

# Bright light therapy as a non-pharmacological treatment option for multiple sclerosis-related fatigue: A randomized sham-controlled trial

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## Abstract

**Background:** Fatigue is a common symptom in people with multiple sclerosis (pwMS) that significantly impairs quality of life. Bright light therapy may be a cheap treatment option with little to no adverse events.

**Objectives:** To evaluate the effectiveness of bright light therapy as a treatment option for MS-related fatigue.

**Methods:** This was randomized sham-controlled trial including 26 pwMS with a Fatigue Severity Scale (FSS) Score  $\geq 36$ . Participants were assigned to receive either bright white light therapy ( $n = 13$ ) or dim red light (sham-intervention;  $n = 13$ ). Participants used the respective intervention for 30 min each morning for two weeks, followed by a two-week washout period. The primary endpoint was the difference in FSS scores following light treatment as calculated by analysis of covariance.

**Results:** There was no significant difference in FSS ( $F(1,23) = 2.39, p = .136$ , partial  $\eta^2 = .094$ ). However, FSS scores generally improved over the course of the study in a clinically relevant manner.

**Conclusion:** Bright light therapy decreased FSS scores over the course of this study. However, this effect was not significant in comparison to a sham intervention.

**Keywords:** Multiple sclerosis, fatigue, MS fatigue, bright light therapy, bright white light, randomized controlled trial

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## Introduction

People with multiple sclerosis (pwMS) frequently report fatigue as their most disabling symptom, particularly as it affects several aspects of their lives.<sup>1,2</sup> It interferes with the desire to be active during the daytime and constrains them to reduce their level of activity. Moreover, it can affect performance at work and lead to premature retirement, occupation loss, or lower income.<sup>3</sup> Having a physical, mental, and psychosocial component, treating the different aspects of fatigue might require a customized approach. So far, it is often treated off-label with medications such as amantadine, modafinil, or methylphenidate. The latest research, however, suggests they are not more effective than a placebo while causing more adverse effects.<sup>4</sup>

Physical exercise and cognitive behavioral therapy as non-pharmacological interventions for fatigue have been shown to be moderately effective, with little to no adverse events.<sup>5,6</sup> Bright light therapy (BLT) has been discussed as another non-pharmacological treatment to alleviate symptoms of MS-related fatigue<sup>7,8</sup> and it has been shown to improve fatigue after a traumatic brain injury<sup>9</sup> or cancer-related fatigue.<sup>10</sup>

Environmental light is known to be the strongest *zeitgeber* for our biological clock, responsible to maintain a circadian rhythm which in turn consolidates sleep and wake periods.<sup>11</sup> Beyond that, light also has acute alerting effects, not only during the night by suppressing melatonin secretion via the circadian system, but also during daytime.<sup>12,13</sup> The limbic system may play a

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relevant role in this context, along with the strengthened circadian rhythm.<sup>14</sup> Fatigue has been shown to correlate negatively with alertness.<sup>15</sup> Exposure to bright light for as short as 12 min already induces alertness. In fact, research shows shorter periods of light exposure (under 1 h) to be more efficient than long continuous exposure, with a sustained positive effect for several hours after exposure.<sup>16</sup>

BLT has previously been reported to significantly improve fatigue in other conditions (e.g., traumatic brain injury<sup>9</sup> and cancer-related fatigue<sup>10</sup>). However, underlying mechanisms of fatigue in general, and MS fatigue specifically, are poorly understood.<sup>17</sup> Furthermore, diagnostic tools do not distinguish between primary, secondary, or comorbid fatigue. Thus far, the fact that fatigue symptoms in some studies did respond to BLT, may not apply to MS-related fatigue.

To our knowledge, one randomized controlled trial has investigated BLT in pwMS. This study demonstrated some improvement in Fatigue Severity Scale (FSS<sup>18</sup>) scores; however, this benefit occurred in the control group as well, suggesting a relevant placebo effect.<sup>8</sup> The results from this study may have been limited by (i) applying BLT twice a day, possibly resulting in reduced sleepiness at night and (ii) the fact that participants were not screened for primary sleep disorders with the use of polysomnography (PSG) and multiple sleep latency tests (MSLTs).

