Blue Light Implemented

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1 Introduction

Ever since the discovery of the melanopsin containing, intrinsically photosensitive retinal ganglion cells (ipRGCs) and their role in non-visual effects on physiology, many studies have demonstrated large potential of blue light for more efficient light treatment solutions [1-5]. Although the visual receptors also seem to play a role in the non-visual effects of light, it is most likely that in the bright light regime the blue-sensitive ipRGCs have the leading role [6]. A majority of those early studies with blue light were performed under controlled laboratory conditions and/or during the biological night. Here we focus on two practical applications of blue light: 1) treatment of seasonal mood and energy problems, a study performed at the University Medical Center in Groningen, The Netherlands, and 2) a morning light intervention for shifting the biological clock in healthy people with a late chronotype, a study performed at the Chronobiology Department of the University of Groningen, The Netherlands.

The randomized controlled study on seasonal affective disorder (SAD, winter depression) explored the effects of blue light therapy compared to the standard bright white light (10000 lux, 30 minutes) therapy, using a single blind outpatient protocol. In subjects suffering from sub-syndromal SAD (winter blues) a 20 minutes intervention of either morning bright white or monochromatic blue light therapy was used.

People with late chronotype [7] underwent a nine days sleep advancing protocol with a 30-minute special light exposure upon waking up. Blue light was compared to equally luminous amber light, both as add on to the normal room illumination at home.

2 Blue light treatment of SAD and sub-SAD

Bright white light therapy has been established as first choice therapy for treatment of seasonal affective disorder (SAD, winter depression) [8-10]. In clinical practice, exposure to 10000 lux white light for 30 minutes in the morning typically brings relief after 1 week of

daily administration although it is known that details of the experimental protocol can influence the pace with which patients recover [11,12]. We shall refer to this modality as standard light therapy (SLT). Bright light therapy was also shown effective for helping people with seasonal problems without a clinical diagnosis of depression (sub-syndromal seasonal affective disorder, sub-SAD, winter blues) [13,14].

The first clinical studies with monochromatic blue light devices have shown their potential for treatment of SAD [15-17] but the daily exposure duration used was longer than in SLT (45 minutes instead of 30 minutes). The blue intervention was compared to either dim red light [15] or to the same photopic intensity of red light [16], both showing that blue light is more effective. One study compared monochromatic blue light (Philips goLITE, 100 lux) to moderate intensity white LED light (containing the same amount and spectrum of blue as well as a broadband peak in longer wavelength visible range, overall 770 lux), which showed that extra visible light did not ad to the effect of the blue light only [17]. A study in SAD patients comparing SLT (Philips EnergyLight, 10000 lux, 5000K) with a light treatment using blue enriched bright white light of the same luminous intensity (Philips Activiva EnergyLight prototype, 10000 lux, 17000 K) revealed no difference between the treatments, irrespective whether the blue enriched light was offered in duration of 20 or of 30 minutes [18]. Similar findings resulted from a smaller study with a similar protocol, comparing SLT with only 750 lux blue enriched light (Philips Activiva EnergyLight prototype, 17000 K), again showing both treatments to be equally effective, and with similar responder percentages as in the other studies [19]. Here we report on an as yet unpublished study by Meesters et al (SLTBR 2011, paper in preparation), concerning direct comparisons between monochromatic blue light intervention and SLT for SAD and sub-SAD populations.

Table 1 provides an overview of the light intervention parameters used across these studies based on the nominal cornea illuminance values in the prescribed usage conditions (distance, position of the device). Besides illuminance and irradiance, the table contains values of a newly proposed measure of ‘equivalent melanopic illuminance’ [6], obtained by convoluting the spectral power distribution of the light source with the melanopsin response function of ipRGCs. As blue light devices are typically used as additional light source to room illumination, one of the typical room light conditions is included in the table as well.

2.1 Methods

Studies were performed in the winters of 2010/2011 (SAD and sub-SAD) and 2011/2012 (sub-SAD) at the Psychiatric Clinic of the University Medical Center Groningen. Subjects

were screened for the absence of any psychiatric diagnosis other than Seasonal Affective Disorder, Depressive episode, according to the DSM-IV-TR (APA, 1994) using the M.I.N.I. structured interview [20]. Based on the outcome of the Structural Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD, [21]) and the Seasonal Pattern Assessment Questionnaire (SPAQ, [22]) subjects were included either in the SAD study (SIGH-SAD >=18) or in the sub-SAD study (SIGH-SAD >=12, <18; complaints not disturbing the daily life of the subject).

