Cerebral Cortex December 2007;17:2788–2795
doi:10.1093/cercor/bhm007
Advance Access publication April 2, 2007

# Wavelength-Dependent Modulation of Brain Responses to a Working Memory Task by Daytime Light Exposure

G. Vandewalle[1], S. Gais[1], M. Schabus[1], E. Balteau[1], J. Carrier[2], A. Darsaud[1], V. Sterpenich[1], G. Albouy[1], D. J. Dijk[3] and Pierre Maquet[1,4]

[1]Cyclotron Research Centre, University of Liège, B-4000 Liège, Belgium, [2]Department of Psychology, Université de Montréal, Montréal, Québec, H3C 3J7, Canada, [3]Surrey Sleep Research Centre, University of Surrey, Guildford, GU2 7XP, UK and [4]Department of Neurology, Centre Hospitalier Universitaire, B-4000, Liège, Belgium

**In addition to classical visual effects, light elicits nonvisual brain responses, which profoundly influence physiology and behavior. These effects are mediated in part by melanopsin-expressing light-sensitive ganglion cells that, in contrast to the classical photopic system that is maximally sensitive to green light (550 nm), is very sensitive to blue light (470–480 nm). At present, there is no evidence that blue light exposure is effective in modulating nonvisual brain activity related to complex cognitive tasks. Using functional magnetic resonance imaging, we show that, while participants perform an auditory working memory task, a short (18 min) daytime exposure to blue (470 nm) or green (550 nm) monochromatic light ($3 \times 10^{13}$ photons/cm$^2$/s) differentially modulates regional brain responses. Blue light typically enhanced brain responses or at least prevented the decline otherwise observed following green light exposure in frontal and parietal cortices implicated in working memory, and in the thalamus involved in the modulation of cognition by arousal. Our results imply that monochromatic light can affect cognitive functions almost instantaneously and suggest that these effects are mediated by a melanopsin-based photoreceptor system.**

**Keywords:** circadian rhythms, functional magnetic resonance imaging, human cognition, light exposure, melanopsin

## Introduction

Whereas the classical visual system generates images of the external world, another "nonvisual" system (also referred to as "non–image-forming" system) detects variations in ambient irradiance and elicits a wide range of responses. These responses include long-term modifications of circadian rhythms and acute changes in hormone secretion, heart rate, sleep propensity, alertness, core body temperature, retinal neurophysiology, pupillary constriction, and gene expression (French et al. 1990; Badia et al. 1991; Duffy et al. 1996; Dkhissi-Benyahya et al. 2000; Brainard et al. 2001; Lucas et al. 2001; Dijk and Lockley 2002; Hankins and Lucas 2002; Lockley et al. 2003, 2006; Cajochen et al. 2005). Converging evidence derived from classical physiology techniques, such as determination of wavelengths of maximum sensitivity (action spectra), and molecular genetic techniques, such as genetic ablation of rods and cones in rodents, point to the unique characteristics and neuroanatomical basis of the "nonvisual" system (Brainard et al. 2001; Lucas et al. 2001; Thapan et al. 2001; Hankins and Lucas 2002). Its wavelength of maximum sensitivity is shifted to shorter wavelengths (blue light) compared with the classical visual system in both animals and humans. The "nonvisual" system depends on input from both retinal ganglion cells expressing melanopsin (Berson et al. 2002; Hattar et al. 2002; Dacey et al. 2005) and the classical visual photoreceptors (Hattar et al. 2003). Melanopsin is a recently discovered photopigment (Provencio et al. 2000) that is most sensitive to blue light at a wavelength ranging from 420 to 480 nm, depending on the study considered (Melyan et al. 2005; Panda et al. 2005; Qiu et al. 2005). The melanopsin-expressing ganglion cells transmit irradiance signals to hypothalamic nuclei such as the suprachiasmatic nuclei (SCN), as well as to a number of nonhypothalamic structures (e.g., superior colliculi, lateral geniculate nuclei, and medial amygdala), suggesting that the melanopsin-dependent photoreception system modulates many brain functions (Gooley et al. 2003; Hattar et al. 2006). However, its action on cortical function has not been studied extensively.

Although it is often stated that light affects behavior and cognition in humans, few studies have been devoted to study these effects. White light has been shown to improve subjective alertness and performance on simple tasks such as reaction time, digit recall, 2-letter search, and simple problem solving both during night and daytime (Campbell and Dawson 1990; French et al. 1990; Badia et al. 1991; Phipps-Nelson et al. 2003). To date, only 2 neuroimaging studies, using positron emission tomography (Perrin et al. 2004) and functional magnetic resonance imaging (fMRI) (Vandewalle et al. 2006) characterized the neural correlates of the nonvisual effects of white light exposure. Two studies have shown that a blue light–sensitive photoreception system modulates the effect of light on alertness and reaction times (Cajochen et al. 2005; Lockley et al. 2006). These latter studies, however, did not include brain imaging, and the neural correlates of the effects of blue light remain unknown. Furthermore, there is currently no direct evidence that light exposures of wavelengths close to the maximum sensitivity of the melanopsin-dependent photoreception system (blue ~470 nm) or of the classical 3 cone photopic system (green 550 nm) elicit different nonvisual brain responses to a complex cognitive task. In the present fMRI study, we aimed at demonstrating that the spectral quality of light influences the activity in brain areas involved in executive functions, even during daytime, a time at which humans are naturally exposed to abundant light.

## Materials and Methods

### *Subjects*

Participants were healthy, young subjects ($N$ = 18, 10 females; age: 18–29 [median: 23]; body mass index: 18.7–29.7 [median: 22.85]). A semi-structured interview established the absence of medical, traumatic, psychiatric, or sleep disorders. Absence of color blindness was assessed by the 38-plate edition Ishihara's Test for Colour-Blindness (Kanehara Shupman Co., Tokyo, Japan). All participants were nonsmokers and moderate caffeine and alcohol consumers and were not on medication. None had worked on night shifts during the last year or traveled through more than 1 time zone during the last 2 months. Extreme morning and evening types, as assessed by the Horne–Ostberg questionnaire (Horne and Ostberg 1976), were not included. None complained of excessive

daytime sleepiness as assessed by the Epworth Sleepiness Scale (Johns 1991) and of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire (Buysse et al. 1989). All participants had normal scores at the 21-item Beck Anxiety Inventory (Beck et al. 1988) and at the 21-item Beck Depression Inventory II (Steer et al. 1997). They were right handed as indicated by the Edinburgh Inventory (Oldfield 1971). Participants gave their written informed consent and received a financial compensation for their participation. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège.

