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Decreased sensitivity to phase-delaying effects of moderate intensity light in older subjects

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Abstract

Aging is associated with a change in the relationship between the timing of sleep and circadian rhythms, such that the rhythms occur later with respect to sleep than in younger adults. To investigate whether a difference in the phase-delaying response to evening light contributes to this, we conducted a 9-day inpatient study in 10 healthy older (≥65 y.o.) subjects. We assessed circadian phase in a constant routine, exposed each subject to a 6.5 h broad-spectrum light stimulus beginning in the early biological night, and reassessed circadian phase. The stimuli spanned a range from very dim (∼2 lx) to very bright (∼8000 lx) indoor light. We found a significant dose–response relationship between illuminance and the phase shift of the melatonin rhythm, with evidence that sensitivity, but not the maximal response to light, differed from that of younger adults. These findings suggest an age-related reduction in the phase-delaying response to moderate light levels. However, our findings alone do not explain the altered phase relationship between sleep and circadian rhythms associated with aging.

Keywords: Biological rhythm; Circadian; Aging; Melatonin; Chronobiology; Light; Phase shift

1. Introduction

Healthy aging is associated with changes in sleep quality, duration, and timing. These changes include less of the deeper sleep stages (stages 3 and 4, slow wave sleep), an increase in the number of awakenings during the night, and earlier sleep–wake times. These age-related changes in sleep occur even in the absence of clinically-significant sleep disorders such as sleep disordered breathing or periodic limb movement disorder.

The circadian timing system is one of the two major regulatory processes influencing sleep [20,22,67], the other being the homeostatic pressure for sleep. It is a major determinant of sleep timing, allows for consolidation of sleep towards the end of the sleep episode, and influences the distribution of sleep stages within a sleep episode. Because of these influences on sleep, age-related changes in the circadian timing system have been hypothesized to contribute to the observed age-related changes in sleep.

The circadian system in humans has an average period (cycle length) that is longer than 24 h [15,18,34,61], and is entrained (synchronized) to the 24 h day by regular exposure to light and darkness [60]. Light has a phase-dependent effect on the circadian system [21], with light exposure during the late subjective day/early subjective night causing phase delay shifts (to a later hour), light during the late subjective night/early subjective day causing phase advance shifts (to an earlier hour), and light exposure during the subjective daytime causing very small phase shifts [35,39,47]. The effects of light on the circadian system are determined not only by the timing of light exposure, but by other factors including the intensity [64], wavelength [7,45,56], duration [49,50] and prior light exposure history [19,32,54]. We and others have reported previously that the relative timing between the phase

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of circadian rhythms and the timing of the nocturnal sleep episode is significantly different between healthy older and young adults [26,27,44], and we have found that this change in phase relationship does not appear to be related to an age-related difference in the length or lability of the endogenous circadian period [18]. As light exposure is required to maintain entrainment of the non-24 h circadian clock to the 24 h day, and the relative phase alignment of the internal clock to the external day is directly dependent upon the qualities of the light, age-related changes in light sensitivity could contribute to the observed age-related differences in the phase relationship between sleep and the circadian timing system.

There is evidence from animal studies that there is a reduction in light sensitivity of the circadian system with advancing age, including smaller phase shifts in response to light [4,66] (see [59] for review), a smaller range of entrainment [48], greater light levels necessary for stable entrainment [43], and changes in the rate of re-entrainment [11,62]. These reductions at the whole animal level may be due to observed age-related changes in the response to light at the cellular level in the suprachiasmatic nucleus (SCN, the locus of the central circadian pacemaker in mammals), including a higher threshold for cellular responses [66] and/or decreased response to light [4,42,55]. There is also evidence that age-related structural changes in the circadian and/or visual systems may contribute to a reduction in light sensitivity, including reduced light transmission through the eye [16,65] (especially of shorter wavelengths [8]), and a reduction in the number of circadian photoreceptors [52].