Subjects were randomized in either the SLT condition (Philips EnergyLight HF3319, 10000 lux, 5000 K), or a blue light condition (Philips goLITE HF3320, 100 lux, 470 nm). Details of the light conditions are shown in Table 1. In the SAD study subjects received 5 consecutive days of 30 minutes morning light therapy at the clinic (between 7:00 and 8:30), whereas in the sub-SAD study, subjects were treated at home where they received 20 minutes of morning light therapy (before 8:20) on 5 consecutive days.

The primary outcome variable of the studies was the SIGH-SAD score, rated by interviewers blind for the light condition. The interview was performed during visits to the clinic on days 1, 8, and 15 of the study. Light treatment was scheduled at days 4-8. All reported side effects were noted.

Statistical analysis involved t-tests and chi-square tests for baseline differences between the two conditions, and repeated measures ANOVA for the comparison of weekly assessments.

2.2 Results

Demographic data are shown in Table 2. There were more female participants (74 out of 93), which is typical for SAD and sub-SAD populations. No differences could be found between conditions regarding age, symptom severity at baseline, or the number of previous users of light therapy.

The SIGH SAD results are shown in Figure 1. Participants responded well to both kinds of light therapy (for SAD: main effect ‘time’ $F(2,42)= 148,3$, $p<0.001$; for sub-SAD $F(2, 45)=53.9$, $p<0.001$). There was no significant difference in SIGH-SAD scores between conditions (main effect ‘condition’ $F(1,43) = 0,9$ ns SAD; $F(1,46)=1.13$, ns sub-SAD), nor over time between conditions (interaction effect “time*condition” $F(2,42) =2,82$, ns SAD; $F(2,45)=0.06$, ns sub-SAD).

The side effects reported are in line with what is known for light therapy. In the SAD group, 4 out of 45 subjects reported side effects: in the SLT condition 1 (4%) subject reported headache and 1 (4%) nausea; in the blue light condition 1 (4%) subject reported headache and 1 (4%) felt hyperactive during the treatment. In the sub-SAD group 8 out of 48

subjects reported side effects: in the SLT condition 2 subjects (12%) had headache, 1 (6%) reported headache and nausea, 2 subjects (12%) reported a headache and felt hyperactive during the treatment; in the blue condition 1 subject (6%) reported a headache, 1 (6%) had a headache and nausea, and 1 (6%) had a headache and palpitations during the treatment.

2.3 Discussion

Just like in previous studies comparing blue enriched treatment modalities to SLT [18,19], also these studies comparing the low luminous intensity of blue LED light to SLT have shown no significant differences in the clinically relevant responses to light, neither for SAD nor for the sub-SAD group.

The blue goLITE device was used as addition to the normal room illumination, so subjects effectively received about 350 lux, 885 m-lux light (see Table 1). The difference in photopic illuminance of the two conditions is two orders of magnitude (10000 lux vs 350 lux), whereas the difference in the equivalent melanopic illuminance [6] is about one order of magnitude (8620 m-lux vs 885 m-lux). The equivalent melanopic illuminance of blue light treatment is of the same order of magnitude as melanopic illuminance of 1000 photopic lux, 5000 K white fluorescent light. Over a broad range of light intensities there is no difference in effects on people with seasonal problems. Similar saturation was reported for alerting effects of light [23], and for melatonin suppression [24], where the responses were already maximal and the same between 1000 and 10000 lux of white 4000 K fluorescent light. The fact that we observe the same magnitude of effects across a larger range of photopic illuminance, but similar range of melanopic illuminance as in the studies above supports the hypothesis that ipRGCs play a dominant role in mediating effects of light when treating SAD and sub-SAD.

3 Morning blue light for phase advancing

Sleep timing differs between individuals, and people with a relatively late sleep phase are called late chronotypes. Late chronotypes often suffer from social jetlag on work days [7] as their biological clock is delayed relative to the required sleep period due to social obligations. Light has been shown to be the most potent Zeitgeber in shifting the biological clock. Morning light exposure could help in advancing their clock, as well as counteracting daytime sleepiness and stimulating cognitive functioning [25-29].