Volunteers followed a 7-day regular sleep schedule before their first visit and kept the same schedule for 2 more days, until their second visit. Compliance to the schedule was assessed using wrist actigraphy (Actiwatch, Cambridge Neuroscience, UK) and sleep diaries. In order to record 2 volunteers on the same day at approximately the same circadian time, volunteers were requested to follow 1 of 2 sleep schedules differing by 1.5 h (2300–0700 h ± 30 min or 0030–0830 h ± 30 min). Volunteers were requested to refrain from all caffeine and alcohol-containing beverages and intense physical activity for 3 days before participating in the study.

### *Protocol*

Volunteers completed the protocol on 2 separate days (Fig. 1). The experimental paradigm was identical on both days, except for the monochromatic light exposure condition (blue or green), the order of which was counterbalanced. On each day, subjects were first maintained in dim light (<5 lux) for 3 h and then scanned during 3 consecutive sessions that were timed before (session 1; <0.01 lux), during (session 2), and after (sessions 3; <0.01 lux) 1 eye was exposed for 18 min (durations varied slightly, see Supplementary Data) to a blue (470 nm) or a green (550 nm) monochromatic light. The photon densities of both light exposures were identical ($3 \times 10^{13}$ photons/cm$^2$/s) so that blue light stimulation of the melanopsin-dependent photoreception system would be equal to the stimulation of the classical photoreception systems elicited by green light during the other visit. Light exposure occurred approximately 5 h after habitual wake-up time, that is, during the biological day when melatonin secretion is low (Dijk and Lockley 2002). During every session, participants performed an auditory "2-back" working memory task (Braver et al. 2001), which does not explicitly depend on visual input, and is reliably executed by a majority of subjects. Subjective alertness scores, as assessed by the Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg 1990), were collected every 30 min during the 3-h preparatory period and every 20 min while in the scanner. Participants performed the 2-back task during two 3-min flanking sessions placed at the beginning and at the end of the fMRI acquisition period. The first flanking session allowed enough time for physiological events related to recent postural changes (sitting, walking to the fMRI scanner, standing for a few minutes, and then lying down in supine position) to dissipate (Bonnet and Arand 1998). The latter events can influence arousal and might have otherwise contaminated our data. The second flanking session took into account potential participants' expectancies about the end of the experiment, which might change their motivational and arousal state. Participants were unaware of the duration of this last flanking session and were told its duration could vary substantially.

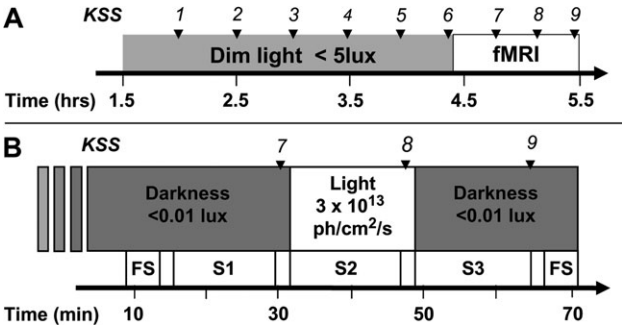


**Figure 1.** Experimental design. (*A*) General time line. Time relative to scheduled wake time (hours). Arrows: subjective sleepiness assessment (KSS 1–9). (*B*) Time line of the fMRI period. S1–S3, 2-back sessions 1–3; FS, flanking sessions. Time in minutes after entering the scanner. Arrows: subjective sleepiness assessment (KSS 7–9).

During the data acquisition period, all subjects interacted with the same investigator who used a standardized set of sentences between every 2-back sessions. This protocol was implemented in order to minimize variation in motivational state due to social interactions (e.g., encouragement by an investigator, which may modify brain responses [cf. Grandjean et al. 2005]). No feedback was given on performance. Volunteers received a small, standardized snack in the middle of the 3-h preparatory period preceding fMRI data acquisition. They were trained on a shortened version of the protocol and habituated to the experimental conditions at least a week before the experiment. Subject had to reach 75% of correct responses on the 2-back task at the end of training to participate in the experiment.

### *The 2-Back Task*

Stimuli consisted of 9 French monosyllabic consonants that were phonologically different so that they could easily be identified. Stimuli were 500 ms long and interstimulus interval was 2500 ms long. For each consonant, volunteers were requested to state whether or not it was identical to the consonant presented 2 stimuli earlier, by pressing a button on a keypad for "yes" and another one for "no." Thirty-four series of 25–30 stimuli were constructed with ~30% positive answers. Interseries interval lasted 10–25 s. Series were presented only once per visit and were randomly assigned to one of the scanning sessions. In both visits, the number of series in each session varied as follow: flanking sessions consisted of 2 series, session 1 of 9 series, session 2 of 10 series, and session 3 of 11 series. Stimuli were produced using COGENT 2000 (http://www.vislab.ucl.ac.uk/Cogent/) implemented in MATLAB (Mathworks Inc., Sherbom, MA) on a 2.8-GHz XEON DELL personal computer (Round Rock, TX) and were transmitted to the subjects using MR CONTROL amplifier and headphones (MR Confon, Magdeburg, Germany). On both visits, the first session was preceded by a short session during which volunteers had to set the volume level to ensure an optimal auditory perception during scanning.