Since there is no agreement on the underlying mechanisms of fatigue within MS,<sup>19</sup> much less across different diseases,<sup>20</sup> we need more MS-specific research on the effects of BLT on fatigue. In this randomized-controlled trial, we aimed to compare a BLT intervention to a sham intervention to determine whether BLT can also significantly improve MS-related fatigue.

## Materials and methods

### Participants

We enrolled pwMS fulfilling current McDonald criteria<sup>21</sup> regardless of their disease phenotype and aged between 18 and 65 years. Recruitment took place from December 2019 to October 2021 at the outpatient clinic at the department of neurology, Vienna General Hospital, and the MS Society of Vienna (Multiple Sklerose Gesellschaft Wien). Written informed consent was obtained. The study was conducted according to the World Medical Association Declaration of Helsinki, and the ethics review board at the Medical University of Vienna

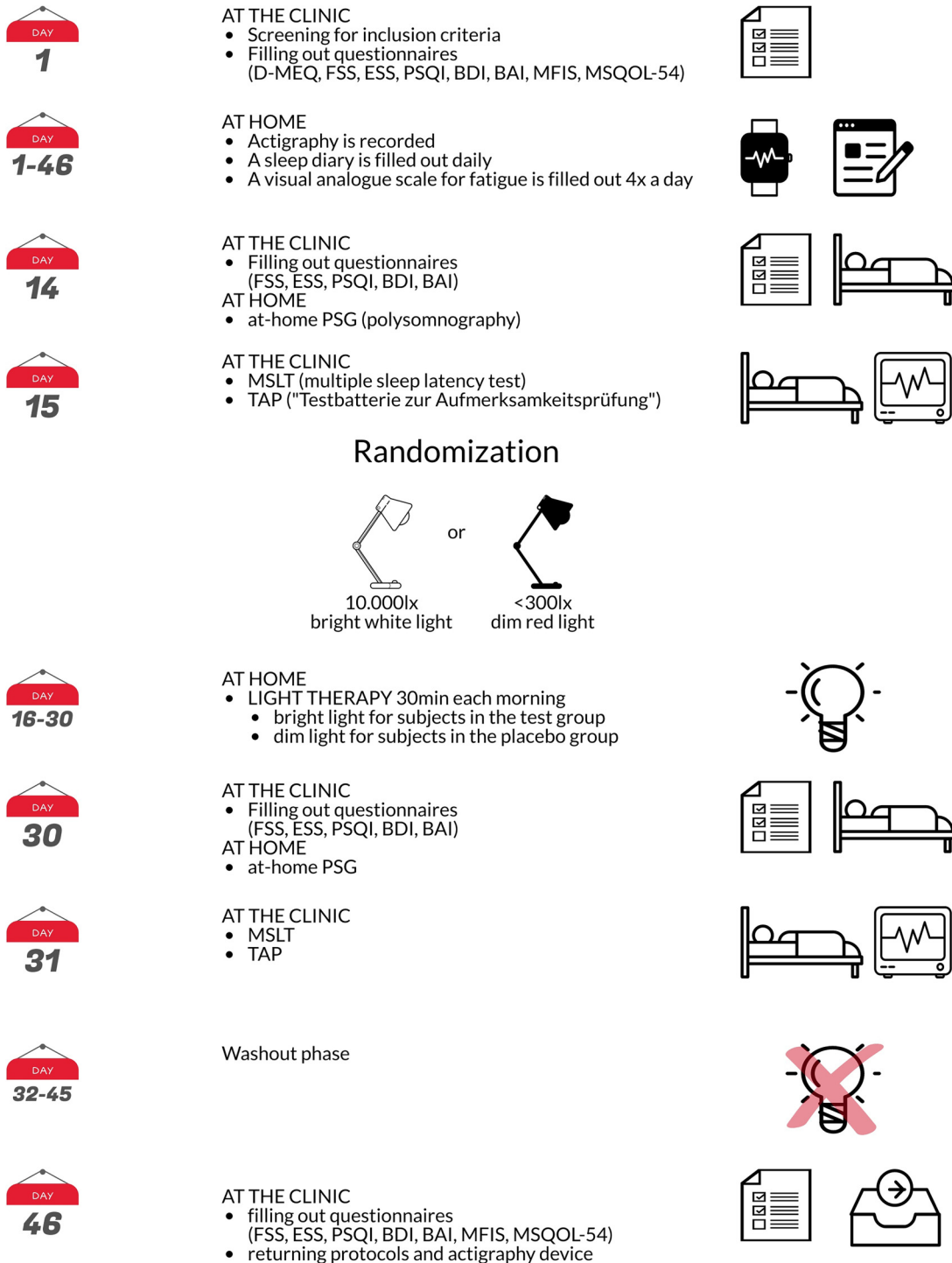
approved this study. All participants included in this analysis fulfilled the following clinical criteria: (1) FSS total score of 36 points or more<sup>22</sup> (2) no MS relapse or change in medications 4 weeks prior to study enrollment or during participation, (3) neutral or moderate chronotypes (Morningness-Eveningness-Questionnaire D-MEQ<sup>23</sup> score between 31 and 69 points), (4) absence of primary sleep disorders (periodic limb movement disorder, sleep apnea, and narcolepsy), as determined by PSG and MSLT within two weeks upon inclusion.

