UC San Diego
UC San Diego Previously Published Works

Title

Examining the Efficacy of Bright Light Therapy on Cognitive Function in Hematopoietic Stem Cell Transplant Survivors

Permalink

https://escholarship.org/uc/item/12c9h491

Journal

Journal of Biological Rhythms, 37(5)

ISSN

0748-7304

Authors

Wu, Lisa M

Valdimarsdottir, Heiddis B

Amidi, Ali

et al.

Publication Date

2022-10-01

DOI

10.1177/07487304221107833

Peer reviewed

Examining the Efficacy of Bright Light Therapy on Cognitive Function in Hematopoietic Stem Cell Transplant Survivors

Lisa M. Wu[*,†,‡,1], **Heiddis B. Valdimarsdottir**[‡,∥], **Ali Amidi**[§], **Kathryn J. Reid**[¶], **Sonia Ancoli-Israel**[#], **Katrin Bovbjerg**[*], **Rina S. Fox**[*,**], **Lauren Walker**[*], **Amreen Matharu**[*], **Erin T. Kaseda**[††], **John P. Galvin**[‡‡], **Kehinde Adekola**[§§], **Gary Winkel**[‡], **Frank Penedo**[*,∥∥], **William H. Redd**[‡]

[*]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[†]Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark

[‡]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York City, New York, USA

[§]Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark

[∥]Department of Psychology, Reykjavik University, Reykjavik, Iceland

[¶]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[#]Department of Psychiatry, School of Medicine, University of California San Diego, San Diego, California, USA

[**]College of Nursing, The University of Arizona, Tucson, Arizona, USA

[††]Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois, USA

[‡‡]Department of Internal Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

[1.]To whom all correspondence should be addressed: Lisa M. Wu, Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, 625 N. Michigan Ave., 21st floor suite, Chicago, IL 60611, USA; lisa.wu1@ northwestern.edu.

AUTHOR CONTRIBUTIONS

L.M.W., H.B.V., S.A.-I., G.W., and W.H.R. conceived and designed the study; L.M.W., H.B.V., K.B., L.W., A.M., J.P.G., K.A., and F.P. facilitated set up and data acquisition; data processing and analysis were performed by L.M.W., K.B., K.A., R.S.F., K.J.R., L.W., A.M., and G.W.; interpretation of data was performed by L.M.W., K.J.R., and A.A.; draft manuscript preparation was performed by L.M.W., A.A., K.J.R., S.A.-I., K.B., R.F., L.W., A.M., and E.T.K.; all authors revised it critically, reviewed the results, and approved the final version of the manuscript. Content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health.

Trial registration: ClinicalTrials.gov Identifier: NCT02677987 (9 February 2016)

ETHICAL APPROvAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Supplementary material is available for this article online.

CONFLICT OF INTEREST STATEMENT

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.A.-I. is a scientific consultant for Eisai, Idorsia, Merck, and Biogen. There are no other conflicts of interest to report.

§§Division of Hematology and Oncology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

‖‖Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida, USA

Abstract

Patients who have undergone hematopoietic stem cell transplant (HSCT) may experience cognitive impairment that can persist after treatment. Several studies have shown that bright light therapy may improve cognition, potentially due to its effects on the circadian system via brain regions that respond preferentially to light. In this double-blind randomized controlled trial, the efficacy of bright light therapy on cognition was examined in HSCT survivors. Forty-seven HSCT survivors at an urban hospital in the United States were screened for mild cognitive impairment, randomized to either bright white light (BWL) or comparison dim red light (DRL) conditions using a block randomization approach, and instructed to use their assigned light box every morning upon awakening for 30 min for 4 weeks. Assessments occurred at baseline, the end of the second week of the intervention, the end of the intervention, and at follow-up (8 weeks later). The primary outcome was objective cognitive function as measured by a global composite score on neuropsychological tests. Secondary outcomes included cognitive performance in individual domains, self-reported cognitive function, fatigue, sleep and sleep quality, and circadian rhythm robustness. Repeated-measures linear mixed models for both objective and self-reported cognitive function indicated significant main effects for time ($ps < 0.05$) suggesting significant improvements in both conditions over time. Time by light condition interaction effects were not significant. Models focused on secondary outcomes yielded no significant effects. Both BWL and DRL groups demonstrated significant improvements in objective cognitive and self-reported cognitive function over time, but there was no hypothesized effect of BWL over DRL nor associations with circadian rhythm robustness. Therapeutic effects of both light conditions, practice effects, and/or placebo effects may account for the findings.

Keywords

cancer; light therapy; circadian rhythms; cognitive impairment; hematological malignancies; hematopoietic cell transplant; sleep; fatigue

As survival rates for patients with hematological malignancies have improved, cancer- and treatment-related morbidities have become more salient to survivors (Copelan, 2006). Among hematopoietic stem cell transplant (HSCT) survivors, cancer-related cognitive impairment is an established late effect that can persist after treatment (Buchbinder et al., 2018) and impair quality of life (Wu et al., 2012; Wu et al., 2019). Close to 50% of HSCT patients show vulnerability to cognitive impairment 3 months after transplant (Jones et al., 2013), and 18% to 36% will continue to experience persistent symptoms even 3 years post-transplant (Sharafeldin et al., 2018). Domains of cognitive functioning that can be affected vary depending on the study, but can include learning and memory, executive function, motor function, and psychomotor speed (Jones et al., 2013; Sharafeldin et al., 2018).

Circadian disruption may be a risk factor for cognitive impairment (Musiek et al., 2018; Reid et al., 2011) due to its significant role in the regulation of physiological and behavioral systems important for healthy cognition (Reid et al., 2011). Indeed, circadian disruption has been implicated both as a precursor and consequence of cancer and its treatment (Ancoli-Israel et al., 2014; Roenneberg and Merrow, 2016; Savard et al., 2009). For HSCT patients, this is of particular importance, as hematopoietic stem cell proliferation and differentiation appear to be under circadian control (Méndez-Ferrer et al., 2009) and HSCT requires exposure to intensive chemotherapy regimens that could lead to circadian disruption (Ancoli-Israel et al., 2014).