The clock response to light is described by the so-called phase response curve (PRC) [30,31], which predicts maximum advancing effects when light is administered about 9 hours after the evening dim light melatonin onset (DLMO, one of the markers for the phase of the biological clock). This is based on laboratory measurements with light pulses lasting

for several hours and dim light during the rest of the day. A blue light PRC study by Rüger et al. [31] has shown that only 11.2 lux of 480 nm blue light can induce about 75% of the phase shift obtained by 10000 lux white light [30].

For real life applications it is of interest to investigate the effects of blue light exposure in the morning on top of the normal light exposure throughout the day. In a pilot home study performed by Geerdink et al. (SLTBR 2011 Abstract, paper in preparation) (N=11, summer) it was established that 30 min of morning blue light exposure at home over 3 days induces a significant phase advance (49 min +- 58 min) of the biological clock as measured in the rhythm of melatonin at night. The pulses were scheduled 9 h after DLMO, and they were effectively administered at 8.3h +-1.2 h after DLMO, due to variation of the phase between the baseline measurement and the start of the intervention.

Here we report on an as yet unpublished study by Geerdink et al. (SLTBR 2013 Abstract, paper in preparation) with healthy late chronotypes undergoing a sleep advance protocol at home with a morning light intervention. Besides the phase shifting effect, the influence of light on daytime alertness and performance was investigated.

3.1 Methods

42 healthy participants (mean age 21.4y SEM +- 6.5, 23f/19m) who suffered from a 'social jetlag' on workdays (mean 2.33h SEM +- 0.7) [7] were included in a study, performed at the Chronobiology Unit of the Centre for Life Sciences, University of Groningen, The Netherlands. Participants were randomly assigned to a sleep advancing protocol supported by either high intensity blue light (Philips GoLite BLU HF3330, peak transmission at 470 nm, intensity at the cornea 300 lux, 2306 m-lux), or control amber light with similar illuminance (adapted Philips GoLite HF3320, peak transmission at 590 nm, intensity at the cornea 250 lux, 6 m-lux). See Table 1 for details of the light interventions. Both intervention lights were used at home in addition to the normal room light conditions, directly after waking-up.

The protocol consisted of 14 baseline days without sleep restrictions, 9 intervention days with either 30-min blue light pulses or 30-min amber light pulses in the morning along with a sleep advancing scheme and 7 post-treatment days without sleep restrictions and no use of light treatment devices. Evening melatonin samples were taken at days 1,7,14 (baseline), day 23 (effect intervention), and day 30 (post-treatment). The timing of sleep and the light exposure was based on the baseline period in such a way that during the first three experimental days (days 15,16,17 in the protocol) the light exposure started about 10 hours after baseline DLMO, on days 18, 19, 20 about 9 hours after baseline DLMO, and on days 21, 22, and 23 about 8 hours after baseline DLMO. During the treatment

period participants were asked to avoid bright light in the last three hours before sleep. During the whole protocol sleep was monitored with the Actiwatch Spectrum (Philips Respironics Inc., Murrysville, USA), these results will be discussed elsewhere. Participants were completing sleep diaries including sleepiness measurements 5 and 30 minutes after waking up (Karolinska Sleepiness Scale, KSS [32]). Performance was measured with a reaction time task (PVT) on a handheld minicomputer (HP Ipaq114) at four time points each day (morning, noon, afternoon, evening). Due to large differences in sleep times between free and workdays typical for this population, comparisons of sleepiness and performance results was limited to workdays only.

3.2 Results

3.2.1 Phase advance

Due to the individual differences in phase on the evening prior to the first light exposure, light was actually administered on average 9.6 +- 1.6(SEM) hours after baseline DLMO on days 18-20 of the protocol. The phase advance in the melatonin rhythm from day 14 to day 23 in the group exposed to amber light was 47min. +- 10 (SEM). The phase advance of the melatonin rhythm in the group exposed to blue light was significantly larger, 81min. +- 12 (SEM), ($t38=2.14$, $P<0.05$). Figure 2 shows the actual clock time of dim light melatonin onset for the blue and amber treatment group on the evening before starting the treatment (day 14) and on the last day of treatment (day 23).

3.2.2 Sleepiness

Sleepiness scores as measured with the Karolinska Sleepiness Scale, 5 min after waking up during the treatment period was not significantly different from baseline in neither of the treatment groups. However, sleepiness 5 min after waking up was significantly less in the post treatment period compared to the baseline period (blue: $\Delta KSS=-0.75+-0.28$(SEM); $t=-2.717$, $p=0.015$; amber: $\Delta KSS=-0.78+-0.23$(SEM), $t=-3.381$, $p=0.003$). No differences in sleepiness scores between light conditions were found directly after waking up.