A change in the photic sensitivity of the human circadian timing system might manifest as a change in sleep patterns. Some reports suggest that older individuals living in their home environments receive lower levels of light exposure and fewer minutes of bright light exposure per day than do young adults [14,28,51], although not all studies agree on this [37]. Institutionalized elderly have been reported to receive even less bright light than healthy elders [53], and there is also an association between daytime light exposure and nighttime sleep quality and consolidation in both institutionalized and healthy older people [36,53,57] with exposure to greater amounts of daytime light associated with better nighttime sleep quality. A recent study comparing light exposure between young and middle-aged subjects found that while the daily exposure to different levels of light did not differ with age, the pattern of light exposure across the day was different [38]. Timed artificial light exposure has been shown to improve sleep maintenance insomnia in community-dwelling older people [13], and increasing the duration and strength of daytime lighting has been reported to be associated with greater nighttime sleep consolidation and improved sleep efficiency in institutionalized elders [2,29,58].

Together, these reports suggest that reduced light exposure levels and/or a decreased sensitivity to light with aging might contribute to age-related increases in sleep disruption and the age-related alteration in the phase relationship between sleep timing and the timing of the biological clock that have been reported previously. The current study was designed to determine whether the sensitivity or capacity of the human circadian system to respond to a single, phase-delaying, broad-spectrum white light pulse was reduced with age.

2. Methods

2.1. Subjects

Subjects were recruited for the study from newspaper advertisements directed to people age 65 and older. Subjects were not taking medications and had no acute or chronic medical problems at the time of study. Subjects were in good health as determined by medical screening (serum chemistry, complete blood count, urinalysis, chest radiograph, physical examination), ophthalmologic screening (including ruling out color-blindness, glaucoma, and a history of eye trauma, as well as an examination of the lens using the LOCSIII classification system [17] to ensure significant cataracts were not present), were in good psychological health (as determined by the Geriatric Depression Scale, Mattis Dementia Rating Scale, Folstein Mini-Mental State Exam, and by clinical interview), and were free from clinically significant sleep disorders (as determined by an all-night polysomnographic study). Each gave written informed consent prior to study; the study was reviewed and approved by the Partners HealthCare Human Subjects Committee and were conducted in accordance with the principles outlined in the Declaration of Helsinki.

A total of 14 subjects began the inpatient portion of the study. Two withdrew consent prior to the first circadian phase estimation procedure and two were disempaneled by the investigators prior to the first circadian phase estimation procedure (one for borderline hypertension, the other developed an upper respiratory infection on the second baseline day in the laboratory). The remaining 10 subjects (two women, eight men; age 68.3 ± 3.7 years) completed the study between late 1999 and early 2003.

2.2. Study protocol

The 9-day inpatient study began with three baseline days, with 8 h of nocturnal sleep and 16 h wake scheduled at each subject's habitual times as determined from a diary they kept during the week prior to entering the lab. Upon waking after the third baseline night, subjects began a 26.7 h constant routine procedure to assess their initial circadian phase (see description below and Fig. 1). Following an 8 h recovery sleep, the subjects woke in the late afternoon to a 16 h waking episode during which the experimental light exposure was presented (see below). After the light exposure day, the subjects woke to a 52 h constant routine procedure to reassess their circadian phase. Following an 11.3 h recovery sleep episode, the subjects were discharged home.