Light is the strongest zeitgeber of the circadian system due to its effects on the brain, including the suprachiasmatic nucleus, via a non-image forming photoreceptor system (Vandewalle et al., 2009). Brain regions involved in alertness respond preferentially to light in the blue light range (~480 nm; LeGates et al., 2014). Hence, light influences alertness, sleepiness, and arousal—all important drivers of cognition—through the circadian system (Cajochen et al., 2014; Smolders and de Kort, 2014). Indeed, recent evidence indicates that disrupted circadian rhythms may increase the risk of cognitive problems in cancer survivors (Ancoli-Israel et al., 2022). Studies have already demonstrated preliminary efficacy of bright light therapy for improving cognitive performance in healthy and neurological populations (Bersani et al., 2008; Killgore et al., 2020; Yamadera et al., 2000). The dose of light delivered in these studies has ranged from exposures of 30 min to 1 h each morning, with lengths of treatment ranging from 5 days to 6 weeks. Studies in cancer populations have tended to adhere to a more standardized protocol based on the early work of Ancoli-Israel and colleagues, in which they compared morning bright white light (BWL) with a comparison dim red light (DRL) as a treatment to prevent fatigue in breast cancer patients undergoing chemotherapy (Ancoli-Israel et al., 2012). Across numerous studies, morning BWL has shown promise in improving or preventing cancer symptoms that may also be mediated by circadian disruption, such as fatigue (Ancoli-Israel et al., 2012; Johnson et al., 2018; Redd et al., 2014), depressed mood (Valdimarsdottir et al., 2018), and sleep disturbance (Wu et al., 2018), and these effects have, in some cases, been sustained even 3 weeks after light therapy had been terminated (Redd et al., 2014; Wu et al., 2018). It is also important to highlight that BWL may also directly modulate cortical and subcortical brain structures responsible for cognitive skills (Vandewalle et al., 2009). In past studies with cancer patients and survivors, researchers have typically used a dose of 30 min of BWL (compared with a comparison DRL) each morning for 4 weeks.

The efficacy of BWL on cancer-related cognitive impairment is yet to be examined. Hence, in this study, we examined the efficacy of BWL therapy among HSCT patients screened for mild cognitive impairment. As mentioned earlier, a range of cognitive functions are likely to be impaired in HSCT patients. Furthermore, a pilot study by Ancoli-Israel and colleagues (unpublished), conducted as part of a larger scale study focused on testing the effect of BWL therapy on fatigue, sleep, and circadian rhythms (Ancoli-Israel et al., 2012), found that breast cancer patients undergoing chemotherapy experienced improvements in global cognition when they received BWL compared with DRL. Therefore, the primary outcome for our study was objective cognitive functioning (i.e., a global composite score of overall cognitive function). Effects on cognitive performance in individual domains, self-reported

cognitive functioning, fatigue, sleep and sleep quality, and circadian activity rhythms were also explored.

MATERIALS AND METHODS

Procedures

This was a double-blind randomized controlled trial (RCT) that compared BWL with a comparison DRL condition in HSCT survivors. Study approval was obtained from Northwestern University's Institutional Review Board (#STU00201700-CR0003). Potential participants were approached either in-person at a pre-scheduled clinic appointment at Northwestern Memorial Hospital or (e)mailed a recruitment letter with a study brochure attached. Recruitment lasted from May 2016 to July 2019. Written informed consent was obtained from all individual participants included in the study. Screenings were conducted by telephone or in-person. Participants who met eligibility criteria were then randomized by the principal investigator to receive 1 of 2 types of light boxes. All boxes were labeled with 1 of 2 codes representing DRL or BWL and only known to a researcher outside the immediate lab team. Outcome measures were assessed at baseline (pre-intervention), the end of the second week of the intervention (for self-report measures only), the end of the 4-week intervention, and 8 weeks post-intervention. If the end-of-intervention assessment could not occur immediately after the intervention, the participant was encouraged to continue the intervention until their appointment so that there would be no time gap between intervention completion and follow-up assessment. Neuropsychological assessments were conducted in-person at Northwestern University's Department of Medical Social Sciences. Questionnaires were administered via REDCap in-person or online at home if participants had time constraints (Harris et al., 2009). Participants wore an Actiwatch (Spectrum Plus, Philips Respironics, Bend, OR) and completed sleep logs for 72 consecutive hours at each time point.

Participants

To be included, participants needed to (1) be older than 18 at screening and at least 16 at the time of HSCT; (2) be 1 to 5 years post-HSCT for a hematological malignancy; (3) stable clinical status (i.e., complete, very good, or partial response); (4) mild (grades 1–2) or no graft-versus-host disease (GvHD); (5) have English language proficiency; (6) have Internet access; and (7) demonstrate scores greater than 3 ("quite a bit") or 4 ("very much") on one or both cognitive questions of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30; Aaronson et al., 1993). The inclusion criteria was expanded to include allogeneic HSCT recipients part way through the study due to the slow pace of recruitment.

Participants were excluded if they met any of the following criteria: (1) pregnancy; (2) confounding medical or psychological diagnosis; (3) visual, hearing, or physical impairment sufficient to interfere with participation; (4) history of brain surgery; (5) history of bipolar disease/mania; (6) history of seasonal affective disorder; (7) current sleep disorder; (8) prior use of light therapy; (9) use of photosensitizing medications; (10) plans to travel across meridians; or (11) employment in shift work.

Apparatus

Light Box.—Litebook 1.2 (Litebook, Ltd. Medicine Hat, Canada) was used to deliver BWL and DRL. The BWL Litebook employs 60 premium white light emitting diode (LED) lights that contain emitters with a spectral emission peak at 464 nm and fluorescent phosphors which provide a secondary spectral peak at approximately 564 nm at a distance of 20 inches. The LEDs are contained in a 3.875×3 inch elliptical display and collectively emit light that appears white (Desan et al., 2007). The DRL Litebook used as a comparison light is identical in appearance and dimensions to the BWL Litebook, with the exception that it contains red LED lights emitting ~50 lux with peak wavelength at 680 nm (Wu et al., 2018). Circadian photoreceptors are less sensitive to the red light frequency (Lee et al., 1997). Participants were instructed to place the Litebook at a 45° angle 18 to 20 inches from the face for 30 min upon awakening every morning for 4 weeks, and to write down when they used it each day. A HOBO data logger (Onset, MA) tracked when the device was turned on and off.

Actiwatch.—The Actiwatch Spectrum Plus (Philips Respironics, Bend, OR) was used for circadian activity rhythm assessment. The Actiwatch has a sampling rate of 32 Hz. Parameters were set to a 1 min epoch length, medium sensitivity, and activity and marker selections were on the default settings. Participants were instructed to wear the Actiwatch continuously on the non-dominant wrist for 72 h and to press the event marker at bedtime and wake time. Participants completed a sleep log (adapted from the consensus sleep diary; Carney et al., 2012) for each night of actigraphy. These data were used to edit actigraphy data.

Measures

Objective Cognitive Function.—Objective cognitive function was assessed with paper-and-pencil neuropsychological tests of the domains found to be impaired in HSCT patients (Jones et al., 2013; Sharafeldin et al., 2018) as well as tests recommended by the International Cognition and Cancer Task Force (Wefel et al., 2011): reaction time (Psychomotor Vigilance Task [Khitrov et al., 2013]); simple attention (Conners Continuous Performance Task 3rd Edition [Conners and Sitarenios, 2011]); processing speed (Trail-making Test A [Reitan, 1958], Wechsler Adult Intelligence Scale–Fourth Edition [WAIS-IV] Coding [Wechsler, 2008], Delis-Kaplan Executive Function System [D-KEFS]—Color-word Inhibition: Color Name and Word Reading Time [Delis et al., 2004]); working memory (WAIS-IV Digit Span [Wechsler, 2008]); verbal fluency (D-KEFS: Verbal Fluency [Delis et al., 2004]); visuospatial construction (WAIS-IV Block Design [Wechsler, 2008]); verbal memory (Hopkins Verbal Learning Test–Revised [HVLT-R; Benedict et al., 1998]); visual memory (Brief Visuospatial Memory Test–Revised [BVMT-R; Benedict et al., 1996]); and executive functioning (Trail-making Test B [Reitan, 1958]), D-KEFS Color-word Inhibition: Combined [Delis et al., 2004]). Alternate forms were used at each time point for HVLT-R and BVMT-R. Global composite and individual domain *z*-scores were calculated as described in Supplementary Materials 1. Premorbid function (Wechsler Test of Adult Reading [WTAR; Wechsler, 2001]) was used to characterize the sample. See Supplementary Table S1 for additional neuropsychological test scoring and domain calculation information.