At the end of the light intervention, 30 minutes after waking up, sleepiness scores of people in the blue group were significantly lower, so they were less sleepy than in the baseline period ($\Delta KSS=-0.6+-0.2$ (SEM); $t=-2.771$, $p=0.014$). There was no difference in sleepiness 30 minutes after waking up in the amber group ($\Delta KSS=-0.1+-0.1$ (SEM); $t=-0.994$, $p=0.333$) between the treatment period and the baseline period. The difference between the blue and amber condition on the sleepiness score 30 minutes after waking up during the treatment period did not reach significance ($t=-1.789$, $p=0.082$). Figure 3 shows the differences of sleepiness scores in the treatment period relative to the baseline period, 5 and 30 minutes after waking up, for the blue and amber group.

3.2.3 Performance

Performance was measured by average reaction time on a PVT test, and results for each time of day point were compared between the treatment periods and treatment conditions. In the amber light group, when compared to the baseline period performance was significantly worse around noon during the intervention period (noon $F_{1,32}=6.24$, $P<0.05$) and both at noon as well as evening during the post-intervention period (noon $F_{1,32}=11.4$, $P<0.01$; evening $F_{1,28}=6.86$, $P<0.05$). In the blue intervention group, performance of the participants at any time of day was not significantly different from the baseline period, neither in the intervention, nor in the post-intervention period. Figure 4 shows results for average reaction time at noon relative to baseline in the treatment and post-treatment period.

3.3 Discussion

Late chronotypes experience difficulty waking up at socially required times as their biological clock is delayed and advancing their sleep is an effort. This protocol was designed with aspiration that people can implement it in real life, and in such a way that sleep is gradually advanced: on the first three light intervention days the scheduled wake-up time was not far from the habitual wake-up time, next three days it was one hour earlier, and next three days another hour earlier. A sleep advancing protocol in at home conditions without any light intervention can by itself induce a phase advance of the biological clock due to accompanying changes in exposure to the light-dark cycle or to the shifted sleep itself [33,34]. The observed phase advance in both groups was therefore expected. Blue light resulted in 72% larger phase advances than the control amber light. Blue light helped in reducing subjective sleepiness 30 minutes after waking up during the intervention period. Once the phase was advanced, participants in both groups experienced lower sleepiness than during the baseline period already at waking up (post-treatment period). Performance measurements suggest that people in the blue group were able to undergo the sleep and phase advancing protocol without significant reduction in their performance throughout the day, whereas this was not the case in the amber light group. This could be due to the fact that the amber group had to sleep in a less convenient circadian time window than the more phase advanced blue group.

4. Conclusion

Results of the recent studies presented confirm the expectations from the laboratory studies and show the effects blue light can have when implemented in real life situations. They show that 1) low luminance blue light is equally effective as traditional bright white light therapy in treating winter depression and in alleviating symptoms of winter blues; 2)

properly timed short pulses of blue light can be very effective in supporting the sleep pattern adaptation of healthy people with late chronotype, by inducing circadian phase advance and reducing sleepiness without deteriorating daily functioning.

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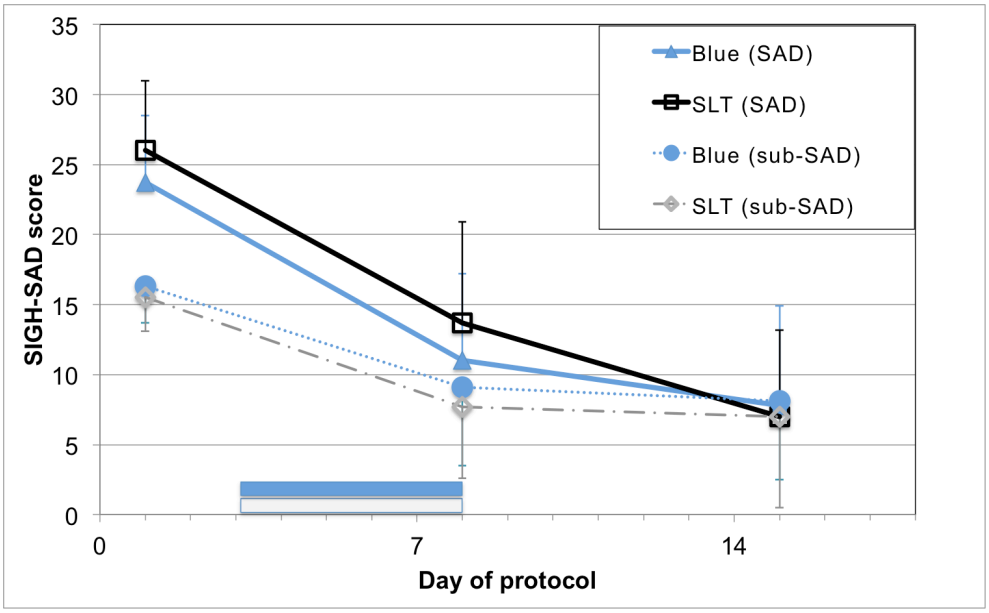

