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Alerting effects of light are sensitive to very short wavelengths

Victoria L. Revell [a,b,*], Josephine Arendt [a], Louis F. Fogg [b], Debra J. Skene [a]

[a] School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey, GU2 7XH, UK
[b] Biological Rhythms Research Laboratory, Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL 60612, USA

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Abstract

In humans a range of non-image-forming (NIF) light responses (melatonin suppression, phase shifting and alertness) are short wavelength sensitive (440–480 nm). The aim of the current study was to assess the acute effect of three different short wavelength light pulses (420, 440 and 470 nm) and 600 nm light on subjective alertness. Healthy male subjects ($n = 12$, aged 27 ± 4 years, mean $\pm$ S.D.) were studied in 39, 4-day laboratory study sessions. The subjects were maintained in dim light (<8 lx) and on day 3 they were exposed to a single 4-h light pulse (07:15–11:15 h). Four monochromatic wavelengths were administered at two photon densities: 420 and 440 nm at 2.3×10^{13} photons/cm^2/s and 440, 470 and 600 nm at 6.2×10^{13} photons/cm^2/s. Subjective mood and alertness were assessed at 30 min intervals during the light exposure, using four 9-point VAS scales. Mixed model regression analysis was used to compare alertness and mood ratings during the 470 nm light to those recorded with the other four light conditions. There was a significant effect of duration of light exposure ($p < 0.001$) on alertness but no significant effect of subject. Compared to 470 nm light, alertness levels were significantly higher in 420 nm light and significantly lower in the 600 nm light ($p < 0.05$). These data (420 nm > 470 nm > 600 nm) suggest that subjective alertness may be maximally sensitive to very short wavelength light.

Keywords: Human; Alertness; Light; Spectral sensitivity; Short wavelength light

The mammalian eye detects light for both image generation and measurement of environmental irradiance. In humans a wide range of non-image-forming (NIF) light responses are influenced by gross changes in environmental irradiance; for example, photoentrainment of circadian rhythms [5,41,44], acute suppression of melatonin [6,21], elevation of body temperature [3,11], and both subjective and objective alertness at night [9] and during the day [30]. Animal studies suggest that these irradiance-dependent responses are most likely mediated via the retinohypothalamic tract (RHT) which projects to a number of brain areas, including the suprachiasmatic nuclei (SCN), olivary pretectal nucleus (OPN), intergeniculate leaflet (IGL) and ventrolateral preoptic nucleus (VLPO) [14].

The rod and cone photopigments involved in visual responses are well characterised, but the identity and relative contribution of the photopigments involved in NIF responses are only just beginning to be understood. In rodents it appears that the primary photic input is provided by the melanopsin expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) which make up the RHT and are maximally sensitive to ≈480 nm light [4,13,16,17,24,28,31]. In addition, the rods and cones, although not absolutely required [12], also appear to be involved in NIF responses [1,17,34]. Knockout mouse models have demonstrated that the classical visual photopigments and melanopsin are the exclusive light detecting systems involved in rodent NIF responses [17].

In humans, short wavelength sensitivity has been demonstrated in a range of NIF responses: melatonin suppression [7,37], phase shifting [22,32,40,42,43], cone ERG [15], nocturnal decline in slow wave activity [27], subjective and objective alertness and elevation of core body temperature [8]. Action spectra for light-induced melatonin suppression [7,37] and the cone ERG [15] have a λ_{max} of ≈460 and 483 nm, respectively. These findings suggest that, like in rodents, a non-rod, non-cone opsin-based photopigment is involved in human NIF responses. Indeed, melanopsin expressing RGCs have been identified in the human retina [10].

Recently, it has been demonstrated that 460 nm monochromatic light was more effective at enhancing subjective alertness at night than 550 nm light [8]. To determine the wavelength of

* Corresponding author at: Biological Rhythms Research Laboratory, Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL 60612, USA. Tel.: +1 312 563 4783; fax: +1 312 563 4900.
E-mail address: Victoria_L_Revell@rush.edu (V.L. Revell).

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maximal sensitivity it will be necessary to test the ability of a range of light wavelengths to enhance alertness. The aim of this study was to assess the effect of three different short wavelength monochromatic light pulses (420, 440 and 470 nm) and one long wavelength monochromatic light pulse (600 nm) on subjective alertness and mood.

Twelve male drug-free subjects aged 27 ± 4 years (mean ± S.D.) were recruited and studied in 39 phase shifting laboratory study sessions. Ethical approval for the study was granted by the University of Surrey Ethics Committee. The experiments were conducted in accordance with the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written consent of the subjects. Subjects had no colour vision deficiencies according to the Ishihara colour blindness plate test. In order to minimise inter-individual variation in circadian phase only subjects with a regular sleep-wake cycle (sleep onset between 22:00 and 24:00 h and wake between 07:00 and 08:00 h) were selected. For 2 weeks prior to the laboratory study session subjects were required to keep regular sleep-wake schedules (23:00–07:00 h) from which they could only deviate by up to 30 min in either direction. Compliance to the protocol was confirmed by sleep diaries and actigraphic recordings (AWL, Cambridge Neurotechnology Ltd., UK).