Self-reported Cognitive Function.—The 33-item Patient Assessment of Own Functioning Inventory (PAOFI) is a reliable and valid measure of perceptions of cognitive functioning (Bell et al., 2013; Chelune et al., 1986). Using a Likert-type scale from 1 (almost always) to 6 (almost never), ratings of 1 to 3 were scored "1" indicating impairment, and ratings from 4 to 6 were scored "0" indicating no impairment. Total impairment was calculated by summing the number of impaired items on the Memory, Language and Communication, and Higher Cognitive Functions subscales (Chelune et al., 1986). There are no established clinical cutoffs for this measure, but one study that compared a clinical group with a non-clinical group of 150 participants deemed a score of 8 to be clinically significant (i.e., 1 standard deviation above the mean; Richardson-Vejlgaard et al., 2009).

Fatigue.—The FACIT-Fatigue scale (Smith et al., 2010) consists of 13 items scored on a Likert-type scale from 0 to 4. Higher scores indicate less fatigue. Scores of <34 indicate clinically significant fatigue (Van Belle et al., 2005).

Sleep Quality.—The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report measure that is used to assess sleep quality (Buysse et al., 1989). A global score >5 indicates poor sleep quality. Internal consistency for the PSQI is generally good, ranging between 0.70 and 0.83 (Mollayeva et al., 2016).

Actigraphy Sleep Outcomes.—The following sleep outcomes were computed at each time point based on actigraphy: total sleep time (in hours), sleep efficiency (the percentage of time in bed when the person is sleeping), and wake time after sleep onset (the amount of nocturnal sleep time when the person is awake).

Circadian Activity Rhythms.—Activity was measured with the Actiwatch Spectrum Plus (Philips Respironics, Bend, OR) and analyzed with Philips Actiware software, V9.4 SAS software (SAS Institute Inc., Chicago, IL, USA). Each participant's activity data were fit to a 5-parameter extended cosine model (Marler et al., 2006) which yielded the pseudo F-statistic, which indicates "goodness of fit" of the fitted function. A larger value indicated more robust rhythms (Liu et al., 2013).

Treatment Credibility and Expectancy.—Treatment credibility and outcome expectancy were assessed at baseline with the mean of the first 3 items of the Credibility/ Expectancy Questionnaire. Items are scored on a Likert-type scale from 1 to 9, and the term "symptoms" was replaced with "thinking, memory and concentration problems." Higher scores represent greater credibility and outcome expectancy (Devilly and Borkovec, 2000).

Treatment Satisfaction.—The item "How do you rate this treatment overall?" from the Functional Assessment of Chronic Illness Therapy—Treatment Satisfaction–General (FACIT-TS-G) scale was used to measure treatment satisfaction (Peipert et al., 2014). Participants responded on a 5-point Likert-type scale from "poor" to "excellent."

Power Analysis

As part of a larger study examining the effect of light therapy on fatigue, sleep, and circadian rhythms (Ancoli-Israel et al., 2012), Ancoli-Israel and colleagues administered a battery of

tests of objective cognitive function before and after light therapy in 10 participants (BWL n = 5; DRL n = 5). The observed effect size in the pilot data was 0.33, indicating that a sample size of at least 19 (i.e., 10 participants in each group) would be required to achieve power at 0.80 at a significance level of 0.05 (unpublished data).

Data Analyses

Descriptive statistics were used to characterize sociodemographic, clinical, and outcome variables. Group differences were analyzed with independent t-tests (i.e., age, time since diagnosis, time since most recent transplant, WTAR, PAOFI, fatigue, sleep outcomes, pseudo F-statistic, and light box use), chi-square tests (i.e., gender, race, marital status, educational level, employment status, annual household income, diagnosis, and type of transplant), and Fisher's exact tests (i.e., conditioning regimen and receipt of total body irradiation) using SPSS Statistics 27 (SPSS Inc., Chicago, IL, US). Analyses of outcomes between groups over time were undertaken using repeated-measures linear mixed models (LMMs) using SAS procedure MIXED. A dummy-coded group variable (DRL vs. BWL) was entered as the independent variable to test main effects and a time by group variable to test interaction effects. Effect sizes were calculated using η_p^2, that is, the proportion of the total variance attributed to the effect over time. For these exploratory analyses, a significance level of $p < 0.05$ was used. Post hoc tests were conducted using the Tukey procedure.

RESULTS

Participant Characteristics

A total of 47 patients participated in the study (see Figure 1). Participants ranged in age from 28 to 78 years old, time since diagnosis ranged from 1.94 to 19.79 years, and time since most recent HSCT was 1.29 to 5.29 years. Table 1 summarizes other core participant characteristics. Groups did not differ significantly in age, gender, race, relationship status, educational level, employment status, annual household income, diagnosis, time since diagnosis, nor time since most recent transplant.

Objective Cognitive Function

There were no significant differences between groups at baseline in premorbid functioning (WTAR; Table 1). The repeated-measures LMM showed a significant main effect for time, $F(2, 77) = 47.43$, $p < 0.0001$, indicating improvement in the global composite score from baseline to follow-up (Figure 2a). This effect was large ($\eta_p^2 = .55$). However, there was no main effect for light condition, $F(1, 45) = 0.00$, $p = 0.99$, nor a time by light condition interaction, $F(2, 77) = 1.20$, $p = 0.31$. Repeated-measures LMMs were also conducted in individual cognitive domains. In sum, there were significant main effects showing significant improvements over time in the areas of simple attention ($p = 0.005$), processing speed ($p = 0.001$), working memory ($p = 0.0004$), visuospatial construction ($p = 0.0001$), and verbal memory ($p < 0.0001$). There was one time × group interaction effect for visual memory that unexpectedly favored the DRL group, that is, visual memory improved over time in the DRL group but declined in the BWL group ($p = 0.03$). All estimates for cognition outcomes over

time, LMM results for cognitive outcomes, and rates of impairment for cognition outcomes over time are presented in Supplementary Tables S2 to S4.

Self-reported Cognitive Function

At baseline, participants in both groups on average reported clinically significant cognitive impairment based on the number of impaired items on the PAOFI, but there were no significant differences between groups (Table 1). A repeated-measures LMM showed a significant main effect for time, $F(3, 122) = 7.55$, $p = 0.0001$, demonstrating a reduction in the number of impaired items on the PAOFI over time (Figure 2b). This was a large effect ($\eta_p^2 = 0.16$). However, there was no main effect for light condition, $F(1, 45) = 0.00$, $p = 0.98$, nor a time by light condition interaction, $F(3, 122) = 0.73$, $p = 0.54$.