Figure 1. SIGH-SAD score throughout the protocol for SAD (full lines) and sub-SAD (dotted lines) subjects randomized to blue therapy group (Blue, circle and triangle) or standard light therapy group (SLT, square and diamond). Horizontal bars denote days on which morning light treatment was received. Error bars show standard deviation in one direction only.

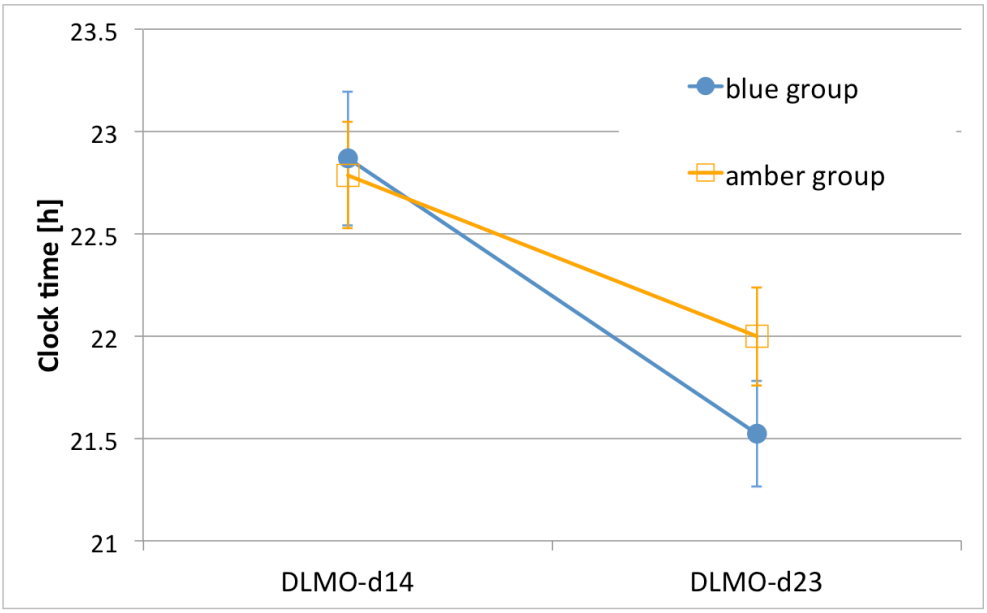

Figure 2. Time of dim light melatonin onset for the blue (circle) and amber (square) treatment group on the evening before starting the treatment (day 14) and on the last day of treatment (day 23).