### Study design

This was a double-blind, randomized sham-controlled trial. Prior to recruitment, we used a randomizer website (<https://randomizer.org/>; © 1997–2022 by Geoffrey C. Urbaniak and Scott Plous) to randomly assign each subject ID to either the bright white light therapy (BWL) group or the dim red light (DRL) group. The process of data collection is illustrated in Figure 1. Participants filled out the following questionnaires as a part of this study: FSS, Epworth Sleepiness Scale (ESS),<sup>24</sup> Pittsburgh Sleep Quality Index (PSQI),<sup>25</sup> Beck Depression Inventory (BDI),<sup>26</sup> Beck Anxiety Inventory (BAI),<sup>27</sup> Modified Fatigue Impact Scale (MFIS),<sup>28</sup> Multiple Sclerosis Quality of Life (MSQOL-54),<sup>29</sup> and D-MEQ. Furthermore, participants provided sleep diaries with daily entries throughout the study period (bedtime, subjective sleep efficiency, subjective sleep onset latency, and mood). Further, they recorded their fatigue levels on a visual analogue scale (VAS), ranging from not fatigued at all to very much fatigued, four times every day (9 a.m., 1 p.m., 5 p.m., and 9 p.m.). Additionally, wrist-worn actigraphs recorded movement every thirty seconds, day and night during all six weeks. Finally, PSG and MSLT were each recorded before and after the intervention.

Participants received a lightbox (SunBox<sup>®</sup> SunLight Jr.<sup>®</sup>, The SunBox Company, Frederick, MD, USA), with the instruction to use it every morning within 3 h of waking up for 30 min. They were instructed to put it on the table in front of them, at a height aligned with their eyes and at a distance of 30 cm, at which 10 000 lux were achieved. Participants were instructed to keep their eyes open during the whole 30 min of light therapy. The light boxes were identical in both groups, with the only difference that we installed a filter that dimmed the light to 200 lux and tinted it red, prior to handing it over to participants in the control group.

# Timeline of the trial



**Figure 1.** Timeline of the BLT in MS-related fatigue trial. D-MEQ: morningness-eveningness questionnaire; FSS: fatigue severity scale; ESS: Epworth sleepiness scale; PSQI: Pittsburgh sleep quality index; BDI: Beck depression inventory; BAI: Beck anxiety inventory; MFIS: modified fatigue impact scale; MSQOL-54: multiple sclerosis quality of life; PSG: polysomnography; MSLT: multiple sleep latency test; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

### Outcome measures

Fatigue, as measured with the FSS with an expected difference in means of 15 and an estimated standard deviation of 15.2 (Cohen's  $d=0.99$ ), is the main variable. Based on this Cohen's  $d$  and a desired statistical power level of 0.8 and a probability level of 0.05, a sample size of 18 per group was the aim.<sup>7</sup> The primary outcome measure was the FSS total score after the intervention. With only nine items it is short and quick to complete. The minimally important difference in the FSS total score is 4.05.<sup>30</sup> The FSS measures fatigue severity and based on current research, measuring fatigue in severity, as opposed to dimensions, depicts profiles of MS-related fatigue in a comprehensive manner.<sup>31</sup> The MFIS, on the other hand, measures dimensions of fatigue and was a secondary outcome. Also, mean values on a VAS that our patients filled out four times every day were analyzed as a secondary outcome. Additionally, actigraphy data were analyzed for the "most 10 (M10) average," that is the average activity level count for the sequence of the 10 h of highest activity level per 24 h.