Fatigue

All participants met the cutoff for clinically significant fatigue (i.e., a score < 34; Van Belle et al., 2005) at baseline and there was no significant difference between groups (Table 1). A repeated-measures LMM indicated no significant main effects for time, $F(3, 122) = 2.42$, $p = 0.07$; condition, $F(1, 45) = 0.97$, $p = 0.33$; nor time by condition, $F(3, 122) = 2.10$, $p = 0.10$.

Sleep and Sleep Quality

There were no significant differences between groups in total sleep time, sleep efficiency, wake after sleep onset, nor sleep quality at baseline (Table 1). Repeated-measures LMM indicated no significant main effects for time, condition, nor time by condition on any of these sleep variables (all ps > 0.50).

Circadian Activity Rhythm Robustness

There was no significant difference between groups on the pseudo F-statistic at baseline (Table 1). A repeated-measures LMM indicated no significant main effect for time, $F(2, 65) = 0.10$, $p = 0.90$; light condition, $F(1, 36) = 1.03$, $p = 0.32$; nor time by light condition interaction, $F(2, 65) = 1.44$, $p = 0.24$ (Figure 2c). Figure 3 shows examples of participant actograms ranging from high to low levels of circadian activity rhythm robustness.

Treatment Credibility, Expectancy, and Satisfaction

Treatment credibility and expectancy did not differ significantly between DRL and BWL participants, but BWL participants were marginally more satisfied with their light box at the end of treatment ($p = 0.07$; Table 1).

Litebook use

DRL and BWL participants both used their light box on average 75% of the prescribed 28 days for at least 20 min in the morning hours with no significant difference between groups ($p = 0.99$). There was also no significant difference between groups in the average number of minutes of morning light box use ($p = 0.55$; Table 1).

DISCUSSION

To the best of our knowledge, this is the first study to test the efficacy of a 4-week BWL intervention to improve cognitive function in HSCT survivors. HSCT survivors demonstrated significant improvement on tests of cognitive performance and in self-reported cognitive function both during and after the intervention. However, there was no hypothesized effect of BWL over DRL in overall cognitive performance, nor in any individual domain. There are a number of possible explanations for these negative findings. First, the improvements in cognition may have represented real therapeutic effects of both conditions with neither wavelength of light demonstrating superiority over the other. Second, practice effects may have been responsible for the improved performance scores on the neuropsychological tests over time. Practice effects are score increases associated with repeated administration of cognitive tests. Although the use of alternate forms may reduce the magnitude of practice effects, they do not always eliminate them (Calamia et al., 2012). Third, participants may have shown improvement due to placebo effects—the expectancy effects that can increase perceived benefits of a treatment. However, this explanation is more applicable to the self-reported improvements in cognition than improvements on the neuropsychological tests, as "objective" performance on neuropsychological tasks tend to be less malleable to expectancy effects (Schwarz and Büchel, 2015). Fourth, DRL (long wavelength light) has frequently been used in light therapy studies as a standard comparison condition to BWL (short wavelength light) but is by no means a pure control condition. There is evidence to suggest that exposure to longer wavelengths of light can enhance subsequent impact of shorter wavelengths of light on brain responses involved in cognitive functions (Chellappa et al., 2014). Thus, it is possible that exposure to long wavelength light in the morning via DRL could even enhance the impact of any subsequent exposure to short wavelength light, such as from daylight.

When individual cognitive domains were examined, there were significant improvements on verbal memory, processing speed, simple attention, working memory, and visuospatial functioning over time. There was one inexplicable group effect favoring the DRL group in the area of visual memory, although due to the small sample size, further work is needed to determine whether this reflects an actual benefit of DRL on visual memory. In addition, unlike earlier studies (Johnson et al., 2018; Redd et al., 2014), there was no differential effect of BWL on the secondary outcome of fatigue, even though all participants exceeded the clinical cutoff for cancer-related fatigue at baseline. Contrary to earlier work (Wu et al., 2018), there were also no differential effects of BWL on objective sleep outcomes (i.e., total sleep time, sleep efficiency, and wake after sleep onset) and sleep quality, although participants were not screened for sleep problems and, therefore, did not always exceed clinically significant cutoffs (e.g., sleep efficiency was, on average, over 85%).

The robustness of circadian activity rhythms and associations with light condition and cognition were not significant, although it is possible that the sample sizes were too small to detect any effects on this secondary outcome as the study was only powered to detect effects on the primary outcome of cognition.

Strengths and Limitations

This study is characterized by a number of strengths. It is the first known study to examine the use of BWL for the treatment of cognitive impairment in cancer survivors. In addition, circadian activity rhythms were also assessed to determine whether BWL might be associated with this purported mechanism of cognitive change. The study also examined cognitive functioning through the gold standard method of assessment, that is, neuropsychological tests, in addition to a self-report measure of cognition, thus tapping into both important facets of cognition (Hutchinson et al., 2012).

However, there were also limitations. First, participants were not screened for circadian disruption at the outset. If circadian rhythm disturbances are purported to underlie cognitive impairment, then screening for such disturbances might enable identification of individuals most likely to benefit from light therapy. Unfortunately, no established demographically similar normative data nor clinical guidelines exist. We did, however, compare the circadian activity rhythms in our sample with community samples of men and women (Rogers-Soeder et al., 2018; Tranah et al., 2011). Our participants scored in the median range or higher compared with those samples, but were also, on average 19 to 26 years younger, which may account for their more robust circadian rhythms. Thus, we cannot conclude that our participants had circadian activity rhythm disruption from the outset. Second, the screening of participants may have been too lenient, and thus participants may have been insufficiently cognitively impaired to benefit from the intervention. Third, the study would have benefited from a no-light control condition, to better understand what may have led to improvements in cognition in both light conditions. Fourth, the study was not powered to examine the secondary outcomes including individual cognitive domains, fatigue, sleep and sleep quality, and circadian activity rhythms, nor to adjust for multiple comparisons. Fifth, although we excluded patients from the study who had received brain surgery or experienced brain cancer, we could not completely exclude HSCT patients who had received treatment without brain involvement; total body irradiation that also includes the brain, is a common conditioning regimen for some HSCT patients. Finally, there was heterogeneity in the participant sample with respect to clinical factors, such as type of transplant, diagnosis, and conditioning regimen. Having said that, there were no statistically significant differences between groups on sociodemographic or clinical factors.

