

Transcranial Bright Light and Symptoms of Jet Lag: A Randomized, Placebo-Controlled Trial

Heidi Jurvelin; Jari Jokelainen; Timo Takala

- BACKGROUND:** Rapid travel over multiple time zones usually results in transient de-synchronization between environmental time and the biological clock of the individual. Common symptoms are increased daytime sleepiness, reduced sleep duration and quality, and performance impairments. Exposure to ocular bright light is known to alleviate jet lag symptoms and facilitate adaptation to a new time zone. Recently, transcranial bright light (TBL) via the ear canals has been shown to have antidepressant, anxiolytic, and psychomotor performance-enhancing effects. In this case we studied whether intermittent TBL exposure can alleviate jet lag symptoms in a randomized, double-blind, placebo-controlled study.
- METHODS:** Intermittent light exposures (4×12 min; day 0: 08:00, 10:00, 12:00, 14:00; days 1-6: 10:00, 12:00, 14:00, 16:00) were administered during the 7-d post-travel period after an eastward transatlantic flight. The symptoms of jet lag were measured by the Visual Analog Scale (VAS), the Karolinska Sleepiness Scale (KSS), and the Profile of Mood States (POMS).
- RESULTS:** We found a significant reduction of overall jet lag symptoms (VAS), subjective sleepiness (KSS), and the fatigue, inertia, and forgetfulness subscales of the POMS when comparing the active TBL treatment group ($N = 25$) to the placebo group ($N = 30$). For example, the normalized values of VAS in the TBL, but not the placebo, group returned to pre-travel levels by the final post-travel day (6.16 vs. 15.34).
- DISCUSSION:** Results suggest a cumulative effect of TBL, as the effects emerged on post-travel days 3-4. Intermittent TBL seems to alleviate jet lag symptoms.
- KEYWORDS:** field study, jet lag, Karolinska Sleepiness Scale, Profile of Mood States, Visual Analog Scale.

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Jet lag is a phenomenon that occurs when the endogenous circadian timing system becomes desynchronized from external time due to rapid travel across several time zones, and has been classified as a circadian rhythm disorder in the DSM-5.¹ The endogenous circadian rhythm is under the control of the suprachiasmatic nucleus. Light, which is the main signal that synchronizes the endogenous circadian clock,⁶ is transmitted to the suprachiasmatic nucleus via intrinsically photosensitive retinal ganglion cells in the eye that contain the photopigment melanopsin.⁹ Light can be used to alleviate symptoms of jet lag, as several laboratory studies in humans have shown that correctly timed bright light can shift the internal biological rhythm to facilitate a faster adaptation to a new time.¹⁹

Symptoms of jet lag include sleep disturbances, drowsiness during the day, reduced alertness, poor overall performance, cognitive deficits, fatigue, irritation, anxiety, depression, and gastrointestinal dysfunction.²⁰ The severity of jet lag symptoms

depends on the number of time zones crossed, the direction of travel, the time of day of the flight, and possibly the time of year,³⁰ as well as individual parameters such as age, chronotype, and physical health.^{2,18} Jet lag symptoms dissipate as the internal clock shifts gradually toward the external time.⁸

There are only a few field studies that have explored light as a countermeasure to treat the symptoms of jet lag. These studies show a modest entraining effect³ and increased sleep effectiveness,²¹ but no effect on performance or subjective jet lag symptoms.^{3,13,27} Earlier studies on the effect of transcranial bright light (TBL) suggest that TBL enhances quantitative

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electroencephalographic power and low-resolution electromagnetic activity in the parahippocampal areas,¹⁵ increases functional connectivity and activity in the sensorimotor and visual cortices in fMRI imaging,²³ and improves motor reaction time.²⁸ The aim of this study was to investigate the effects of intermittent TBL exposure on overall jet lag symptoms in a placebo-controlled, double-blind field study.

METHODS

Subjects

A total of 55 healthy male subjects 25–50 yr old (mean age \pm SD: 39 ± 7 yr) completed the study. In order to minimize interindividual variation and the impact of confounding variables other than the administration of TBL, we only studied male subjects and excluded women. Subjects were recruited through newspaper ads. To qualify for the study, subjects were required to travel by plane from Finland (time zone: +2) to North America (time zone: –5 to –8) and stay a minimum of 1 wk in their destination time zone. Subjects reporting alcohol or drug abuse, unstable somatic disease, psychotic medication, medication affecting the central nervous system, shift work during the preceding 2 mo, or travel across several time zones during the preceding month were excluded from the study. The research protocol was approved by the Ethical Committee of Oulu University Hospital, Finland, in compliance with the Declaration of Helsinki and conformed to international ethical standards. Written informed consent was obtained from the subjects prior to the study.

