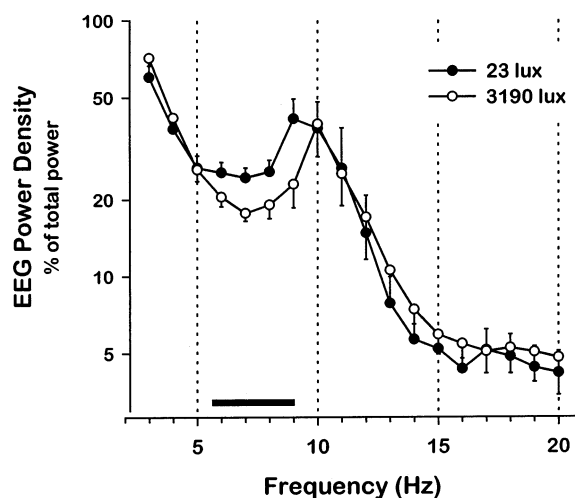


Fig. 4. EEG power density in single-frequency bins (1–20 Hz) in the low light level group (filled symbols; geometric mean 23 lux) and high light level group (open symbols; geometric mean 3190 lux). Mean values \pm S.E.M. represent the log ratio of total EEG power density in the range of 1–32 Hz during the last 90 min of light exposure. Symbols above the abscissa indicate frequency bins for which a significant difference between the two groups was observed ($P < 0.05$).

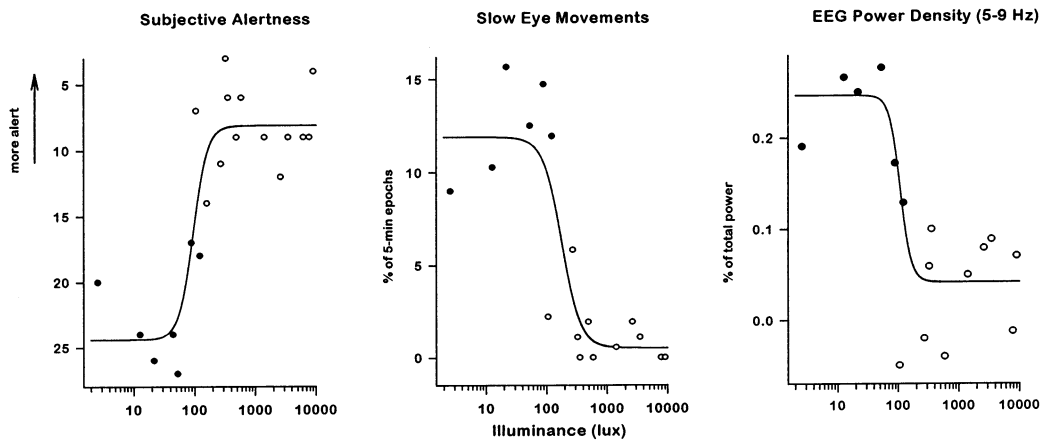


Fig. 5. Dose-response relationship between illuminance and subjective alertness, the incidence of slow eye movements (SEMS) and EEG theta–alpha activity (5–9 Hz). Data points represent the sum of alertness ratings, the number of 30-s epochs containing at least one SEM and normalized EEG power density during the last 90 min of the light exposure episode for a single individual. Open symbols identify individuals in whom light exerted more than 50% suppression of plasma melatonin, closed symbols identify individuals in whom melatonin suppression was less than 50%. The line represent a logistic regression model fit to the individual data points (For statistics on the residual analysis of the logistic regression model fit see Section 2).