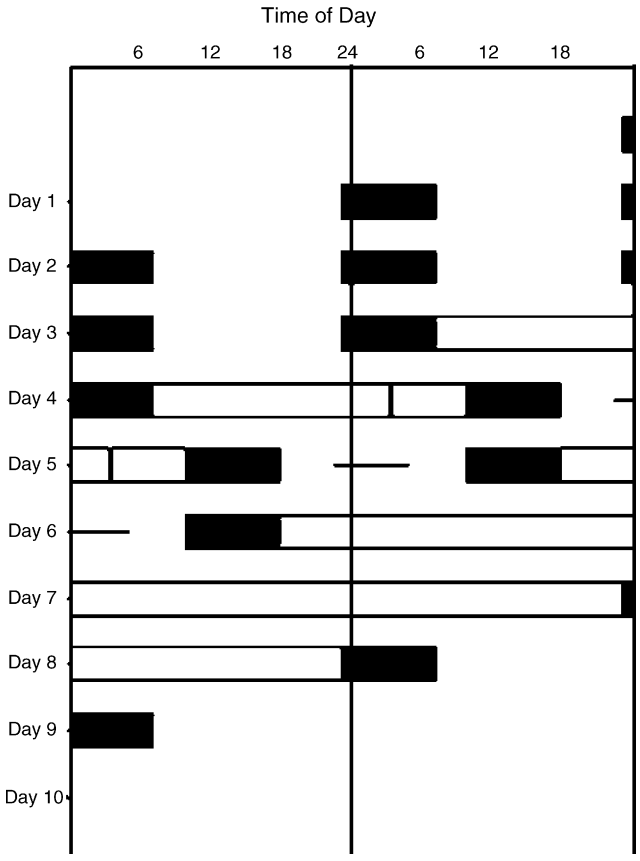

Fig. 1. Double raster plot of study protocol. Time of day is presented on the horizontal axis, with each day of the experiment shown both to the right of, and beneath, the previous day. Scheduled sleep episodes are shown in the black boxes, constant routine (CR) circadian phase estimation procedures are shown in the open bars on days 4–5 (CR1) and days 6–8 (CR2), the predicted timing of the melatonin phase (MELmax) is shown with the vertical bar on day 5, and the 6.5 h experimental light exposure session is shown with the horizontal line on day 5–6. The timing of each subject's protocol was adjusted to his/her own habitual sleep–wake times during the week prior to study.

2.3. Circadian phase assessment

Circadian phase was assessed using core body temperature and melatonin collected throughout the two constant routine (CR) procedures. The constant routine is a protocol designed to assess endogenous circadian phase by eliminating or distributing across the 24 h day periodic changes in behavior and the environment that can obscure the underlying contribution from the circadian pacemaker on the data being recorded [25,46]. Throughout the CR, the subjects were restricted to semi-recumbent bed rest in constant dim light (see below), were required to remain awake, and were given hourly snacks designed to spread their caloric and fluid intake evenly across the 24 h day. A technician remained in the room with the subject throughout the CR to converse with them and ensure they remained awake.

Throughout each CR, core body temperature was collected each minute via a rectal thermistor, blood was collected every 30 min via an indwelling intravenous catheter, and saliva was collected hourly. Blood samples were placed into tubes containing EDTA and placed on ice for up to an hour before being centrifuged and the resulting plasma was frozen until analysis. Saliva samples were placed on ice for up to an hour before being frozen. Plasma samples were assayed for melatonin using a radioimmunoassay (assay sensitivity 0.7 pg/mL; intra-assay coefficient of variation 12.1% at 16.5 pg/mL, 5.7% at 68.7 pg/mL; inter-assay coefficient of variation 13.2% at 17.3 pg/mL, 8.4% at 69 pg/mL; Pharmasan Labs, Osceola, WI). In one subject from whom we were unable to obtain blood samples, saliva samples were assayed for melatonin using the same radioimmunoassay.

2.4. Light conditions and experimental light exposure

All lighting was provided by ceiling-mounted fluorescent lamps (T8 or T12 lamps with CCT of 4100K, Philips Lighting Eindhoven, The Netherlands; see Fig. 2) transmitted through ultraviolet (UV)-shielding ceiling filters (Lexan, GE Plastics, Pittsfield, MA). All lighting was controlled by the experimenters at all times and subjects had no access to any other lighting. During the first two complete baseline days, the ambient lighting was approximately 0.23 W/m^2 (∼89 lx) at 137 cm from the floor in the horizontal angle and had a maximum of 0.48 W/m^2 (150 lx) at 187 cm from the floor in the horizontal angle anywhere in the room. Throughout the two constant routine circadian phase assessment procedures, the ambient lighting was reduced to approximately 0.0087 W/m^2 (∼3.3 lx) at 137 cm from the floor in the horizontal angle and had a maximum of 0.048 W/m^2 (15 lx) at 187 cm from the floor in the vertical angle anywhere in the room. Ambient lighting on the experimental light exposure day was further reduced to approximately 0.0048 W/m^2 (∼1.8 lx) at 137 cm from the floor in the horizontal angle and had a maximum of 5 lx at 187 cm from the floor in the vertical angle anywhere in the room. During scheduled sleep episodes, all lights were switched off.