In conclusion, although cognition improved in both treatment groups, we did not observe a hypothesized effect of bright light exposure on cognitive functions. Further research is necessary to address some of the aforementioned limitations to determine whether bright light therapy may ameliorate cognitive impairment in cancer survivors. Importantly, this study adds to the growing body of light therapy research among cancer survivors and highlights the need for further work in this area, including across different cancer types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI J Natl Cancer Inst 85:365–376. [PubMed: 8433390]

Ancoli-Israel S, Liu L, Natarajan L, Rissling M, Neikrug AB, Youngstedt SD, Mills PJ, Sadler GR, Dimsdale JE, Parker BA, et al. (2022) Reductions in sleep quality and circadian activity rhythmicity predict longitudinal changes in objective and subjective cognitive functioning in women treated for breast cancer. Support Care Cancer 30:3187–3200. [PubMed: 34957532]

Ancoli-Israel S, Liu L, Rissling M, Natarajan L, Neikrug AB, Palmer BW, Mills PJ, Parker BA, Sadler GR, and Maglione J (2014) Sleep, fatigue, depression, and circadian activity rhythms in women with breast cancer before and after treatment: a 1-year longitudinal study. Support Care Cancer 22:2535–2545. [PubMed: 24733634]

Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker BA, Lawton S, Desan P, and Liu L (2012) Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. Support Care Cancer 20:1211–1219. [PubMed: 21660669]

Bell MJ, Terhorst L, and Bender CM (2013) Psychometric analysis of the patient assessment of own functioning inventory in women with breast cancer. J Nurs Meas 21:320–334. [PubMed: 24053059]

Benedict RHB, Schretlen D, Groninger L, and Brandt J (1998) Hopkins Verbal Learning Test–Revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 12:43–55.

Benedict RHB, Schretlen D, Groninger L, Dobraski M, and Shpritz B (1996) Revision of the Brief Visuospatial Memory Test: studies of normal performance, reliability, and validity. Psychol Assess 8:145–153.

Bersani G, Marconi D, Limpido L, Tarolla E, and Caroti E (2008) Pilot study of light therapy and neurocognitive performance of attention and memory in healthy subjects. Psychol Rep 102:299–304. [PubMed: 18481690]

Buchbinder D, Kelly DL, Duarte RF, Auletta JJ, Bhatt N, Byrne M, DeFilipp Z, Gabriel M, Mahindra A, and Norkin M (2018) Neurocognitive dysfunction in hematopoietic cell transplant recipients: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Complications and Quality of Life Working Party of the EBMT. Bone Marrow Transplant 53:535–555. [PubMed: 29343837]

Buysse DJ, Reynolds CF, Monk TH, Bermann SR, and Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213. [PubMed: 2748771]

Cajochen C, Chellappa SL, and Schmidt C (2014) Circadian and light effects on human sleepiness-alertness. In: Garbarino S, Nobili L, Costa G, editors. Sleepiness and human impact assessment. Milan (Italy): Springer-Verlag Italia Srl. *p.* 9–22.

Calamia M, Markon K, and Tranel D (2012) Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol 26:543–570. [PubMed: 22540222]

Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein K, and Morin CM (2012) The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 35:287–302. [PubMed: 22294820]

Chellappa SL, Ly JQM, Meyer C, Balteau E, Degueldre C, Luxen A, Phillips C, Cooper HM, and Vandewalle G (2014) Photic memory for executive brain responses. Proc Natl Acad Sci USA 111:6087–6091. [PubMed: 24616488]

Chelune GJ, Heaton RK, and Lehman RAW (1986) Neuropsychological and personality correlates of patients' complaints of disability. In: Tarter RE and Goldstein G, editors. Advances in clinical neuropsychology (Vol.3). New York (NY): Plenum Press. p. 95–126.

Conners CK and Sitarenios G (2011) Conners' Continuous Performance Test (CPT). In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. New York (NY): Springer. p. 681–683.

Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826. [PubMed: 16641398]

Delis DC, Kramer JH, Kaplan E, and Holdnack J (2004) Reliability and validity of the Delis-Kaplan Executive Function System: an update. J Int Neuropsychol Soc 10:301–303. [PubMed: 15012851]

Desan PH, Weinstein AJ, Michalak EE, Tam EM, Meesters Y, Ruiter MJ, Horn E, Telner J, Iskandar H, Boivin DB, et al. (2007) A controlled trial of the litebook light-emitting diode (LED) light therapy device for treatment of Seasonal Affective Disorder (SAD). BMC Psychiatry 7:38. [PubMed: 17683643]

Devilly GJ and Borkovec TD (2000) Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 31:73–86. [PubMed: 11132119]

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, and Conde JG (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381. [PubMed: 18929686]

Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, and Wilson C (2012) Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. Cancer Treat Rev 38:926–934. [PubMed: 22658913]

Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JSA, Ancoli-Israel S, and Campbell TS (2018) Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. J Cancer Surviv 12:206–215. [PubMed: 29127575]

Jones D, Vichaya EG, Wang XS, Sailors MH, Cleeland CS, and Wefel JS (2013) Acute cognitive impairment in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplant. Cancer 119:4188–4195. [PubMed: 24105672]

Khitrov MY, Laxminarayan S, Thorsley D, Ramakrishnan S, Rajaraman S, Wesensten NJ, and Reifman J (2013) PC-PVT: a platform for psychomotor vigilance task testing, analysis, and prediction. Behav Res Methods 46:140–147.

Killgore WDS, Vanuk JR, Shane BR, Weber M, and Bajaj S (2020) A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. Neurobiol Dis 134:104679.

Lee TMC, Chan CCH, Paterson JG, Janzen HL, and Blashko CA (1997) Spectral properties of phototherapy for seasonal affective disorder: a meta-analysis. Acta Psychiatr Scand 96:117–121. [PubMed: 9272195]

LeGates TA, Fernandez DC, and Hattar S (2014) Light as a central modulator of circadian rhythms, sleep and affect. Nat Rev 15:443–454.

Liu L, Rissling M, Neikrug A, Fiorentino L, Natarajan L, Faierman M, Sadler GR, Dimsdale JE, Mills PJ, Parker BA, et al. (2013) Fatigue and circadian activity rhythms in breast cancer patients before and after chemotherapy: a controlled study. Fatigue Biomed Health Behav 1:12–26.

Marler MR, Gehrman P, Martin JL, and Ancoli-Israel S (2006) The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. Stat Med 25:3893–3904. [PubMed: 16381069]

Méndez-Ferrer S, Chow A, Merad M, and Frenette PS (2009) Circadian rhythms influence hematopoietic stem cells. Curr Opin Hematol 16:235–242. [PubMed: 19417648]

Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, and Colantonio A (2016) The Pittsburgh Sleep Quality Index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med Rev 25:52–73. [PubMed: 26163057]

Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, and Ju YS (2018) Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. JAMA Neurol 75:582–590. [PubMed: 29379963]

Peipert JD, Beaumont JL, Bode R, Cella D, Garcia SF, and Hahn EA (2014) Development and validation of the functional assessment of chronic illness therapy treatment satisfaction (FACIT TS) measures. Qual Life Res 23:815–824. [PubMed: 24062239]

Redd WH, Valdimarsdottir H, Wu LM, Winkel G, Byrne EE, Beltre MA, Liebman ES, Erazo T, Hayes JA, Isola L, et al. (2014) Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. Psycho-oncology 23:1431–1434. [PubMed: 24798589]

Reid KJ, McGee-Koch LL, and Zee PC (2011) Cognition in circadian rhythm sleep disorders. Prog Brain Res 190:3–20. [PubMed: 21531242]

Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 8:271–276.