### *Light Exposure*

In a previous fMRI study, we reported that 21 min of white light exposure (>7000 lux) was sufficient to counteract the decrease in alertness and brain activity otherwise observed in continuous darkness (Vandewalle et al. 2006). However, we could not easily separate the changes in responses related to the light-related increase in alertness from the effect of light per se. We specifically designed the present study in order to avoid the confounding effects of variation in alertness and performance. First, we used a monochromatic light stimulus with a photon density about a hundred times lower than in our previous fMRI study. Second, only one eye was exposed. Previous investigations demonstrated additivity of binocular compared with monocular illumination (Brainard et al. 1997). Third, the monochromatic light exposure was limited to 18 min, a short exposure as compared with previous studies investigating the effect of light on behavior (Cajochen et al. 2005; Lockley et al. 2006) and melatonin secretion (Brainard et al. 2001; Thapan et al. 2001; Lockley et al. 2003). Thus, the total number of photons administered in our study is 10–15 times smaller than in behavioral investigations (Cajochen et al. 2005; Lockley et al. 2006) and most endocrine studies (Brainard et al. 2001; Lockley et al. 2003), but not all (Thapan et al. 2001). Using this experimental strategy, we were aiming to characterize the changes in brain responses independent of behavioral changes.

Narrow interference band-pass filters (full width at half maximum [FWHM]: 10 nm; Edmund Optic, York, UK) were used to produce 2 monochromatic illuminations at 470 and 550 nm. The exposed eye and monochromatic light exposure were assigned pseudorandomly in a counterbalanced manner. The light was transmitted by a metal-free optic fiber from a source (PL900, Dolan-Jenner Industries, Boxborough, MA) to a small diffuser placed in front of the subjects' eye. The diffuser was designed for the purpose of this study and ensured a uniform illumination of the eye. Light was administered through a 4 × 5.5 cm frame placed 3–4 cm away from the eye. Irradiance could not be measured directly in the magnet, but the light source was calibrated and irradiance estimated to be $3 \times 10^{13}$ photons/cm$^2$/s (840-C power meter, Newport, Irvine, CA).

The nonilluminated eye of the subject was monitored at all times using an infrared eye-tracking system (ASL, Model 504; Applied Science Group, Bedford, MA). The images of the eye-tracking system were monitored online, video taped, and subsequently examined in order to ensure that all volunteers included in the analyses had their eyes open at all time and were looking toward the light during the illumination.

### *fMRI Data Acquisition*

fMRI time series were acquired using a 3 T MR scanner (Allegra, Siemens, Erlangen, Germany). Multislice T2*-weighted fMRI images were obtained with a gradient echo–planar sequence using axial slice orientation (32 slices; voxel size: 3.4 × 3.4 × 3 $mm^3$; matrix size 64 × 64 × 32; time repetition (TR) = 2130 ms; time echo (TE) = 40 ms; flip angle = 90°). The 4 initial scans were discarded to allow for magnetic saturation effects. There was little variation in the number of scans of the homologous sessions of both visits (first flanking sessions: 95.3 ± 4.2 (mean ± standard deviation); sessions 1: 408.6 ± 8.3; sessions 2: 454.6 ± 7.1; sessions 3: 506.8 ± 7.6; second flanking sessions: 96.6 ± 3.5). Head movements were minimized using a vacuum cushion. A structural T1-weighted 3D MP-RAGE sequence (TR 1960 ms, TE 4.43 ms, time to inversion 1100 ms, field of view 230 × 173 $cm^2$, matrix size 256 × 256 × 176, voxel size: 0.9 × 0.9 × 0.9 mm) was also acquired in all subjects.

### *fMRI Data Analysis*

Functional volumes were analyzed using statistical parametric mapping 2 (SPM2—http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB. They were corrected for head motion, spatially normalized (standard SPM2 parameters) to an echo-planar imaging template conforming to the Montreal Neurological Institute (MNI) space, and spatially smoothed with a Gaussian Kernel of 8-mm FWHM. The analysis of fMRI data, based on a mixed effect model, was conducted in 2 serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated using a general linear model in which the activity evoked by the 2-back series in each session was modeled by boxcar functions, convolved with a canonical hemodynamic response function. As we reported previously (Vandewalle et al. 2006), the dynamics of the light-induced modulations of brain activity in some areas is fast. Such rapid changes do not necessarily give rise to significant changes in activity when averaged over a whole session and consequently, do not appear in between-session contrasts. We therefore added 2 further regressors in our analyses, representing the modulation of brain responses to the 2-back series by linear and quadratic time. We used these regressors to compare the within-session modulation of brain responses by (linear and quadratic) time in the different sessions in order to identify any nonvisual brain response that would build up and dissipate with time after lights were turned on and off, respectively. Movement parameters derived from realignment of the functional volumes were included as covariates of no interest. High-pass filtering was implemented in the matrix design using a cutoff period of 128 s to remove low-frequency drifts from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood algorithm. The effects of interest were then tested by linear contrasts, generating statistical parametric maps (SPM(T)). Because no inference was made at this (fixed effects) level of analysis, summary statistic images were thresholded at $P_{uncorrected} = 0.95$. The summary statistic images resulting from these different contrasts were then further smoothed (6-mm FWHM Gaussian Kernel) and entered in a second-level analysis. This second step accounts for intersubject variance in the main effects of light (random-effect model) and corresponds to a 1-sample *t*-test for brain responses to the 2-back series. Both time modulators were included in a separate parametric within-subject 1-way analysis of variance (ANOVA). For the latter analysis, the error covariance was not assumed independent between regressors and a correction for nonsphericity was used for final inferences (Glaser and Friston 2004). The resulting set of voxel values for each contrast constituted maps of the *t*-statistics (SPM(T)) for the main responses and *F* statistics (SPM(F)) when they were modulated by time, thresholded at $P_{uncorrected} = 0.001$. Statistical inferences were performed after correction for multiple comparisons on small spherical volumes (svc; 10 mm radius) at a threshold of $P_{svc} = 0.05$, around a priori locations of activation in structures of interest, taken from published work on "*n*-back" tasks and executive processing, multimodal binding and from our own work on the effects of white light on brain responses in fMRI. Before performing any svc, peaks reported in Talairach (Talairach and Tournoux 1988) space were transformed to MNI space using Matthew Brett's bilinear transformation (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach; no coordinates were shifted more than 5 mm). Standard stereotactic coordinates of previously published a priori locations, used for spherical svc, are as follows:

Locations involved in working memory and executive functions: Left intraparietal sulcus (IPS) –26 –58 47 mm (Collette, Van der Linden, et al. 2005), –20 –66 46 mm, –20 –66 48 mm (Wager et al. 2004), –12 –71 47 mm; right insula 32.32 22.44 5.53 mm (Cohen et al. 1997) (transformed to MNI space), 40 16 2 mm (Wager et al. 2004); left thalamus –8 –12 –11 mm; left supramarginal gyrus –38 –50 42 mm (Wager and Smith 2003), –40.40 –51.68 45.15 mm (Cohen et al. 1997) (transformed to MNI space); left middle frontal gyrus (MFG) –43 24 27 mm (Braver et al. 2001), –40 22 21 mm (Cohen et al. 1997).