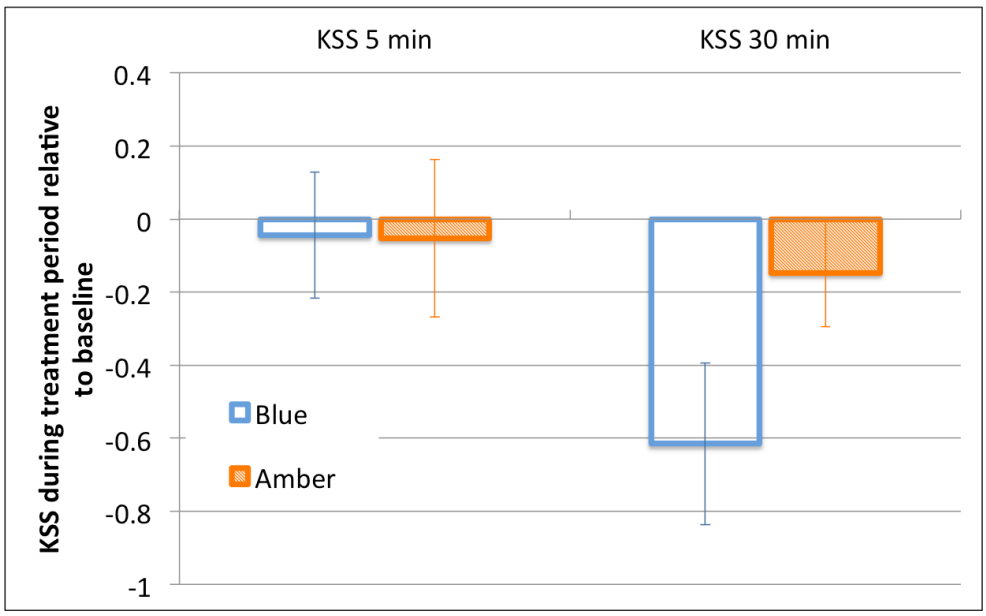

Figure 3. Sleepiness ratings on workdays during the treatment period relative to baseline, 5 and 30 minutes after waking up, for blue and amber (striped) light group.

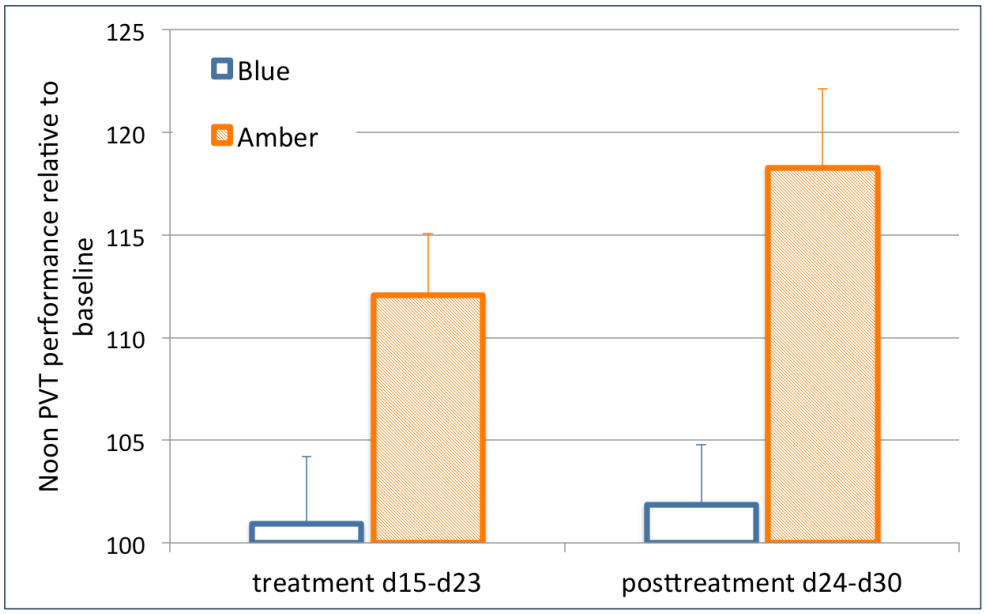

Figure 4. Average reaction time (on workdays, at noon) in the treatment and post-treatment period relative to baseline for blue and amber (striped) light group.

Table 1. Parameters of light interventions used in studies discussed. Interventions discussed in chapters 2 and 3 are shown in bold.

Light source	Reference	Photopic illuminance [lux]	Irradiance [Watt/m2]	Equivalent melanopic illuminance [m-lux]
5000 K TL	[19, 18] Meesters et al.	10000	31.7	8620
17000K TL	[18]	10000	40.9	14390
17000K TL	[19]	750	3.1	1080
LED Blue 470nm	[17] Meesters et al.	100	1.0	770
3000 K TL	room light	250	0.7	115
LED Blue 470nm	Geerdink et al.	300	3.0	2310
LED Amber 590nm	Geerdink et al.	250	0.5	6

Table 2. Subjects included in the SAD and sub-SAD studies were randomized in one of the two conditions balanced for age and baseline seasonal depression score SIGH-SAD.

Condition	N [total (female)]	Age [years (SD)]	SIGH-SAD (SD) on day 1
SAD SLT	21 (16)	36.7 (12.6)	26 (5)
SAD Blue	24 (18)	39.5 (13.9)	24 (5)
sub-SAD SLT	22 (18)	39.6 (10.5)	16 (2)
sub-SAD Blue	26 (22)	39.6 (12.1)	16 (3)