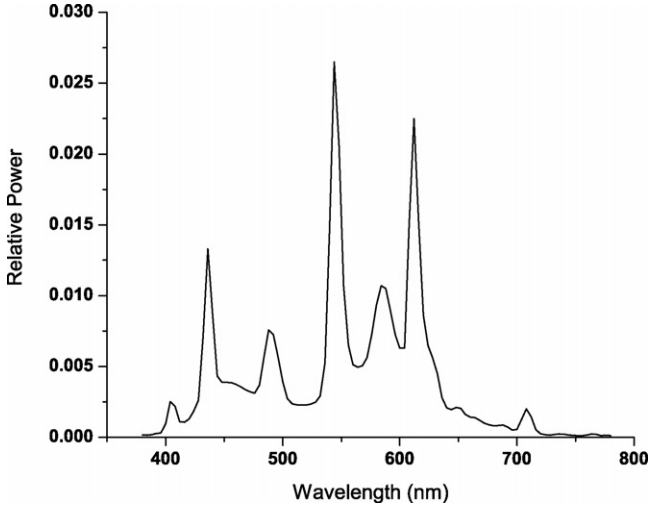

Fig. 2. Spectral distribution of the fluorescent lamps used in the studies.

The 6.5 h experimental light exposure was timed such that it was centered in the middle of the waking episode, and occurred during the early biological nighttime (beginning 30 min before habitual bedtime and continuing until 2 h before habitual wake time). This resulted in the light exposure day being scheduled at an inverted time relative to the subject's usual schedule (see Fig. 1). Approximately 30 min before the start of the experimental light exposure, the subject was seated in a chair in a fixed position within the study room where they remained until the 6.5 h light exposure was completed. Throughout the 6.5 h light exposure, the subject wore clear, UV-excluding glasses (UVEX Ultraspec 2000, UVEX Safety, Smithfield, RI). In alternating 6 min segments throughout the light exposure session, the subject was instructed to gaze at a target on the wall, which had been calibrated prior to the study to achieve the experimental light level. At other times, the subject was free to direct their gaze around the room, except during brief intervals (<1 min) every 30 min, when they looked at a computer screen to rate their alertness on a nine-point scale. A technician was present in the room for the duration of the light exposure session to ensure the subject remained seated with their eyes open and gazed at the target during the alternating 6 min segments, and to record the actual light level with a research photometer (IL1400 radiometer/powermeter with an SEL-033/F/W detector, International Light Inc., Peabody, MA). Throughout each experimental light exposure day, blood or saliva was collected and later assayed for melatonin as described above in order to assess the acute suppressive effects of the light on melatonin.

A total of 10 target experimental light levels were chosen to span the range from 5 to 8000 lx (see Table 1). Subjects were assigned at random to an experimental light level on the day of their admission to the laboratory; in cases where a study was not completed the next subject admitted to the study was assigned to that randomized light level.

2.5. Data analysis

The subject's pre-study bedtime and wake time were determined by averaging the times recorded in the sleep diary from the seven nights prior to entering the laboratory.

Core body temperature phase was assessed by the maximum likelihood fit of a two-harmonic regression model with first-order autoregressive noise [9,10], and melatonin phase was assessed by the maximum likelihood fit of a three-harmonic regression model. The first 5 h and the final 30 min of data from the CR were excluded from analysis due to the potential masking effects of waking and changing posture at the beginning and end of the CR. Core body temperature phase was defined as the minimum of the fitted waveform (CBTmin) and melatonin phase was defined as the maximum of the fitted waveform (MELmax). Phase shift was defined as CR2 phase − CR1 phase (see Fig. 3, lower panel).

Melatonin suppression was calculated by determining the area under the curve (AUC) during the 6.5 h experimental light exposure (see Fig. 3, middle panel) and comparing it with the AUC from the same clock hours on the previous night (during CR1). Suppression was calculated as $(\mathrm{AUC}_{\mathrm{CR1}} - \mathrm{AUC}_{\mathrm{light\ exposure}})/\mathrm{AUC}_{\mathrm{CR1}}$.

Dose–response analysis was done by fitting the data with a four-parameter logistic model: $y = [(a - c)/(1 + (x/b)^d)] + c$ [64], a model derived from the Michaelis-Menton equation. In this model, a is the estimated response of the system to an illuminance of 0 lx, b is the illuminance at which 50% of the estimated maximum response occurs, c is the asymptotic maximum estimated response of the system, and d is a factor related to the steepness of the rise of the linear portion of the curve. Goodness-of-fit is estimated by the adjusted R^2, which takes into account the number of parameters used to fit the data. The R-term is also given as a familiar comparison.