Locations involved in multimodal activation/cross-modal binding: Left thalamus (Bushara et al. 1999) –14 –20 8; right insula 36 24 –4 mm, 38 22 –6 mm (Bushara et al. 2001); left inferior parietal lobule –44 –38 42 mm (Bushara et al. 1999).

Location modulated by white light exposure: Right insula 40 20 8 mm (Vandewalle et al. 2006).

#### *Masking Procedures*

In all analyses, we excluded brain areas that were not recruited by the 2-back task from all the interaction analyses, by masking our results with a map of all regions that showed any positive response to the task (inclusive mask $P_{uncorrected} = 0.9$). In the light condition (blue > green) by session (2 > 1) interaction, we applied an exclusive mask for baseline differences (session 1 green > session 1 blue; $P_{uncorrected} = 0.05$) in order to rule out possible confounds arising from these differences. In the light condition (blue > green) by session (2 > 3) interaction, we also applied an exclusive mask for differences at the end of the visits (session 3 green > session 3 blue; $P_{ted} = 0.05$), which ruled out possible confounds arising from these differences. In order to verify which effect contributed to the light condition (blue > green) by session (2 > 3) interaction, we employed 2 independent masks. We applied a mask ($P_{uncorrected} = 0.05$) including areas for which activity decreased from the second to the third session during the blue light condition. Interaction effect in the regions remaining after the application of this mask would be mostly related to the latter decrease in activity in the blue light condition. A second verification employed another mask ($P_{uncorrected} = 0.05$) excluding areas for which activity increased from the second to the third session of the green light condition. Interaction effect in the regions remaining after the application of this mask would not be mostly related to the latter increase in activity in the green light condition.

#### *Bayesian Inferences and Posterior Probability Maps*

In the random-effect analyses, we aimed at verifying that the absence of significant statistical effects in one contrast in a location of the brain was not merely due to an error of type II (false negative). We computed posterior probability maps (PPMs) enabling conditional or Bayesian inferences about regionally specific effects (Friston and Penny 2003), which provide the posterior distribution of an activation given the data, that is, the probability that the responses are greater than some specific threshold. PPMs and effect size were computed for response to the 2-back series in the light condition (blue > green) by session (3 > 1) interaction to verify the absence of remaining light modulation in the post–light exposure period. We estimated the posterior probabilities for each of the regions we reported in the light condition (blue > green) by session (2 > 1 and 2 > 3) interactions. PPMs were also computed on the second sessions of both visits, in order to check that no activation was present in the occipital cortex during the illumination period.

## Results

A repeated measure ANOVA on accuracy and reaction times with session and light condition (blue vs. green) as within-subject

factors revealed significant effects of session (Supplementary Data). Likewise, a significant effect of repetition was observed on KSS scores. Although light did not significantly affect alertness, it seemed to counteract the increase in subjective sleepiness observed in KSS scores on both days (Fig. 2). However, as intended (see Light Exposure in Materials and Methods), the repeated measure ANOVA on accuracy and reaction times did not reveal any main effect of light condition nor any light condition by session interaction (Fig. 2; Supplementary Data). Likewise, there was no effect of light condition nor any light condition by repetition interaction for KSS scores.

Therefore, when fMRI data were considered, any difference in brain activity between visits could only be attributed to the difference in light conditions. We first aimed at characterizing the wavelength-specific time courses of brain responses from sessions 1 to 3. We therefore computed 2 separate light conditions by session interaction contrasts. The first one compared the differences of brain activity found in both light conditions when comparing the illumination periods (sessions 2) with the baseline sessions (sessions 1; light condition [blue > green] by session [2 > 1] interaction), whereas the second one evaluated the differences of brain activity obtained between light conditions when comparing the illuminations with the postexposure periods (sessions 3; light condition [blue > green] by session [2 > 3] interaction). Both interactions revealed significant differences in the left IPS, left supramarginal gyrus, left MFG, right insula, and left thalamus (Table 1 and Fig. 3; Supplementary Tables S1 and S2). The activity estimates (right panels, Fig. 3) showed that blue light exposure prevented the progressive decline in brain responses observed during green