Richardson-Vejlgaard R, Dawes S, Heaton RK, and Bell MD (2009) Validity of cognitive complaints in substance-abusing patients and non-clinical controls: the Patient's Assessment of Own Functioning Inventory (PAOFI). Psychiatry Res 169:70–74. [PubMed: 19619901]

Roenneberg T and Merrow M (2016) The circadian clock and human health. Curr Biol 26:R432–R443. [PubMed: 27218855]

Rogers-Soeder TS, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Cauley JA, Ensrud KE, Paudel M, Barrett-Connor E, LeBlanc E, et al. (2018) Rest-activity rhythms and cognitive decline in older men: the osteoporotic fractures in men sleep study. J Am Geriatr Soc 66:2136–2143. [PubMed: 30136716]

Savard J, Liu L, Natarajan L, Rissling MB, Neikrug AB, He F, Dimsdale JE, Mills PJ, Parker BA, Sadler GR, et al. (2009) Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep 32:1155–1160. [PubMed: 19750920]

Schwarz KA and Büchel C (2015) Cognition and the placebo effect—dissociating subjective perception and actual performance. PLoS ONE 10:e0130492.

Sharafeldin N, Bosworth A, Patel SK, Chen Y, Morse E, Mather M, Sun C, Francisco L, Forman SJ, Wong FL, et al. (2018) Cognitive functioning after hematopoietic cell transplantation for hematologic malignancy: results from a prospective longitudinal study. J Clin Oncol 36:463–475. [PubMed: 29252122]

Smith E, Lai JS, and Cella D (2010) Building a measure of fatigue: the functional assessment of Chronic Illness Therapy Fatigue Scale. PM R 2:359–363. [PubMed: 20656617]

Smolders KCHJ and de Kort YAW (2014) Bright light and mental fatigue: effects on alertness, vitality, performance and physiological arousal. J Environ Psychol 39:77–91.

Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, Cauley JA, Redline S, Hillier TA, Cummins SR, et al. (2011) Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol 70:722–732. [PubMed: 22162057]

Valdimarsdottir HB, Figueiro MG, Holden W, Lutgendorf S, Wu LM, Ancoli-Israel S, Chen J, Hoffman-Peterson A, Granski J, Prescott N, et al. (2018) Programmed environmental illumination during autologous stem cell transplantation hospitalization for the treatment of multiple myeloma reduces severity of depression: a preliminary randomized controlled trial. Cancer Med 7:4345–4353. [PubMed: 30099857]

Van Belle S, Paridaens R, Evers G, Kerger J, Bron D, Foubert J, Ponnet G, Vander Steichel D, Heremans C, and Rosillon D (2005) Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. Support Care Cancer 13:246–254. [PubMed: 15549424]

Vandewalle G, Maquet P, and Dijk DJ (2009) Light as a modulator of cognitive brain function. Trends Cogn Sci 13:429–438. [PubMed: 19748817]

Wechsler D (2001) Wechsler test of adult reading (WTAR). San Antonio (TX): Harcourt Assessment.

Wechsler D (2008) Wechsler Adult Intelligence Scale. 4th ed. San Antonio (TX): Pearson.

Wefel JS, Vardy J, Ahles T, and Schagen S (2011) International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 12:703–708. [PubMed: 21354373]

Wu LM, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, Byrne EE, Vallejo Sefair A, Vega A, Bovbjerg K, et al. (2018) The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. J Clin Sleep Med 14:31–39. [PubMed: 29198295]

Wu LM, Austin J, Hamilton JG, Valdimarsdottir H, Isola L, Rowley S, Warbet R, Winkel G, Redd WH, and Rini C (2012) Self-efficacy beliefs mediate the relationship between subjective cognitive functioning and physical and mental well-being after hematopoietic stem cell transplant. Psycho-oncology 21:1175–1184. [PubMed: 21739524]

Wu LM, Kuprian N, Herbert K, Amidi A, Austin J, Valdimarsdottir H, and Rini C (2019) A mixed methods analysis of perceived cognitive impairment in hematopoietic stem cell transplant survivors. Palliat Support Care 17:396–402. [PubMed: 30238868]

Yamadera H, Ito T, Suzuki H, Asayama K, Ito R, and Endo S (2000) Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in Alzheimertype dementia. Psychiatry Clin Neurosci 54:352–353. [PubMed: 11186110]

Figure 1.