The actual experimental light level to which each subject was exposed was estimated by averaging the light readings taken after each of the 33 fixed gaze episodes during the 6.5 h light exposure session. All analyses and figures are presented with respect to these averaged readings, rather than the target levels. All data are presented as average ± S.E.M., except for model parameters, which are presented as average ± S.D.

3. Results

The average bed- and wake-times of the subjects were 22:53 ± 0:15 and 06:55 ± 0:15, respectively. Initial mela-

Table 1
Individual subject data

Subject	Age	Sex	Habitual bed time	Habitual wake time	Initial MELmax	Initial CBTmin	Illuminance (lx)	MELmax shift (h)	CBTmin shift (h)	Melatonin suppression (%)
2021	65	M	23:32	7:32	2:33	3:36	1.35	−0.56	−0.63	−3.4
1993	67	F	22:32	6:31	2:13	4:56	22.8	−0.29	0.66	49.8
19F6	66	M	22:36	6:36	4:48	7:35	65.6	−1.02	0	17.4
2215	70	M	23:01	7:04	3:26	5:31	122	−0.68	−0.63	0
22AA	65	M	21:27	5:32	3:42	6:02	207	−1.68	−1.79	56.4
22L1	69	M	23:05	7:10	2:58	7:43	319	−1.7	−0.3	78.6
2002	76	M	23:30	7:25	3:40	7:39	1570	−2.97	−1.6	61.1
19G7	65	M	23:14	7:16	3:21	6:03	3527	−2.32	−2.03	78.3
2033	67	M	23:51	8:06	4:06	–	6464	−2.71	–	57.1
2001	73	F	21:59	5:59	0:05	1:56	7960	−3.22	−1.84	50.9

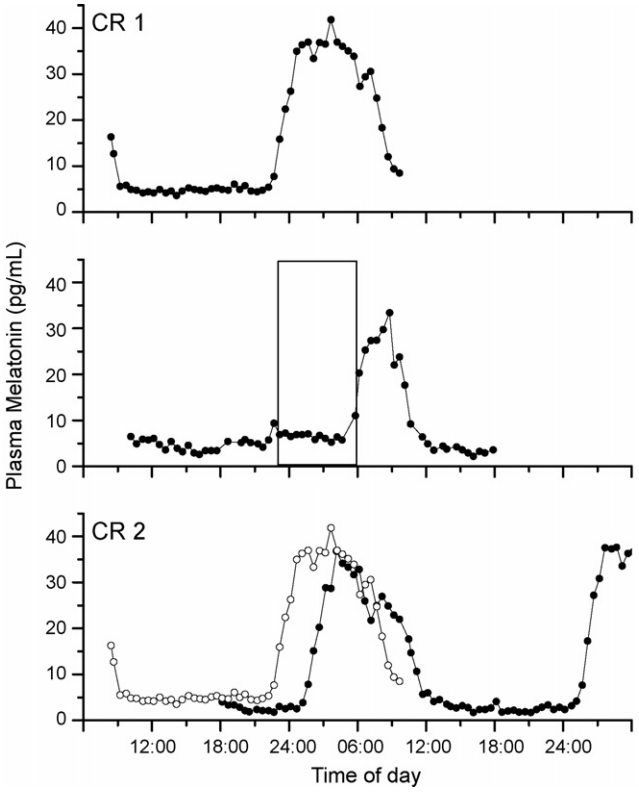

Fig. 3. Plasma melatonin data from subject 19G7, a 65-year-old man who was exposed to a 3527 lx light stimulus. Upper panel: plasma melatonin data from the initial circadian phase estimation procedure (CR1); middle panel: plasma melatonin data from the intervention day, with the 6.5 h experimental light exposure indicated by the open box; lower panel: plasma melatonin data from the final circadian phase estimation procedure (CR2) shown in the solid symbols, with data from CR1 replotted from above in the open symbols. During CR1, the fitted peak of the melatonin secretion (MELmax) occurred at 03:45, 3.5 h before habitual wake time. During CR2 MELmax occurred at 06:30, a 3.5 h phase delay. Melatonin was suppressed by 78% during the 6.5 h 3527 lx light stimulus.