Equipment

During the post-travel period, subjects were exposed to TBL or placebo treatment four times per day for 12 min each (48 min per day total) at predetermined times. TBL or placebo exposures were administered every 2 h between 08:00 and 14:00 on travel day 0 and every 2 h between 10:00 and 16:00 on post-travel days 1–6. The bright light (luminous flux: 3.5 lm; illuminance: 9100 lux measured at a distance of 1 cm; irradiance: $4.3 \text{ mW} \cdot \text{cm}^{-2}$ measured at a distance of 1 cm; photon density: $1.13 \times 10^{16} \text{ photons} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$) was produced using white LEDs with a peak in the short-wavelength blue region at 448 nm. The study device and spectral distribution of the LEDs is presented in **Fig. 1A**.

Procedure

The study was divided into three consecutive periods: the baseline period (1 wk), the travel period (at least 1 wk of travel), and the post-travel period (1 wk). The post-travel period started on the day of return (i.e., post-travel day 0). Jet lag symptoms were measured at home using the following self-rating questionnaires on the first study day (Baseline) and during the post-travel period: the Karolinska Sleepiness Scale (KSS),³¹ the Horne-Östberg Morningness-Eveningness Questionnaire,¹⁰ the Visual Analog Scale (VAS), the State-Trait Anxiety Inventory (STAI-Y1),²² and the shortened Finnish version¹¹ of the

Profile of Mood States (POMS).¹⁴ The questionnaires were filled out twice per day at predetermined times (12:00 and 17:00). Subjects recorded their sleep-wake schedules in a sleep diary. Subjects were also asked to report any adverse effects during the trial. The details of the protocol are presented in **Fig. 1B**.

The subjects were randomly assigned to the bright light treatment ($N = 25$) group or the placebo ($N = 30$) group. The randomization was planned and implemented by a person outside of the research group to ensure that both subjects and researchers were blind to the group assignment. In the treatment group, bright light was administered transcranially via the ear canals. The study set-up for the placebo group was the same except that the bright light device was inactive. For both groups, the headset part of the bright light device was covered using customized earmuffs during the exposures to ensure that the subjects were blind to the condition they received. The earmuffs were equipped with detectors that ensured that the exposure was automatically discontinued if the device was used inappropriately, displaced, or removed during the treatment. In addition, the device could not be started if the headset was not in place on the head. Neither the subject nor the researcher could know or visually determine to which group a subject belonged due to the placebo-controlled, double-blind study design.

Statistical Analysis

Data were analyzed using the intent-to-treat method. Two-sample independent *t*-tests with equal variance were conducted in OriginPro 8.5 (OriginLab Corporation, Northampton, MA) to compare demographic data, baseline questionnaire responses, and sleep parameters across the two groups. To account for any possible differences between the two groups at baseline, the questionnaire and sleep data collected during the intervention week (i.e., post-travel days 0–6) were normalized, i.e., *z*-score transformed as a function of the baseline (pre-travel) population mean and SD across all subjects.

Two-way repeated measures ANOVA (PROC Mixed in SAS 9.3; SAS Institute, Cary, NC) were conducted for the normalized VAS, KSS, STAI-Y1, and POMS subscales. Model 1 tested group (TBL vs. placebo) as a between-subjects factor and time of data collection (12:00 and 17:00) as a within-subjects factor with a group \times time interaction. Model 2 tested group and trial (within-subject factor) and group \times trial interactions. Model 3 combined measurements that occurred on the same day (e.g., measurements 3 and 4 = day 0, etc.) to test group and day (within-subject factor) and group \times day interactions. Sleep diary data were analyzed using two-way repeated measures ANOVAs for the effect of the group (TBL vs. placebo), day, and group \times day interactions. Post hoc analyses were conducted in PROC Multtest (SAS 9.3) using a Bonferroni correction for multiple comparisons. All $P < 0.05$ were considered significant.

The recovery analysis was conducted to determine the effectiveness of TBL in alleviating jet lag symptoms. For this purpose, we determined a criterion for recovery such that subjects were defined as ‘recovered’ from jet lag if their normalized VAS score was less than 2 (where 0 = baseline value) by the end of the post-travel period.