Consort flow diagram. Abbreviations: DRL = dim red light; BWL = bright white light.
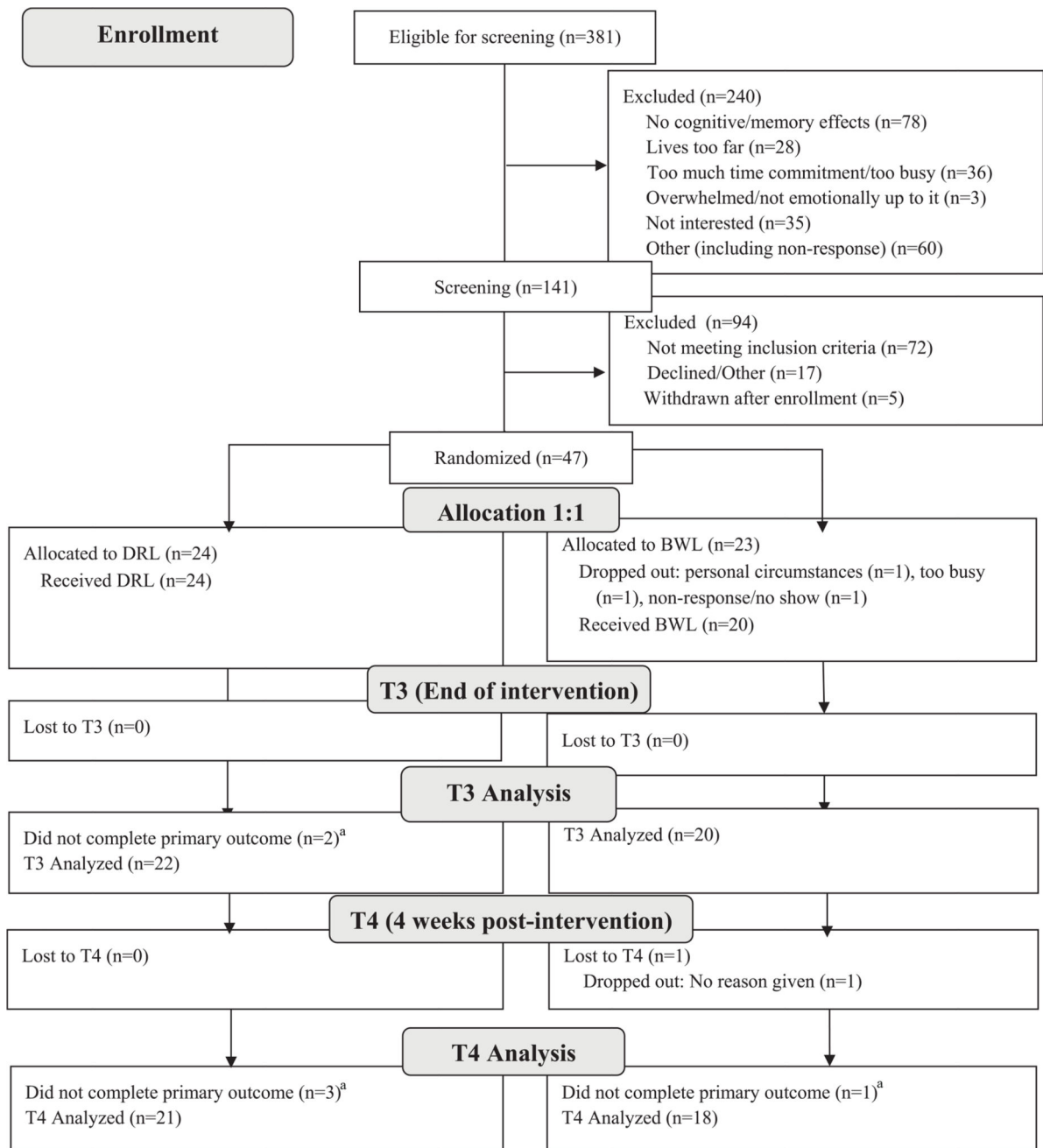
[a]Neuropsychological assessment not completed, but self-report outcomes were analyzed.
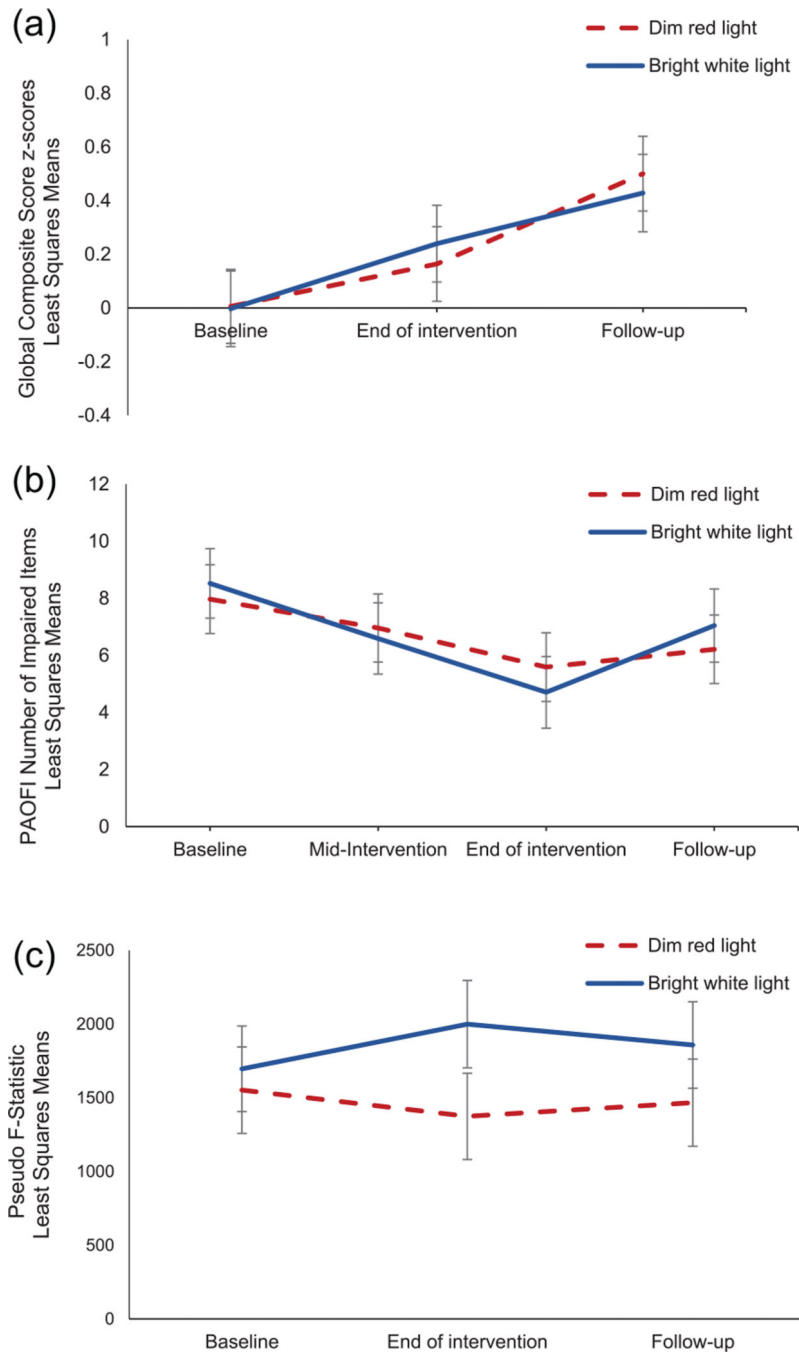
Figure 2.
Repeated-measures linear mixed models were undertaken to examine mean changes in primary and secondary outcomes between groups over time. Least squares means and standard error bars are shown for (a) the Global Composite Score (z-scores) for objective cognitive function based on neuropsychological test performance, (b) the number of impaired items on the PAOFI, and (c) the pseudo F-statistic, a measure of circadian activity rhythm robustness, by group over time. Abbreviation: PAOFI = Patient Assessment of Own Functioning Inventory.
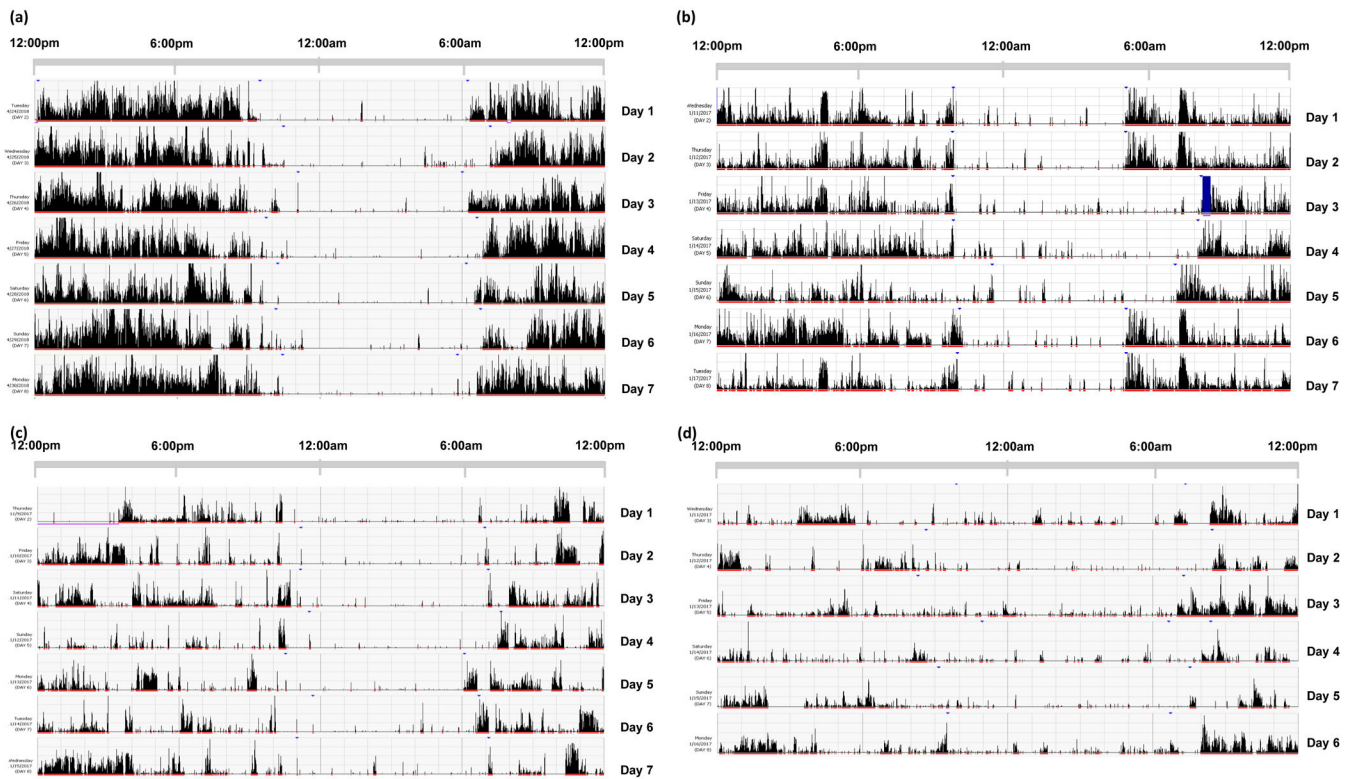
Figure 3.
These figures show examples of participant actograms ranging from strong to weak circadian activity rhythms. The pseudo *F*-statistics are as follows: (a) = 6888, (b) = 1572, (c) = 734, and (d) = 217.