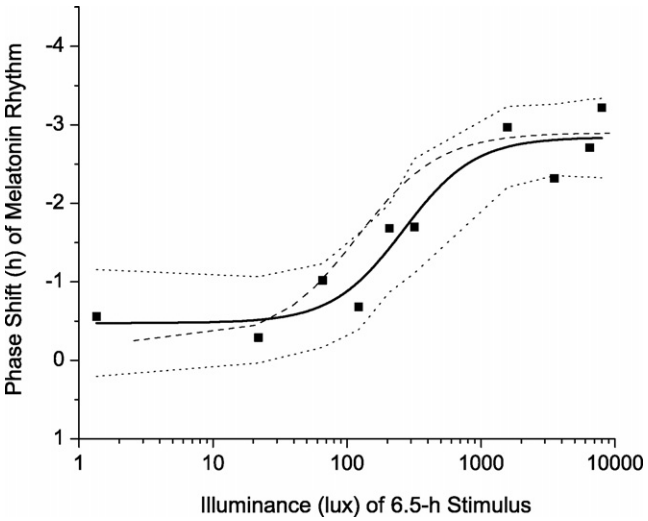

Fig. 4. Phase shift of fitted plasma melatonin peak (MELmax) vs. illuminance of experimental light stimulus. Data from each of the 10 subjects are plotted individually and shown with square symbols. Solid line represents the four-parameter logistic model fit to the data, with the 95% confidence interval of the model shown in the dotted lines. For comparison, the four-parameter logistic model fit to the data from our previous study in younger adults [64] is shown in the dashed line.

tonin phase (MELmax) occurred at 03:05 ± 0:24, an average of 3.83 ± 0.4 h before habitual wake time, while initial core temperature phase occurred at 05:40 ± 0:39 ($n = 9$), an average of 1.12 ± 0.63 h before habitual wake time.

The 6.5 h light exposure session following CR1 was scheduled to begin 0.5 h before the subjects' usual bedtimes (see Fig. 1) so as to be centered 3.5 h before the predicted CBTmin, at the same relative circadian phase as in our study of younger adults [64]. Because of the variability between bedtime, CBTmin, and MELmax between individuals, this resulted in the light exposure session beginning 4.67 ± 0.39 h before MELmax (range 2.6–6.7 h). Actual light exposure levels were within 5% of target levels for all but the two lowest target levels (5 and 25 lx targets), in which cases lower than targeted levels were achieved (1.35 and 21.8 lx, respectively).

Core body temperature phase delay shifts in response to the light exposure ranged from +40 to −122 min, with the size of the shift having a dose–response relationship with the illuminance of the experimental light exposure (four-parameter log model, $R = -0.80$, adjusted $R^2 = 0.27$, $p < 0.01$). Melatonin phase delay shifts in response to the experimental light exposure ranged from −17 to −193 min, with the size of the phase delay shift significantly related to the illuminance of the 6.5 h stimulus (four-parameter log model, $R = -0.96$, adjusted $R^2 = 0.86$, $p < 0.01$; see Fig. 4). The circadian rhythms of core body temperature and plasma melatonin shifted in parallel in response to the light exposure (Pearson correlation, $r = 0.79$, $p < 0.02$; see Table 1).

Melatonin suppression during the 6.5 h light exposure ranged from 0 to 79% (see Table 1). While the lowest intensity of light (1.35 lx) had little effect on melatonin and many of the higher intensities caused robust suppression (e.g. 207–6464 lx elicited greater than 50% suppression), there were striking discrepancies. The subject exposed to 22 lx had 50% suppression while the subject exposed to 7960 lx, the highest intensity tested, had only 51% suppression. There was no detectable relationship between melatonin suppression and illuminance over the range of illuminances tested, nor was there a correlation between melatonin suppression and phase shift.

We conducted a comparison of the illuminance-resetting response results from these older subjects to that observed in a group of younger subjects studied in our laboratory between late 1997 and late 1998 [64]. That group of younger subjects had a similar sex distribution (82% male) as our older group, and their number of baseline days and the baseline and CR lighting conditions were also the same. The 6.5 h experimental light exposure began on average 5.21 ± 0.21 h before MELmax (range 4.12–7.58 h) in the younger subjects, a phase of light exposure that was not significantly different from that in the current group of older subjects ($p = 0.19$, t-test).