### Statistics

Statistical analyses were performed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA). To test our main hypothesis, we calculated analysis of covariances with (ANCOVA) with the group (BLT or sham) as the independent variable, the FSS score at the end of the intervention period as the dependent variable, and the FSS score at the end of the baseline period as the covariate. We did this to factor out an improvement that is solely based on the heightened awareness of fatigue due to study participation that requires monitoring fatigue levels and the anticipation of improvement due to being enrolled in a study.

To analyze secondary outcomes (MFIS subscores, mean VAS scores, BDI scores, and BAI scores), we calculated student's  $t$ -tests to compare scores pre- and post-intervention, in both the active group and in the control groups. Also, we correlated M10 daytime activity with FSS total scores and calculated student's  $t$ -tests to compare the active group with the control group regarding the change in M10 between baseline and intervention.

All multiple analyses were Bonferroni-corrected. A value of  $p < .05$  was considered statistically significant.

### Results

Initially, we enrolled 39 participants, three volunteers dropped out prematurely, three were excluded due to periodic limb movement disorder, two did not meet

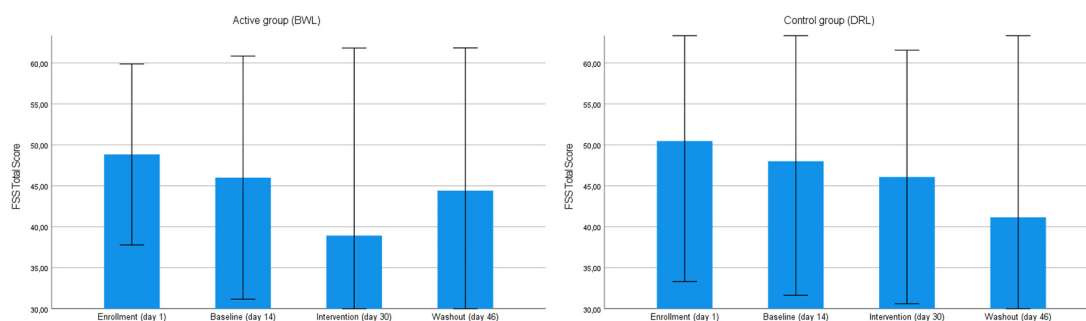
our chronotype criterium, three did not meet the FSS cut-off, one was excluded because of technical errors during PSG and one outlier was excluded. The extreme outlier that was excluded was concerning FSS scores after baseline, which was detected using a boxplot, with an FSS score of 26 when the mean of the sample was  $M=46.26 \pm 8.46$ . 26 (age  $M=43 \pm 11.17$ ; 22 female, 4 male) participants were included in the final analyses. Their clinical characteristics were distributed equally between the two intervention groups (Table 1). Median Expanded Disability Status Scale (EDSS) scores were  $Mdn=3$  for the whole sample,  $Mdn=2$  in the BWL group, and  $Mdn=3.5$  in the DRL group. Regarding the subtypes, 10 were diagnosed with RRMS, and three were diagnosed with SPMS in the BWL group. In the DRL group, eight were diagnosed with RRMS, four were diagnosed with SPMS, and one was diagnosed with PPMS.

As depicted in Figure 2, FSS scores change over the course of the study in both groups. In the BWL group, FSS scores at enrollment are  $M=48.92 \pm 5.3$  and  $M=46.08 \pm 7.11$  after the two-week baseline. It then drops to  $M=39.62 \pm 11.25$  after the intervention. This difference in total scores exceeded the minimally important difference<sup>30</sup> of 4.05. Then, it goes back up to  $M=44.42 \pm 8.71$  after the washout. In the DRL group, FSS scores at enrollment are  $M=50.46 \pm 8.58$  and  $M=48 \pm 8.19$  after the two-week baseline. It then only drops to  $M=46.08 \pm 7.74$  after the sham-intervention, which does not exceed the minimally important difference of 4.05, before it drops further to  $M=41.15 \pm 12.9$  after the washout. However, when comparing the BWL with the DRL group concerning FSS total scores after the intervention and controlling for FSS scores at baseline, ANCOVA revealed no significant difference between groups ( $F(1,23)=2.39$ ,  $p=.136$ , partial  $\eta^2=.094$ ).