Alertness and mood assessments were made during the 4-day protocol previously described in detail [32,40]. Briefly, during the study session subjects were confined to the Clinical Investigation Unit (CIU). Lighting and posture were controlled throughout. Environmental lighting was maintained at <8 lx: 2 lx in the direction of gaze and 5–7 lx when looking directly at the overhead white lights. A 4-h monochromatic light pulse was administered at the end of the second night (i.e. day 3) immediately after wake time (07:00 h) from 07:15 to 11:15 h.

The lighting equipment and light conditions have previously been described in detail [32]. Briefly, four monochromatic wavelengths were tested at two photon densities: 420 and 440 nm at 2.3×10^{13} photons/cm^2/s; 440, 470 and 600 nm at 6.2×10^{13} photons/cm^2/s. The range of light intensities used was 11–28 μW/cm^2 or 0.7–17.5 lx. Subjects placed their heads in a specially designed visor that delivered monochromatic light. The light source was a PL900 light box fitted with a 150 W quartz halogen bulb (Dolan Jenner Industries, Lawrence, USA) delivering light via a fibre optic cable (Edmund Optics, UK). The monochromatic filters (12.7 mm diameter, Coherent Ealing Europe Ltd., Watford, UK) had half maximal bandwidths ($\Delta\lambda_{0.5}$) of <5 nm. Diffuser paper and Kodak Wratten neutral density filters (Richard Frankfurt, Croydon, Surrey, UK) were used to adjust irradiance. The spectral distribution of each light pulse was confirmed using a Spectrascan 650 portable spectrometer (Photoresearch, Chatsworth, CA, USA). The visor was positioned so subjects could move it towards their face for the 10-min light exposure and push it away (90° rotation) for the 5-min dim light period (<8 lx). This cycle was repeated 16 times during the 4-h trial. The sample size in each light condition was as follows: 2.3×10^{13} photons/cm^2/s at 420 nm ($n = 7$) and 440 nm ($n = 6$); and 6.2×10^{13} photons/cm^2/s at 440 nm ($n = 8$), 470 nm ($n = 8$) and 600 nm ($n = 10$). One subject received one light condition, four subjects received two light conditions, one subject received three light conditions, three subjects received four light conditions and three subjects received five light conditions.

Alertness and mood were subjectively rated on day 3 (07:10–12:00 h) using four 9-point visual analogue scales (VAS): (i) 1—very alert, 9—very sleepy, (ii) 1—very calm, 9—very tense, (iii) 1—very cheerful, 9—very miserable, and (iv) 1—depressed, 9—elated. Subjects gave verbal responses to the investigator every 30 min during the 4 h light exposure at 07:40; 08:10, 08:40, etc. until 11:10 h, and then every 15 min (11:25; 11:40; 11:55) until 12:00 h. From 07:00 to 12:00 h subjects remained in a semi-recumbent position. The ratings at 07:10 h occurred before the light pulse began at 07:15 and the ratings at 11:10 h occurred while the light was still on. Only alertness and mood ratings recorded during the light pulse were used in the analysis (07:40–11:10 h). The investigators and all written information about the study (subject information sheets, advertisements) were careful to avoid giving the subjects any expectation about the efficacy of the different light treatments on alertness. For ease of presentation and understanding the data were adjusted post-collection so that all positive effects on mood or alertness are reflected by an increase in numeric rating, e.g. 1—very alert, 9—very sleepy was altered to 1—very sleepy, 9—very alert.

The data was analysed using a Mixed Effects Linear Regression Analysis [18]. This technique properly deals with both inter-individual and intra-individual variation. The model included both fixed effects, which are systematic relationships such as changes over time, and random effects, which account for variability among subjects [39]. In addition, this model can account for the fact that not all subjects were equally distributed across the five light conditions. Light condition and subject were treated as random effects whilst time was treated as a fixed effect. Subject effects were dummy-coded with one subject (S24) used as a comparison condition. For light condition, 470 nm was used as the comparison condition because the literature would predict that this would be the most effective wavelength of those tested. The resulting analysis estimated effects for both light condition and individual subject for each mood and alertness scale. This type of analysis has been used previously to demonstrate inter-individual variability in response to factors such as workload [33] and impairment from sleep loss [38].

The results of the Mixed Effects Linear Regression Analysis for the alertness ratings are given in Table 1. There was no

Table 1
Mixed Effects Linear Regression Analysis for subjective alertness ratings during a 4-h monochromatic light pulse (07:15–11:15 h)

Variable	Photons/cm^2/s	Estimate (S.E.)	p-value
Intercept		4.47 (1.29)	0.00053**
Time		−0.10 (0.03)	0.00053**
420 nm	2.3×10^{13}	0.73 (0.36)	0.04*
440 nm	2.3×10^{13}	−0.09 (0.36)	0.79
440 nm	6.2×10^{13}	0.53 (0.41)	0.19
600 nm	6.2×10^{13}	−0.85 (0.40)	0.03*

For light condition, the data were compared with 470 nm light.
* $p < 0.05$ (significant results).
** $p < 0.001$.