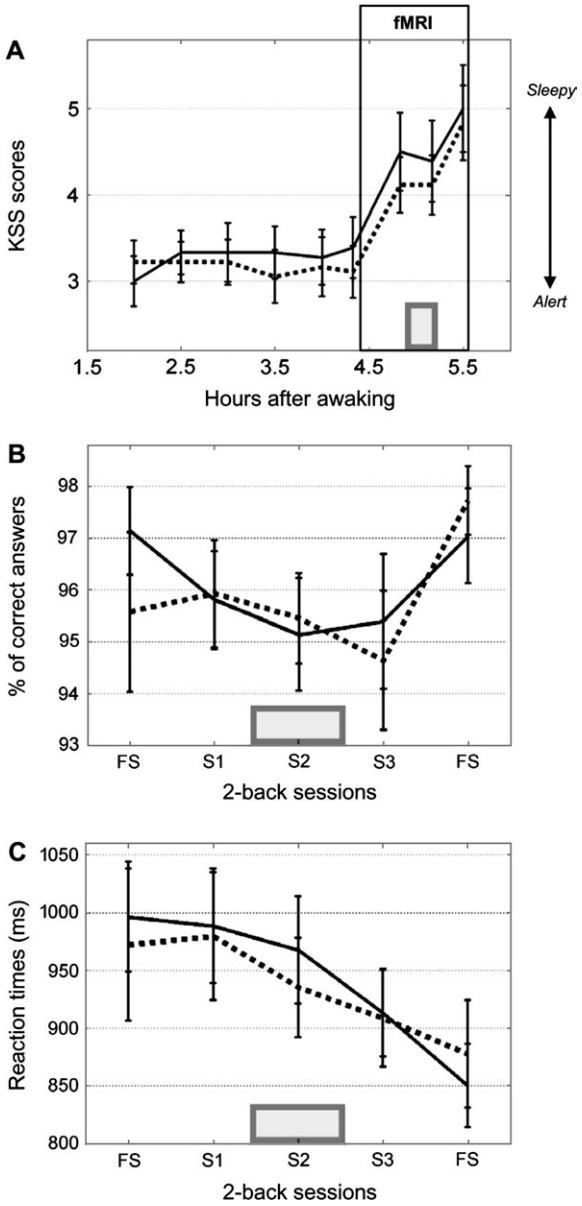


**Figure 2.** Behavioral results. Solid line, blue light condition; dotted line, green light condition; gray rectangle, light exposure period. (*A*) Mean KSS scores (±standard error of the mean [SEM]). Box: fMRI period. Time relative to scheduled wake time (hours). (*B*) Mean accuracy (±SEM). S1–S3: 2-back sessions 1–3. (*C*) Mean reaction times (±SEM). S1–S3: 2-back sessions 1–3. FS, flanking sessions.

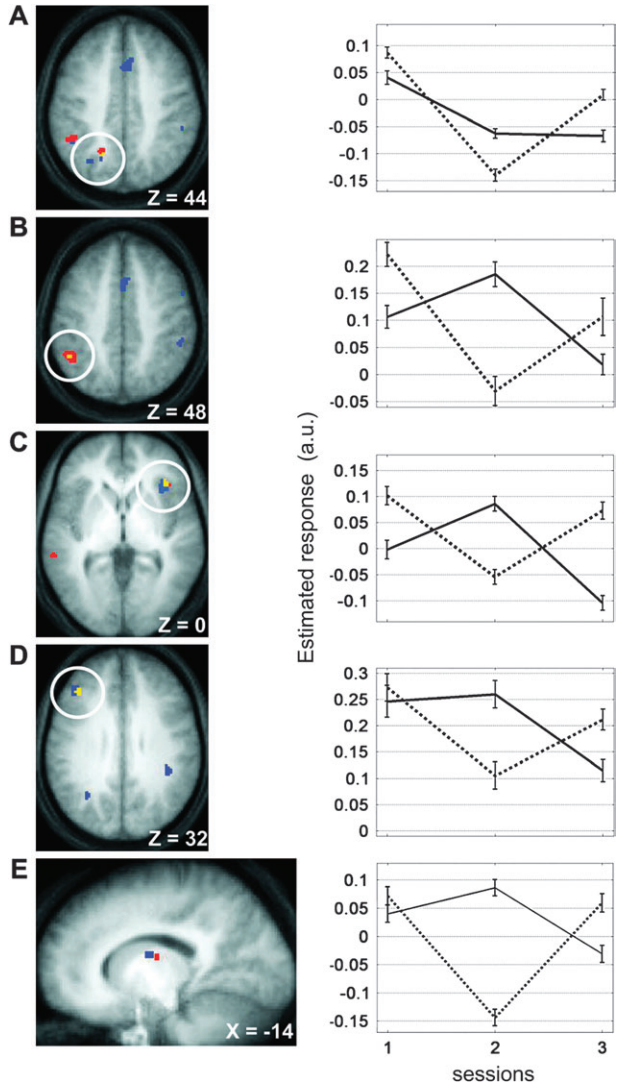


**Figure 3.** Comparison of the brain modulations observed during blue light condition (470 nm) and green light condition (550 nm). (*A*) Left IPS; (*B*) left supramarginal gyrus; (*C*) right insula; (*D*) left MFG; (*E*) left thalamus. Left panels: responses are displayed over the mean structural image of all subjects ($P_{uncorrected} < 0.001$). The light condition (blue > green) by session (2 > 1) interaction is displayed in red. The light condition by session (2 > 3) interaction is displayed in blue. Overlaps are in yellow. Right panels: mean parameter estimates in the first, second, and third sessions (arbitrary units ± standard error of the mean). Solid line, blue light day; dotted line, green light day.

**Table 1**
Comparison of the responses to blue and green light exposure (MNI coordinates)

| Brain regions | Light condition (blue > green) by session (2 > 1) interaction | | | | | Light condition (blue > green) by session (2 > 3) interaction | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *x* | *y* | *z* | *Z* score | *P* value (svc) | *x* | *y* | *z* | *Z* score | *P* value (svc) |
| Left IPS | −18 | −60 | 44 | 4.03 | 0.004 | −34, −20 | −62, −64 | 34, 42 | 4.30, 3.45 | 0.027, 0.023 |
| Left supramarginal gyrus | −46 | −50 | 48 | 3.58 | 0.016 | −44 | −50 | 38 | 3.93 | 0.005 |
| Left thalamus | −14 | −14 | 16 | 3.16 | 0.049 | −10 | −4 | 16 | 4.16 | 0.002 |
| Left MFG | −38 | 32 | 34 | 3.63 | 0.014 | −40 | 32 | 28 | 4.20 | 0.002 |
| Right insula | 40 | 28 | 0 | 3.31 | 0.033 | 38 | 28 | 0 | 3.77 | 0.008 |

light exposure (from first to second sessions). As a rule, blue light exposure increased regional responses, as compared with baseline, except in the left IPS.

Activity estimates also revealed that the responses in these regions decreased from the second to the third session during the blue light condition, whereas they increased from the second to the third session of the green light condition. Further analyses (see Masking Procedures in Materials and Methods) revealed that in the right insula, left supramarginal gyrus, and left MFG, the significant effects were essentially due to the decrease in response during the postexposure period of the blue light condition. In contrast, in the left IPS and thalamus, the effects were largely influenced by the increase in activity after the green light is switched off.