Regarding our secondary outcome, the exploratory analysis revealed no significant difference in mean VAS scores during baseline versus intervention in either group (BWL  $t(11)=1.98$ ,  $p=.074$ ; DRL  $t(11)=0.64$ ,  $p=.533$ ). MFIS total scores improved in the BWL group only (BWL  $t(11)=2.31$ ,  $p=.041$ ; DRL  $t(12)=1.69$ ,  $p=.116$ ). Specifically, scores in the physical subscale ( $t(11)=2.24$ ,  $p=.035$ ) and in the cognitive subscale ( $t(11)=2.71$ ,  $p=.02$ ) improved in the BWL group. However, MFIS scores after the intervention did not significantly differ in both study groups ( $t(23)=1.203$ ,  $p=.241$ ). Further, analyses of daytime activity levels (actigraphy M 10) did not

**Table 1.** Demographics and scores of subjects according to treatment group. Age in years, BWL: bright white light; DRL: dim red light; FSS: fatigue severity scale; ESS: Epworth sleepiness scale; PSQI: Pittsburgh sleep quality index, BDI: Beck depression inventory, BAI: Beck anxiety inventory, MFIS: modified fatigue impact scale.

Variable	BWL group ( <i>n</i> = 13)	DRL group ( <i>n</i> = 13)	<i>p</i> -value
Sex (number of female participants)	10	12	.3
EDSS (median)	2	3.5	.08
Age (mean $\pm$ standard deviation)	42.5 $\pm$ 13.4	43.4 $\pm$ 8.9	.85
Years since diagnosis (mean $\pm$ standard deviation)	10.3 $\pm$ 11.2	14.8 $\pm$ 7.1	.25
FSS (mean $\pm$ standard deviation)	48.9 $\pm$ 5.3	50.5 $\pm$ 8.6	.59
ESS (mean $\pm$ standard deviation)	11.2 $\pm$ 3.2	12.9 $\pm$ 2.9	.2
PSQI (mean $\pm$ standard deviation)	7.9 $\pm$ 2.7	7.7 $\pm$ 4.2	.88
BDI (mean $\pm$ standard deviation)	18.1 $\pm$ 11.9	12.9 $\pm$ 7.8	.2
BAI (mean $\pm$ standard deviation)	14.4 $\pm$ 10.6	14.5 $\pm$ 8.9	.98
MFIS (mean $\pm$ standard deviation)	43 $\pm$ 14.9	45.6 $\pm$ 14.5	.66



**Figure 2.** Mean FSS scores according to time point and treatment group; error bars indicate  $\pm 2$ SD. BWL: bright white light; DRL: dim red light; FSS: fatigue severity scale.

**Table 2.** Scores in the questionnaires after the intervention according to treatment group. BWL: bright white light; DRL: dim red light; ESS: Epworth sleepiness scale; PSQI: Pittsburgh sleep quality index; BDI: Beck depression inventory; BAI: Beck anxiety inventory.

Variable	BWL group ( <i>n</i> = 13)	DRL group ( <i>n</i> = 13)	<i>p</i> -value
ESS post-intervention (mean $\pm$ standard deviation)	8.9 $\pm$ 4	12 $\pm$ 3.1	.038
PSQI post-intervention (mean $\pm$ standard deviation)	6.4 $\pm$ 2.3	7.3 $\pm$ 3.3	.436
BDI post-intervention (mean $\pm$ standard deviation)	15.1 $\pm$ 12.1	9.3 $\pm$ 9.1	.188
BAI post-intervention (mean $\pm$ standard deviation)	12.2 $\pm$ 11.9	10.4 $\pm$ 7.3	.654

correlate with FSS Scores ( $r = .26$ ,  $p = .195$ ). Also, when comparing the active group with the control group regarding the change in M10 between baseline in intervention, there was no significant group difference ( $t(24) = -1.01$ ,  $p = .322$ ). When comparing questionnaire scores (ESS, PSQI, BDI, and BAI) after the

intervention period, there were significant differences between the groups only concerning ESS (see Table 2).