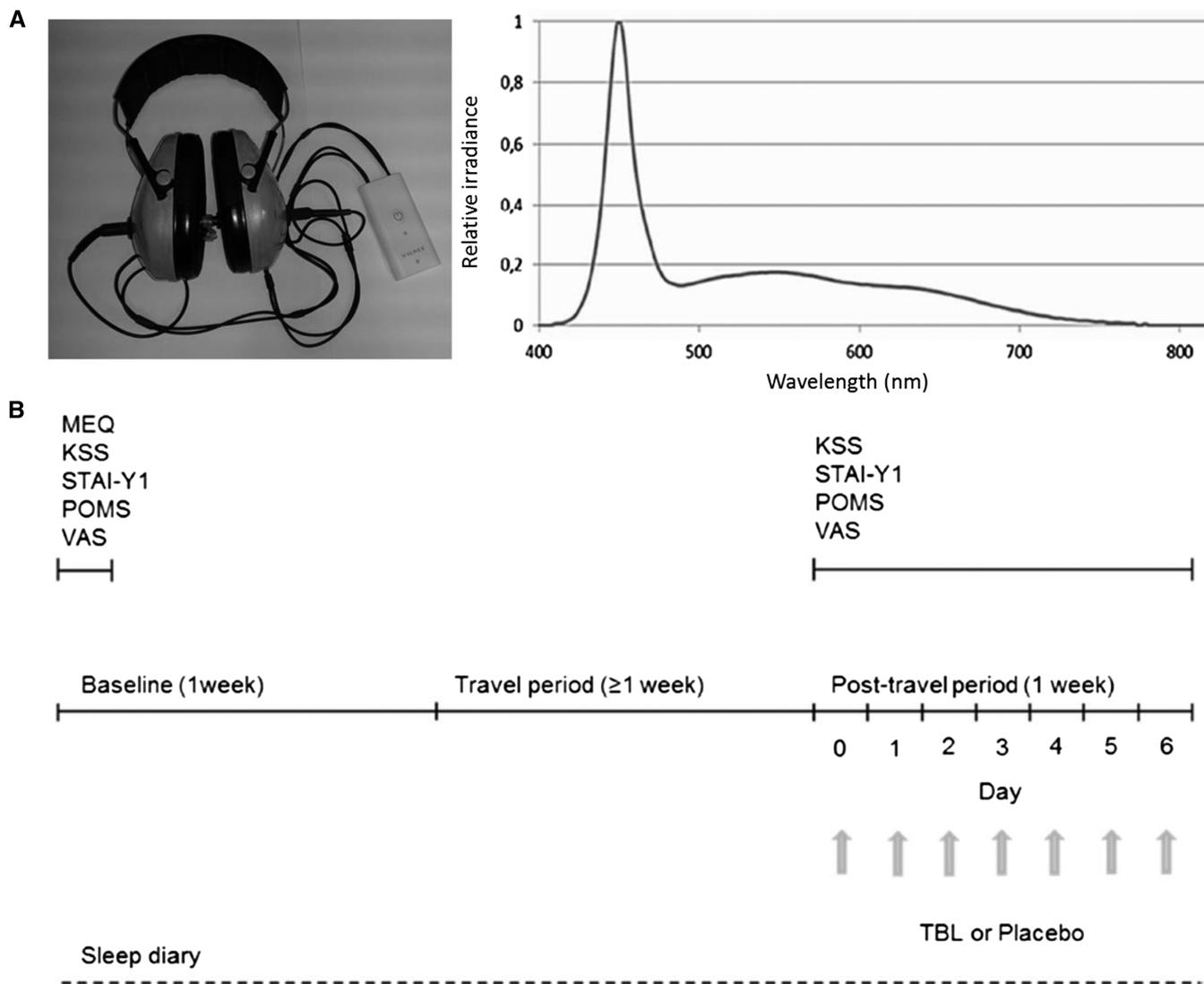


Fig. 1. The experimental design for the jet lag study. A) The study device and spectral distribution of transcranially administered bright light. Irradiance and photon density measured in a distance of 1 cm from the light source were $4.3 \text{ mW} \cdot \text{cm}^{-2}$ and $1.13 \times 10^{16} \text{ photons} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$, respectively. B) Study protocol. TBL, transcranial bright light; MEQ, Morningness-Eveningness Questionnaire; VAS, Visual Analog Scale; KSS, Karolinska Sleepiness Scale; POMS, Profile of Mood States; STAI-Y1, State-Trait Anxiety Inventory.

RESULTS

A total of 55 subjects completed the study and were included in the intent-to-treat analysis. Demographic data and baseline questionnaire responses are presented in **Table I**. There were no significant differences between the TBL and placebo group for any of the demographic data or baseline questionnaire responses, except for the baseline KSS score, for which the placebo group reported higher subjective sleepiness at baseline.