Table 1.

Participant characteristics.

Variable	Dim Red Light (*n* = 24)		Bright White Light (*n* = 23)		All Participants (*n* = 47)		
	M (SD)	n (%)	M (SD)	n (%)	M (SD)	n (%)	p Value
Age (years; *n* = 47; range 28–78)	55.5 (13.0)		58.0 (11.2)		56.8 (12.1)		0.48
Gender							
Female		13 (54.2)		17 (73.9)		30 (63.8)	0.16
Male		11 (45.8)		6 (26.1)		17 (36.2)	
Race							
White[a]		19 (79.2)		19 (82.6)		38 (80.9)	1.00
African American/Black		2 (8.3)		1 (4.3)		3 (6.4)	
Other		3 (12.5)		3 (13.0)		6 (12.8)	
Marital status							
Married / partnered		19 (79.2)		15 (65.2)		34 (72.3)	0.29
Not married/partnered		5 (20.8)		8 (34.8)		13 (27.7)	
Educational level							
Less than a college degree		7 (29.2)		12 (52.2)		19 (40.4)	0.11
College degree or higher		17 (70.8)		11 (47.8)		28 (59.6)	
Employment status							
Employed		12 (50.0)		8 (34.8)		20 (42.6)	0.29
Not employed		12 (50.0)		15 (65.2)		27 (57.4)	
Annual household income							
Up to $79,999		9 (37.5)		9 (39.1)		18 (38.3)	0.19
$80,000 or above		15 (62.5)		14 (60.9)		29 (78.4)	
Time since diagnosis (years; *n* = 47; range 1.94–19.79)	4.4 (2.8)		5.3 (4.3)		4.9 (3.6)		0.40
Time since most recent transplant (years; *n* = 47; range 1.29–5.29)	2.4 (1.1)		2.4 (1.1)		2.4 (1.1)		0.96
Diagnosis							
Multiple myeloma[b]		13 (54.2)		15 (65.2)		28 (59.6)	0.44
Lymphomas		6 (25.0)		4 (17.4)		10 (21.3)	
Leukemias		4 (16.7)		1 (4.3)		5 (10.6)	
Myelodysplastic Syndrome		1 (4.2)		2 (8.7)		3 (6.4)	
Amyloidosis		—		1 (4.3)		1 (4.3)	
Type of transplant							
Allogeneic		18 (75.0)		19 (82.6)		37 (78.7)	0.52
Autologous		6 (25.0)		4 (17.4)		10 (21.3)	
Conditioning regimen							
Myeloablative		22 (91.7)		19 (82.6)		41 (87.2)	0.42
Reduced intensity conditioning		2 (8.3)		4 (17.4)		6 (12.8)	
TBI							

Variable	Dim Red Light (*n* = 24)		Bright White Light (*n* = 23)		All Participants (*n* = 47)		
	M (SD)	*n* (%)	M (SD)	*n* (%)	M (SD)	*n* (%)	*p* Value
No TBI		22 (91.7)		21 (91.3)		43 (91.5)	1.00
Received TBI		2 (8.3)		2 (8.7)		4 (8.5)	
Baseline scores							
Wechsler Test of Adult Reading standard score (*n* = 46)[c]	110.3 (11.1)		105.6 (9.5)		108.0 (10.5)		0.12
Patient Assessment of Own Functioning Inventory (*n*=46)	8.2 (5.4)		8.5 (5.8)		8.3 (5.5)		0.83
Fatigue (*n*=46)	30.2 (8.0)		30.4 (8.6)		30.0 (7.6)		0.87
Sleep							
Total sleep time, h (*n*=37)	6.8 (0.9)		7.0 (1.0)		6.9 (0.9)		0.50
Sleep efficiency, % (*n* = 37)	85.8 (5.2)		85.2 (7.3)		85.5 (6.2)		0.80
Wake after sleep onset, min (*n*=37)	45.9 (20.4)		42.3 (15.8)		49.4 (23.8)		0.30
Sleep quality, PSQI score (*n* = 43)	7.3 (3.9)		8.5 (3.2)		7.9 (3.6)		0.30
Pseudo F-statistic (*n*=37)	1554.2 (1195.9)		1696.2 (1573.3)		1627.1 (1385.0)		0.76
Light box use (days)[d] (*n* = 44)	21.1 (7.5)		21.0 (8.7)		21.0 (8.0)		0.99
Light box use (min)[e] (*n* = 44)	26.2 (7.7)		28.3 (14.7)		27.2 (11.3)		0.55
Treatment credibility (mean score out of 9; *n* = 46)	6.9 (1.5)		6.3 (1.4)		6.6 (1.5)		0.18
Treatment satisfaction (out of 5; *n* = 42)	2.0 (1.0)		2.5 (0.8)		2.2 (0.9)		0.07

Abbreviations: TBI = total body irradiation; PSQI = Pittsburgh Sleep Quality Index.

[a] Dichotomized into White and Other for *t*-test analyses.

[b] Dichotomized into Multiple Myeloma and Other Diagnoses for *t*-test analyses.

[c] Numbers indicate the sample size of complete data on each outcome.

[d] This is the number of days of at least 20 min of light box use.

[e] This is the number of minutes of light box use in the morning.