### Discussion

We aimed to study the effect of BWL on fatigue severity in pwMS. While we found a clinically

relevant decrease in fatigue severity in the BWL group simultaneously with the intervention, this effect was not significant in comparison to our sham group receiving DRL. We report that no participants had complaints of adverse events or discontinued the intervention prematurely in neither group.

To our knowledge, this study is the first study on BLT in MS-related fatigue to conduct PSG and MSLTs to exclude primary sleep disorders as underlying causes of secondary fatigue. We believe this enabled a more homogenous sample in terms of pathophysiology. Further, we report a decrease in fatigue levels following BLT that is clinically relevant, as it exceeds the minimal clinically meaningful difference.

The exact pathophysiological and cognitive mechanisms of MS fatigue remain elusive<sup>19</sup> and placebo effects are reported in pharmacological<sup>4</sup> as well as non-pharmacological trials.<sup>8</sup> Utilizing the placebo effect poses less of an ethical problem<sup>32</sup> in non-pharmacological treatment options, like BLT, since they have no relevant side effects. It is worth noting that the timepoint of decreased fatigue levels in the group that received a sham intervention is not concurrent to the timepoint of the two week-intervention, while in the group receiving BLT, fatigue improved simultaneously with the two-week intervention period (see Figure 2).

Our study had some limitations. First, our sample size was considerably small. In our case, the main reason for slow recruitment was our elaborate study design which included in-person visits to our outpatient clinic, and rigorous sleep analysis (PSG and MSLT) and filling out protocols up to four times a day for six weeks. Hence, participation may not have been feasible or attractive for a relevant amount of pwMS. Further, we started recruiting less than three months before our country issued the first COVID-19 lockdown severely affecting our capacity to recruit patients. We also believe the current pandemic also diminished the therapeutic effect of BLT itself. Studies on the impact of the COVID-19 pandemic on pwMS revealed a greater personal impact of fatigue, decreased sleep quality, and poorer mental health.<sup>33,34</sup> Another limitation of our study is that exposure to natural light varies across the four seasons and we did not ask our participants to monitor their time spent outside. Light intensity in an everyday indoor environment is 50–200 lux in a living room or 300–500 lux in an office. In contrast, bright light therapy lamps

usually provide 5 000–10 000 lux<sup>35</sup> and natural daylight ranges from 10 000 lux on cloudy days to up to 100 000 lux on days with clear skies.

While failing to demonstrate an effect of BWL that goes beyond that of a placebo effect, our results are in agreement with the favorable impact of BWL on MS-fatigue reported.<sup>8</sup> Future studies should include a larger sample and could benefit from monitoring environmental light exposure. This could help determine whether bright light is effective to counteract MS-related fatigue. Our study included an analysis of daytime activity levels in an effort to have an objective marker of decreased activity resulting from fatigue. However, in accordance with another study,<sup>36</sup> fatigue and daytime activity levels in our study did not correlate either. The fact that the subjective complex symptom “fatigue” did not correlate with daytime activity in our study emphasizes the need for good and validated fatigue scales in future research to objectify a possible therapeutic effect of BLT. Since mean M10 over the course of two weeks did not correlate with fatigue levels, a more detailed analysis of smaller time frames of actigraphy data could also shine a light on a possible real-time connection between fatigue levels and physical activity.

### Conclusion

In our sample, bright light therapy decreased FSS scores. However, this effect was not significant in comparison to a sham intervention.

This study was registered with [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04681586).




### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Supplemental material

Supplemental material for this article is available online.