We then assessed whether the differences in the effects of the light conditions persisted after the light exposures. However, no significant difference in brain activity was identified in the contrast comparing the postexposure sessions with the baseline sessions, suggesting that no differential effects of light conditions remained during the postexposure period, as compared with the baseline. Accordingly, probabilities of activation, as inferred by Bayesian statistics (Friston and Penny 2003), were low ( <22%) in all the 5 areas for which we detected an effect of light exposure during the illumination period (see Bayesian Inferences in Materials and Methods).

Importantly, no regions were significantly more deactivated by blue than green light exposure during or after the illumination period, as compared with baseline (Table S3). Likewise, no brain areas were more activated by blue light as compared to green light exposure after as compared to during the illumination.

Collectively, our results speak for specific time-limited enhancement in brain responses during blue, as compared to green, light exposure. We point out that blue light exposure has been reported to induce greater pupillary constriction than green light exposure and is consequently associated with reduced light input to the retina (Cajochen et al. 2005). Although we could not assess pupil size in the present study, it is very likely that, if pupillary constriction differed between light conditions, constriction would have been greater under blue light exposure. Consequently, any superiority of blue light in modulating brain responses is unlikely to be related to the effect on pupil size.

Noteworthy, no difference between light conditions was found in the occipital cortex for any of the comparisons. Bayesian statistic inferences confirmed that the probability of activation never exceeded 2% in the occipital cortex in both light conditions during the illumination period. This finding speaks against the involvement of the classical visual system in the observed effects.

Finally, we did not identify any brain areas where responses changed with time within each session and differently between light conditions (see fMRI Data Analysis in Materials and Methods). This absence of temporal modulation implies that the light-related differences in brain activity reported above appeared almost immediately after lights were switched on and dissipated very quickly after lights were turned off.

## Discussion

The present results demonstrate that brain responses to a complex cognitive task are modulated by light exposure in a wavelength-dependent manner. When compared with a green light exposure of identical photon density, a short exposure to a $3 \times 10^{13}$ photon/cm$^2$/s blue light on a single eye during daytime is sufficient to induce almost immediate changes in brain activity. These changes persist for the duration of the exposure, but cease when light is switched off. These findings cannot be accounted for by any measurable difference in alertness or performance nor by any order or placebo effects (see Supplementary Data). In addition, because the experimental design contrasted 2 narrow-band monochromatic lights, our findings suggest that the melanopsin-dependent photoreception system contributed to modulate these responses.

The light-induced modulation of brain responses was located in structures typically involved in executive functions (Cohen et al. 1997; Cabeza and Nyberg 2000; Collette, Hogge, et al. 2005). The left MFG, supramarginal gyrus, and IPS have been repeatedly implicated in *n*-back tasks. The insula and the thalamus, both in the left and right hemispheres, have been involved in several aspects of working memory (Cabeza and Nyberg 2000). Areas are mostly located in the left hemisphere in keeping with the left lateralization of verbal working memory (Braver et al. 2001; Collette, Hogge, et al. 2005). The thalamus is a key structure modulating arousal, reported in studies exploring the interplay between alertness and cognition (Coull et al. 2004; Foucher et al. 2004). Additionally, the right insula, left parietal cortex, and thalamus are also involved in visuoauditory cross-modal binding (Bushara et al. 1999, 2003; Downar et al. 2000) and would respond during the performance of an auditory task under visual stimulation.

We previously reported that white light exposure induced nonvisual responses outlasting the illumination period (Vandewalle et al. 2006). In contrast, in the present study, the monochromatic light exposures we used elicited immediate changes in brain responses, which did not outlast the exposure and dissipated swiftly. This reveals a new aspect of the dynamics of the nonvisual responses to light, which, except for pupillary constriction (Lucas et al. 2001), are typically assumed to develop over tens of minutes (Brainard et al. 2001; Thapan et al. 2001; Lockley

et al. 2003, 2006; Cajochen et al. 2005). The swift dynamics observed in the present study are probably related to the low dose of light administered. Our design implies that the melanopsin-dependent photoreception system contributed to modulate brain responses to the cognitive task (Brainard et al. 2001; Lucas et al. 2001; Thapan et al. 2001; Hankins and Lucas 2002; Dacey et al. 2005; Melyan et al. 2005; Qiu et al. 2005). The melanopsin-dependent photoreception system is known to transmit irradiance signal to numerous subcortical structures including the SCN, site of the master circadian clock, the ventrolateral preoptic nuclei, involved in sleep regulation, the superior colliculus and the lateral geniculate nucleus of the thalamus, both part of the classical visual system, the intergeniculate leaflet, implicated in circadian photoentrainment, the medial amygdala, involved in reproduction behavior modulation, the olivary pretectal nucleus, implicated in pupillary constriction, the lateral habenual, etc. (Hattar et al. 2006). These structures are connected to many other major physiological systems; it is therefore difficult to designate a unique pathway mediating our effects. Likewise, indirect projections from the SCN to cholinergic, orexin, and aminergic cell groups involved in arousal regulation exist in the forebrain and brainstem (Abrahamson et al. 2001; Aston-Jones 2005; Deurveilher and Semba 2005; Saper et al. 2005) and might be responsible for the increased responses observed in the thalamus. In addition, direct projections of the melanopsin retinal ganglion cells to the lateral geniculate of the thalamus have been reported in primates (Dacey et al. 2005) and might represent the pathway followed by irradiance information to influence thalamic activity, if they are also present in humans. Because performance and alertness did not differ across days in the present study, light-induced cortical and subcortical response changes occurred independently from behavioral modifications. It can also be argued that they are very likely to occur very early in the cascade of events elicited by melanopsin-dependent responses because modulation appeared almost instantaneously. Our previous fMRI studies, which used bright white light exposure in an attentional paradigm, also reported significant effects of light on thalamic and insular activity in the period of darkness following the illumination (Vandewalle et al. 2006). Collectively, these data suggest that the thalamus and the anterior insula are key structures in mediating the effects of light on brain activity related to different cognitive functions during and after the exposure.