Table 2
 $f(x) = \frac{a-d}{1+(x/b)^c} + d$ Parameter estimates ± 1 S.E. and adjusted r^2 of the four parameter logistic model: $f(x) = (a-d/1+(x/b)^c) + d$ for the variables: subjective alertness (KSS), slow eye movements (SEMS) and EEG theta–alpha activity (EEG)^a

Variable	<i>a</i>	<i>b</i> (lux)	<i>c</i>	<i>d</i>	adj r^2
KSS	-24.4 ± 2.1	94.8 ± 17.5	3.7 ± 2.5	-8.11 ± 1.2	0.94
SEMS	-11.9 ± 1.7	179.4 ± 62	2.8 ± 1.7	-0.52 ± 1.3	0.84
EEG	-0.25 ± 0.02	88.8 ± 1.1	98.2 ± 0.0	-0.04 ± 0.02	0.84

^a The *a* term is the estimated response of the system to 0 lux of light, the *b* term is the lux value at which 50% of the maximal effect is observed, the *d* term is the asymptotic maximal responsiveness of the system, and the *c* term is a measure of the steepness of the rising portion of the curve.

the circadian responses to light. There is considerable evidence that the circadian photoreceptive system is functionally and structurally distinct from the image forming visual system [15,27,34,37]. Key characteristics of the circadian photoreceptive system that are different from the image forming visual system include the relatively high threshold for responses to light and the long duration stimulus integration time [32,33,37]. In addition, it has been suggested that the circadian photoreceptive system does not exhibit adaptation to previous light exposure [32] although experiments to establish conclusively this characteristic have not been reported to the authors' knowledge. The potential role of adaptation of this circadian photoreceptive system is important for the implications of the data. If adaptation does not play a major role, the results can be expected to be valid for real life situations in which subjects may have been exposed to higher light intensities during the day. This issue needs further investigation before it can be concluded that an increase of ambient light levels will be beneficial for those who experience undesirable sleepiness in the early nighttime hours.

The circadian responses to ocular light are mediated by a direct retinal projection to the SCN. The retinal projections involved in the direct effects of light on alertness have not been identified. Candidate projections areas include the SCN, the pretectal area [30], the intergeniculate leaflet [17] and the ventrolateral preoptic nucleus (VLPO)[26]. The projections to the SCN mediate the acute effect of light on melatonin synthesis in the pineal and associated suppression of circulating melatonin [19]. Both the present data as well as previous studies have provided evidence that melatonin may be involved in both the subjective alerting effect as well

Table 3
 Pearson product moment correlation between plasma melatonin suppression vs. subjective alertness (KSS), slow eye movements (SEMS) and EEG theta–alpha activity (EEG)

Variable	<i>N</i>	r^2	<i>p</i>
KSS	20	0.89	<0.0001
SEMS	17	0.90	<0.0001
EEG	16	0.72	<0.0001

as the effect of light on the EEG [7,35,38]. Thus in the present experiment strong association between melatonin suppression and the alerting effects elicited by light were observed. Previously it was shown that administration of supraphysiologic doses of melatonin lead to changes in the waking EEG opposite to those induced by bright light and the effect of light on the EEG can be counteracted by exogenous melatonin [7]. It has been hypothesized that melatonin elicits these effects by attenuating the SCN-dependent mechanisms responsible for promoting and maintaining cortical and behavioral arousal at particular times in the circadian cycle [13,21,36]. Although melatonin suppression mediated by the retinal projection to the SCN is likely to be involved in some of the direct effects of light other possibilities should be considered. The recently described retinal projection to sleep-active neurons in the VLPO may represent an alternative or additional anatomical substrate by which light exerts direct effects on EEG and alertness. The VLPO innervates all of the major nuclei of the ascending monoaminergic and in particular the histaminergic system, which is thought to play a key role in wakefulness and EEG arousal [1,24].

The current data in conjunction with the newly discovered multiple direct retinal projections to hypothalamic areas may further stimulate research on the direct effects of light and the neurophysiologic mechanisms by which they are mediated. In addition, these data may lead to new approaches to prevent and treat undesirable sleepiness and performance decrements during the early nighttime hours in some subject populations, such as older people, and as well as nighttime sleepiness and performance decrements in night shift workers.

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