## References

1. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler* 2006; 12: 367–368.
2. Krupp LB, Alvarez LA, LaRocca NG, et al. Fatigue in multiple sclerosis. *Arch Neurol* 1988; 45: 435–437.
3. Krause JS, Dismuke-Greer C, Jarnecke M, et al. Employment and gainful earnings among those with multiple sclerosis. *Arch Phys Med Rehabil* 2018; 100: 931–937.
4. Nourbakhsh B, Revirajan N, Morris B, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol* 2021; 20: 38–48.
5. Razazian N, Kazeminia M, Moayedi H, et al. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurol* 2020; 20: 93.
6. Braley TJ and Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* 2010; 33: 1061–1067.
7. Mateen FJ, Manalo NC, Grundy SJ, et al. Light therapy for multiple sclerosis-associated fatigue: study protocol for a randomized controlled trial. *Medicine (Baltimore)* 2017; 96: e8037.
8. Mateen FJ, Vogel AC, Kaplan TB, et al. Light therapy for multiple sclerosis-associated fatigue: a randomized, controlled phase II trial. *J Neurol* 2020; 267: 2319–2327.
9. Quera Salva MA, Azabou E, Hartley S, et al. Blue-enriched white light therapy reduces fatigue in survivors of severe traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil* 2020; 35: E78–E85.
10. Johnson JA, Garland SN, Carlson LE, et al. Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv* 2018; 12: 206–215.
11. Dijk D-J and Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995; 15: 3526–3538.
12. Cajochen C. Alerting effects of light. *Sleep Med Rev* 2007; 11: 453–464.
13. Xu Q and Lang CP. Revisiting the alerting effect of light: a systematic review. *Sleep Med Rev* 2018; 41: 39–49.
14. Rautkylä E, Puolakka M and Halonen L. Alerting effects of daytime light exposure - a proposed link between light exposure and brain mechanisms. *Lighting Res Technol* 2012; 44: 238–252.
15. Shahid A, Chung SA, Maresky L, et al. The Toronto hospital alertness test scale: relationship to daytime sleepiness, fatigue, and symptoms of depression and anxiety. *Nat Sci Sleep* 2016; 8: 41–45.
16. Chang A-M, Santhi N, St Hilaire M, et al. Human responses to bright light of different durations. *J Physiol* 2012; 590: 3103–3112.
17. Penner IK and Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol* 2017; 13: 662–675.
18. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121–1123.
19. Manjaly Z-M, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *Neurol Neurosurg Psychiatry* 2019; 90: 642–651.
20. Finsterer J and Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care* 2014; 31: 562–575.
21. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
22. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler* 2002; 8: 523–526.
23. Griefahn B, Künemund C, Bröde P, et al. The validity of a German version of the morningness-eveningness-questionnaire developed by Horne and Östberg. *Somnologie - Schlafforschung und Schlafmedizin* 2001; 5: 71–80.
24. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
25. Buysse DJ, Reynolds CF3rd, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193–213.
26. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561–571.
27. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; 56: 893–897.
28. Larson RD. Psychometric properties of the modified fatigue impact scale. *Int J MS Care* 2013; 15: 15–20.
29. Vickrey BG, Hays RD, Harooni R, et al. A health-related quality of life measure for multiple sclerosis. *Qual Life Res* 1995; 4: 187–206.
30. Rooney S, McFadyen A, Wood L, et al. Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis. *Mult Scler Relat Disord* 2019; 35: 158–163.
31. Beckerman H, Eijssen IC, Meeteren J, et al. Fatigue profiles in patients with multiple sclerosis are based on severity of fatigue and not dimensions of fatigue. *Sci Rep* 2020; 10: 4167.
32. Nourbakhsh B, Waubant E, Evers AWM, et al. Ethical considerations in the treatment of multiple sclerosis fatigue. *Mult Scler Relat Disord* 2021; 54: 103129.

33. Stojanov A, Vojinovic S, Stojanov J, et al. Quality of sleep and fatigue in patients with the relapsing-remitting multiple sclerosis during the coronavirus disease-2019 pandemic. *Clin Neurol Neurosurg* 2021; 205: 106640.
34. Motolese F, Rossi M, Albergo G, et al. The psychological impact of COVID-19 pandemic on people with multiple sclerosis. *Front Neurol* 2020; 11: 580507.
35. Münch M and Bromundt V. Light and chronobiology: implications for health and disease. *Dialogues Clin Neurosci* 2012; 14: 448–453.
36. Braakhuis H, Berger M, van der Stok G, et al. Three distinct physical behavior types in fatigued patients with multiple sclerosis. *J Neuroeng Rehabil* 2019; 16: 105.