A significant difference between the TBL and placebo group [group \times trial interaction: $F(13, 625) = 1.81$; $P = 0.0383$; group \times day interaction: $F(6, 296) = 3.35$; $P = 0.0033$] was observed for the VAS for overall jet lag symptoms. The TBL group reported a significantly lower VAS score on post-travel days 4 and 5 ($P = 0.0071$ and $P = 0.0403$, respectively) and a

trend toward significance on post-travel day 6 ($P = 0.0685$) compared with the placebo group (see **Fig. 2A**).

Subjective sleepiness (KSS) was lower in the TBL group compared with the placebo group when each trial was binned by measurement day [group \times day interaction: $F(6311) = 2.13$; $P = 0.05$], but not when the trials were analyzed separately [group \times trial interaction: $F(13,659) = 1.32$; $P = 0.1958$]. The TBL group rated themselves as significantly less sleepy on post-travel days 4 and 5 ($P = 0.0029$ and 0.0043 , respectively) with a trend toward significance on post-travel days 3 and 6 ($P = 0.0592$ and 0.0809 , respectively) compared with the placebo group (see **Fig. 2B**).

No significant difference in anxiety (STAI-Y1) symptoms was observed between the TBL and placebo groups across trials (group \times trial interaction: $P = 0.7244$) or across days (group \times day interaction, $P = 0.3943$; see **Fig. 2C**). Significant differences