Model estimates for illuminance response changes in melatonin phase in the older subjects were: $a = -0.475 \pm 0.279$, $b = 263 \pm 88.9$, $c = -2.84 \pm 0.224$, and $d = 1.63 \pm 1.02$. Model estimates for illuminance response changes in melatonin phase in the younger subjects were: $a = -0.240 \pm 0.409$, $b = 119 \pm 43.1$, $c = -2.90 \pm 0.238$, and $d = 1.42 \pm 0.661$ [64]. The a, c, and d model terms were statistically indistinguishable between the two age groups ($p > 0.3$). This indicates that the response to 0 lx of light (the a model term, representing the drift in phase in response to a longer than 24 h circadian period and non-photic cues), the maximum phase shift that was achieved (the c model term), and the steepness of the slope (the d model term, a measure of the "squareness" of the sigmoidal waveform) were similar in the young and older groups. In contrast, the sensitivity term (b) of the older group was significantly greater than that of the younger subjects ($p < 0.005$), indicating that the older subjects were less sensitive to light of moderate illumination, and required higher illumination to evoke the same response when the illumination was non-saturating.

4. Discussion

Our current study examined the relationship between light intensity and the circadian phase delay response to a single 6.5 h light stimulus in healthy older people. We found that in healthy older people, the circadian rhythms of both core body temperature and plasma melatonin were shifted in parallel in response to the 6.5 h experimental light stimulus, and that there was a significant relationship between illuminance and the phase-delay shift of both the melatonin and temperature rhythms. The illuminance–response relationship using melatonin data provided a much better model fit (adjusted $R^2 = 0.86$) than did the core body temperature data (adjusted $R^2 = 0.27$), likely due to the greater confidence in the accuracy of the melatonin phase data [41].

We also compared the results of our study in older subjects to a previous study we had conducted in younger adults in order to determine if there was an age-related difference in the response to this phase-delaying light stimulus. We found that some aspects of the circadian response to the light stimulus in older subjects did not differ from responses observed previously in young adults. The maximum phase shift obtainable to a single 6.5 h light stimulus in the older adults in this study (the c term in the four-parameter model) was equivalent to that obtained in young adults in similar studies [31,45,64]. The progressive delay drift of phase due to the 24.2 h average intrinsic period and non-photic influences on the circadian timing system was also similar between the healthy older and younger adults, as evidenced by the similar values obtained for the a term in the four-parameter models fit to the data, representing the predicted shift in response to a 0 lx stimulus.

We did observe a difference in the sensitivity of the system (the b term in the four-parameter model, representing the illuminance level at which 50% of the asymptotic maximum response is observed) between the older and young subjects (Fig. 4, compare solid and dashed lines). The greater b term reflects a rightward shift of the model fit to the data from the older subjects, indicating that they are less responsive to low-to-moderate levels of light (~50–1000 lx). Given that pupil dynamics and lens opacity can change with aging, corneal light exposure may be quite different from retinal light exposure in older subjects, and the change we observed may be due to a change in the effective retinal illumination, rather than representing an age-related reduction in circadian light sensitivity. Future studies focused on this narrow illuminance range, with larger numbers of older and young participants may be able to address this question.

Our current findings are consistent with several previous studies in humans that also did not find significant differences in the magnitude of phase delay shifts elicited by late evening/early night light exposure when those light levels were very high or very low. In a previous study we conducted in which subjects were exposed to three consecutive nights of exposure to 5 h bright indoor light, we did not find significant differences between young and older subjects in the size of the phase delay shifts [40]. The intensity of light used in that study, however, was so large (9500 lx) as to saturate the circadian timing system's ability to respond to light. It would therefore only have been able to detect a change in the maximum response to light, as opposed to any change in sensitivity. A recent study of the melatonin-suppressing effects of monochromatic evening light in young and older females found no change in response to long wavelength (548 nm) visible light [33]. Another recent study that compared circadian phase-shifting responses to dim (10 lx) and bright (3500 lx) light in young and older adults found no differences between the two age groups [3], consistent with our finding of no difference in the response to very dim light or to very bright light.