Although our design used a wavelength close to the peak sensitivity of the melanopsin-dependent photoreception system (470 nm) and the data are consistent with an involvement of the melanopsin system, we are not in a position to assess the specific contribution of each photoreceptor. Short, medium, and long cones were reported to input to the melanopsin pathway (Dacey et al. 2005) and all classical photoreceptors were shown to be necessary for a complete nonvisual response to light in rodents (Hattar et al. 2003). A recent human study also reported a novel type of cones expressing exclusively melanopsin (Dkhissi-Benyahya et al. 2006). Lights of various spectral compositions and dose–response protocols should specifically address this question.

Our protocol also revealed intriguing brain deactivations during green light exposure followed by a subsequent increase in activity. Current knowledge about the effects of green light exposures only allows very speculative interpretations of these findings. On the one hand, the effects of green light are reminiscent of those we observed during continuous darkness in a previous experiment. We reported that the repetition of an auditory oddball task in continuous darkness induced a temporary deactivation in several brain areas that were counteracted by bright white light (Vandewalle et al. 2006). On the other hand, although, to our knowledge, no report supports this hypothesis, it is tantalizing to suggest that green light exposure would have a genuine effect on brain responses, different from blue light exposure. In such perspective, the deactivations we observe would be the result of a specific process induced by the 550-nm light exposure. Future experiments should be specifically designed to separately assess the effects of blue and green light exposures.

The vast majority of studies on the effects of light exposure mediated by the melanopsin-dependent photoreception system took place at night and/or after extended wakefulness episodes (Campbell and Dawson 1990; Badia et al. 1991; Brainard et al. 2001; Lockley et al. 2003; Cajochen et al. 2005). The few studies carried out during daytime imposed partial sleep deprivation to increase sleepiness and thereby maximize the sensitivity of their design (Phipps-Nelson et al. 2003; Ruger et al. 2005). As light exposure occurred during the day in well-rested subjects, our data have a broader impact. The spectral composition of common artificial light is geared toward the classical photopic system and does not consider the contribution of light to nonvisual functions. Future research should establish the optimal light regime (wavelength, duration, photon density, and light history) required to efficiently enhance human cognition during daytime, especially for demanding tasks (e.g., education) or professions (e.g., military personnel, healthcare professional, police, spaceship crew, and plane crews).

## Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

## Notes

The authors would like to thank M. Boly, F. Collette, T. Dang-Vu, M. Desseilles, F. Peters, and G. Rauchs for their collaboration to this study and helpful comments on the manuscript. The authors also thank P.-Y. Berken, C. Degueldre, and V. Moreau for their technical assistance. The authors are also very grateful to A. Luxen for his continuous support. This study was supported by the Fonds National de la Recherche Scienctifique (Belgium; FNRS), the Fondation Médical Reine Elisabeth (Belgium), the University of Liège, the PAI/IAP P5/04, the Wellcome Trust-GR069714MA (DJD), the Fonds de la Recherche en Santé du Québec, and the Instituts de recherche en santé du Canada (JC). DJD is a consultant to Philips. GV, EB, AD, VS, and PM are supported by the FNRS. *Conflict of Interest*: None declared.

Address correspondence to Pierre Maquet, Centre de Recherches du Cyclotron, Université de Liège, B30, Sart Tilman, B-4000 Liège, Belgium. Email: pmaquet@ulg.ac.be.

## References

Abrahamson EE, Leak RK, Moore RY. 2001. The suprachiasmatic nucleus projects to posterior hypothalamic arousal systems. Neuroreport. 12:435–440.

Akerstedt T, Gillberg M. 1990. Subjective and objective sleepiness in the active individual. Int J Neurosci. 52:29–37.

Aston-Jones G. 2005. Brain structures and receptors involved in alertness. Sleep Med. 6(Suppl 1):S3–S7.

Badia P, Myers B, Boecker M, Culpepper J, Harsh JR. 1991. Bright light effects on body temperature, alertness, EEG and behavior. Physiol Behav. 50:583–588.