Our study also found a difference in the degree of melatonin suppression between the older and young subjects' responses to light. The greatest amount of melatonin suppression that was observed in this study was 78.6%. In response to the same experimental light exposure procedures, all young subjects in our previous study who were exposed to at least 350 lx of light showed at least 92% melatonin suppression [64]. Those young subjects also displayed a strong dose–response relationship between illuminance and melatonin suppression, with robust melatonin suppression occurring at illuminances at least as bright as room light (>100 lx) and little suppression occurring at illuminances less than room light [64]. Our current cohort of healthy older individuals, in addition to having a lower capacity to suppress melatonin at any intensity of light, did not show a dose–response relationship between melatonin suppression and illuminance. As there was a normal responsiveness of the circadian timing system to the phase delaying effects of light, the melatonin suppression data suggest that there may be an age-related change in the light transmission system between

the SCN and the source of plasma melatonin (pineal gland). Alternatively, there may be a pathway from the retina to the SCN or other hypothalamic target that is involved in the acute cessation of melatonin production, but not in entrainment, and this pathway may be selectively affected by aging. In fact, sympathetic innervation of the eye, which is also responsible for sympathetic innervation of the pineal gland [63], may have diminished capacity with aging [6] and could account for the variability in melatonin suppression we observed in our subjects.

A recent study by Herljevic et al. reported that melatonin suppression in older women was reduced compared with younger women in response to short wavelength (456 nm) visible light, but they found no age-related change in melatonin suppression in response to longer wavelength (548 nm) light [33]. That finding is of interest due to the fact that the circadian system of humans and other mammals is most sensitive to shorter wavelengths of visible light [7,45,56], and the specialized retinal ganglion cells that serve as the primary circadian photoreceptors [5,30] have a peak sensitivity in that same range. While our broad-spectrum white light stimulus was quite different than the stimulus used by Herljevic et al., it is also the case that both our older and young study populations were predominantly male (80% and 82%, respectively), which may explain why we observed age-related differences in melatonin suppression and they did not.

It is important to note that in our study, subjects were extremely healthy, had no sleep complaints, and were screened for major visual deficits and age-related changes in lens pigmentation. Despite this, they had the common features of an aging circadian system, including early habitual wake times (before 07:00), melatonin and core body temperature phases occurring in the latter half of their habitual sleep time, and baseline night sleep efficiencies below 80% [23,26,27]. While we found no significant differences in the response to dim or very bright light in our very healthy older subjects when compared with young adults, we did find differences in the response to moderate levels of light. It should be noted that results from the older subjects in the current study were compared with results from a group of young subjects whose study was completed before the current study began. However, the lighting conditions in both studies were highly controlled, and the protocol and lighting conditions in the current study of older subjects was designed to be the same as that in the prior study in young adults in order that such a comparison could be performed.

It is possible that in older individuals with ocular problems (e.g. cataracts), light transmission to the circadian pacemaker could be altered, which in turn could further reduce their responsiveness to moderate levels of light, and even reduce their response to bright light. Even with an intact circadian responsiveness to light, older individuals are likely to be less responsive to the use of light as a treatment for transient circadian rhythm sleep disorders such as jet lag and shift work disorder [1], due to their reduced ability to sleep at adverse circadian phases [24]. In a study that used a bright light treatment regimen in middle-aged subjects scheduled to a night work schedule, while the subjects were found to phase-shift by >6 h in response to the bright light treatment, they did not fully adapt to the 9 h shift in sleep timing and therefore had high rates of sleep disruption [12].

Our current finding that older subjects show a reduced circadian phase shifting response to moderate levels of nighttime light exposure cannot itself explain the difference in entrained circadian phase we and others have observed in older people [26,27,44]. We have also reported that a change in circadian period does not occur with healthy aging [18]. Together, these findings suggest that the observed age-related difference in the phase relationship between the timing of sleep and the timing of circadian rhythmicity, and the increased variability in this relationship, are more likely due to differences in the phase-advancing response to morning light and/or differences in light exposure patterns across the waking day between young and older adults. Further investigations focused on the response to morning light and to light exposure patterns across the 24 h day should provide a better understanding of these observations.

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