Beck AT, Epstein N, Brown G, Steer RA. 1988. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 56:893–897.
Berson DM, Dunn FA, Takao M. 2002. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 295:1070–1073.
Bonnet MH, Arand DL. 1998. Sleepiness as measured by modified multiple sleep latency testing varies as a function of preceding activity. Sleep. 21:477–483.
Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD. 2001. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci. 21:6405–6412.
Brainard GC, Rollag MD, Hanifin JP. 1997. Photic regulation of melatonin in humans: ocular and neural signal transduction. J Biol Rhythms. 12:537–546.
Braver TS, Barch DM, Kelley WM, Buckner RL, Cohen NJ, Miezin FM, Snyder AZ, Ollinger JM, Akbudak E, Conturo TE, et al. 2001. Direct comparison of prefrontal cortex regions engaged by working and long-term memory tasks. Neuroimage. 14:48–59.
Bushara KO, Grafman J, Hallett M. 2001. Neural correlates of auditory-visual stimulus onset asynchrony detection. J Neurosci. 21:300–304.
Bushara KO, Hanakawa T, Immisch I, Toma K, Kansaku K, Hallett M. 2003. Neural correlates of cross-modal binding. Nat Neurosci. 6:190–195.
Bushara KO, Weeks RA, Ishii K, Catalan MJ, Tian B, Rauschecker JP, Hallett M. 1999. Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans. Nat Neurosci. 2:759–766.
Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28:193–213.
Cabeza R, Nyberg L. 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci. 12:1–47.
Cajochen C, Munch M, Kobialka S, Krauchi K, Steiner R, Oelhafen P, Orgul S, Wirz-Justice A. 2005. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab. 90:1311–1316.
Campbell SS, Dawson D. 1990. Enhancement of nighttime alertness and performance with bright ambient light. Physiol Behav. 48:317–320.
Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. 1997. Temporal dynamics of brain activation during a working memory task. Nature. 386:604–608.
Collette F, Hogge M, Salmon E, Van Der Linden M. 2006. Exploration of the neural substrates of executive functioning by functional neuroimaging. Neuroscience. 139(1):209–221.
Collette F, Van der Linden M, Laureys S, Delfiore G, Degueldre C, Luxen A, Salmon E. 2005. Exploring the unity and diversity of the neural substrates of executive functioning. Hum Brain Mapp. 25:409–423.
Coull JT, Jones ME, Egan TD, Frith CD, Maze M. 2004. Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. Neuroimage. 22:315–322.
Dacey DM, Liao HW, Peterson BB, Robinson FR, Smith VC, Pokorny J, Yau KW, Gamlin PD. 2005. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature. 433:749–754.
Deurveilher S, Semba K. 2005. Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. Neuroscience. 130:165–183.
Dijk DJ, Lockley SW. 2002. Integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol. 92:852–862.
Dkhissi-Benyahya O, Rieux C, Hut RA, Cooper HM. 2006. Immunohistochemical evidence of a melanopsin cone in human retina. Investig Ophthalmol Vis Sci. 47:1636–1641.
Dkhissi-Benyahya O, Sicard B, Cooper HM. 2000. Effects of irradiance and stimulus duration on early gene expression (Fos) in the suprachiasmatic nucleus: temporal summation and reciprocity. J Neurosci. 20:7790–7797.
Downar J, Crawley AP, Mikulis DJ, Davis KD. 2000. A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci. 3:277–283.
Duffy JF, Kronauer RE, Czeisler CA. 1996. Phase-shifting human circadian rhythms: influence of sleep timing, social contact and light exposure. J Physiol. 495(Pt 1):289–297.
Foucher JR, Otzenberger H, Gounot D. 2004. Where arousal meets attention: a simultaneous fMRI and EEG recording study. Neuroimage. 22:688–697.
French J, Hannon P, Brainard GC. 1990. Effects of bright illuminance on body temperature and human performance. Annu Rev Chronopharmacol. 7:37–40.
Friston KJ, Penny W. 2003. Posterior probability maps and SPMs. Neuroimage. 19:1240–1249.
Glaser DE, Friston KJ. 2004. Variance components. In: Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Price CJ, Zeki S, Ashburner J, Penny W, editors. Human brain function. San Diego (CA): Academic Press. p. 781–791.
Gooley JJ, Lu J, Fischer D, Saper CB. 2003. A broad role for melanopsin in nonvisual photoreception. J Neurosci. 23:7093–7106.
Grandjean D, Sander D, Pourtois G, Schwartz S, Seghier ML, Scherer KR, Vuilleumier P. 2005. The voices of wrath: brain responses to angry prosody in meaningless speech. Nat Neurosci. 8:145–146.
Hankins MW, Lucas RJ. 2002. The primary visual pathway in humans is regulated according to long-term light exposure through the action of a nonclassical photopigment. Curr Biol. 12:191–198.
Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM. 2006. Central projections of melanopsin-expressing retinal ganglion cells in the mouse. J Comp Neurol. 497:326–349.
Hattar S, Liao HW, Takao M, Berson DM, Yau KW. 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science. 295:1065–1070.
Hattar S, Lucas RJ, Mrosovsky N, Thompson S, Douglas RH, Hankins MW, Lem J, Biel M, Hofmann F, Foster RG, et al. 2003. Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. Nature. 424:76–81.
Horne JA, Ostberg O. 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 4:97–110.
Johns MW. 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 14:540–545.
Lockley SW, Brainard GC, Czeisler CA. 2003. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab. 88:4502–4505.
Lockley SW, Evans EE, Scheer FAJL, Brainard GC, Czeisler CA, Aeschbach D. 2006. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 29:161–168.
Lucas RJ, Douglas RH, Foster RG. 2001. Characterization of an ocular photopigment capable of driving pupillary constriction in mice. Nat Neurosci. 4:621–626.
Melyan Z, Tarttelin EE, Bellingham J, Lucas RJ, Hankins MW. 2005. Addition of human melanopsin renders mammalian cells photoresponsive. Nature. 433:741–745.
Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 9:97–113.
Panda S, Nayak SK, Campo B, Walker JR, Hogenesch JB, Jegla T. 2005. Illumination of the melanopsin signaling pathway. Science. 307:600–604.
Perrin F, Peigneux P, Fuchs S, Verhaeghe S, Laureys S, Middleton B, Degueldre C, Del Fiore G, Vandewalle G, Balteau E, et al. 2004. Nonvisual responses to light exposure in the human brain during the circadian night. Curr Biol 14:1842–1846.
Phipps-Nelson J, Redman JR, Dijk DJ, Rajaratnam SMW. 2003. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. Sleep. 26:695–700.
Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD. 2000. A novel human opsin in the inner retina. J Neurosci. 20:600–605.
Qiu X, Kumbalasiri T, Carlson SM, Wong KY, Krishna V, Provencio I, Berson DM. 2005. Induction of photosensitivity by heterologous expression of melanopsin. Nature. 433:745–749.

Ruger M, Gordijn MC, Beersma DG, de Vries B, Daan S. 2005. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. Am J Physiol Regul Integr Comp Physiol.

Saper CB, Lu J, Chou TC, Gooley J. 2005. The hypothalamic integrator for circadian rhythms. Trends Neurosci. 28:152–157.

Steer RA, Ball R, Ranieri WF, Beck AT. 1997. Further evidence for the construct validity of the Beck depression Inventory-II with psychiatric outpatients. Psychol Rep. 80:443–446.

Talairach J, Tournoux P. 1988. Co-planar steriotaxic atlas of the human brain. New-York: Thieme.

Thapan K, Arendt J, Skene DJ. 2001. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. J Physiol. 535:261–267.

Vandewalle G, Balteau E, Phillips C, Degueldre C, Moreau V, Sterpenich V, Albouy G, Darsaud A, Desseilles M, Dang-Vu TT, et al. 2006. Daytime light exposure dynamically enhances brain responses. Curr Biol. 16:1616–1621.

Wager TD, Jonides J, Reading S. 2004. Neuroimaging studies of shifting attention: a meta-analysis. Neuroimage. 22:1679–1693.

Wager TD, Smith EE. 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 3:255–274.