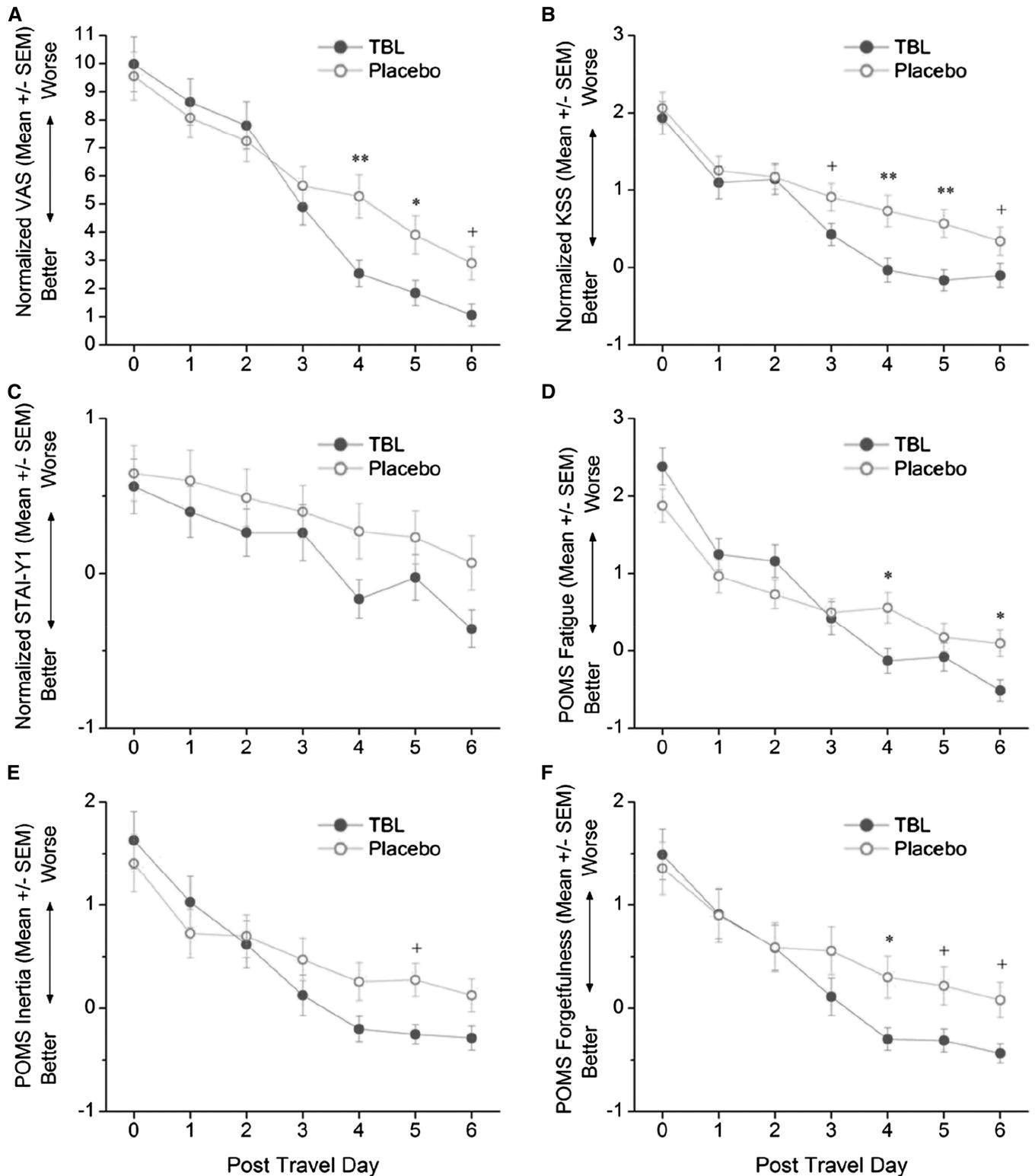


Fig. 2. The effect of TBL treatment on subjective symptoms of jet lag studied by Visual Analog Scale (VAS), Karolinska Sleepiness Scale (KSS), and State-Trait Anxiety Inventory (STAI-Y1) for the jet lag symptoms and the Profile of Mood States (POMS) subscales for fatigue, inertia, and forgetfulness. Positive values on the y-axis represent a Z-score worse than the pre-travel baseline value, negative values indicate a Z-score better than baseline, and 0 indicates a Z-score equivalent to baseline. Data are represented as mean \pm SEM, * $P < 0.1$; * $P < 0.05$; ** $P < 0.01$. A) Results for the VAS. B) Results for the KSS. C) Results for the STAI-Y1. D) Results for the POMS fatigue scale. E) Results for the POMS inertia scale. F) Results for the POMS forgetfulness scale.

Table 1. Jet Lag Study Baseline Demographic Characteristics.

PARAMETER	TBL (MEAN ± SD)	PLACEBO (MEAN ± SD)	P-VALUE
N	25	30	
Age (yr)	38 ± 7	39 ± 7	0.79
Weight (kg)	83 ± 11	82 ± 10	0.78
Height (cm)	181 ± 6	179 ± 6	0.34
Travel length (d)	11 ± 4	11 ± 5	0.70
Time zone	-6 ± 2	-6 ± 1	0.92
MEQ	17.5 ± 3.7	18.9 ± 3.6	0.17
VAS (cm)	0.03 ± 0.06	0.21 ± 0.52	0.10
KSS	2.5 ± 0.9	3.3 ± 1.3	0.02
STAI-Y1	32.4 ± 4.7	33.1 ± 5.6	0.64
POMS fatigue	2.3 ± 1.7	2.9 ± 1.8	0.21
POMS inertia	1.1 ± 1.3	1.2 ± 1.6	0.90
POMS forgetfulness	1.1 ± 1.2	1.4 ± 1.6	0.52
POMS tension	1.7 ± 1.9	2.0 ± 1.8	0.56
POMS depression	0.8 ± 1.3	1.0 ± 2.3	0.62
POMS irritability	1.6 ± 2.3	1.1 ± 1.8	0.43
POMS confusion	1.1 ± 1.5	1.0 ± 1.9	0.87
POMS vigor	16.9 ± 4.0	14.9 ± 4.9	0.10
Sleep Duration (h)	7.1 ± 0.7	7.2 ± 0.8	0.36
Sleep Quality	2.6 ± 0.5	2.5 ± 0.5	0.34
Caffeine Use (dl)	3.5 ± 2.1	4.3 ± 2.6	0.19
Alcohol Use (portion)	1.5 ± 1.3	1.2 ± 1.1	0.47
Number of naps	0.1 ± 0.2	0.2 ± 0.2	0.17
Nap duration (h)	0.1 ± 0.2	0.2 ± 0.3	0.13

The values for the TBL and placebo groups are presented as the mean ± SD. TBL, transcranial bright light; MEQ, Morningness-Eveningness Questionnaire; VAS, Visual Analog Scale; KSS, Karolinska Sleepiness Scale; STAI-Y1, State-Trait Anxiety Inventory; POMS, Profile of Mood States.

between the TBL and placebo groups were observed in subscales of POMS for feelings of fatigue, inertia, and forgetfulness [group × day interactions: $F(6309) = 5.62$; $P < 0.0001$; $F(6309) = 2.62$; $P = 0.0171$; and $F(6309) = 3.55$; $P = 0.0021$, respectively] (Fig. 2D, Fig. 2E, and Fig. 2F). Compared with the placebo group, the TBL group reported less fatigue on post-travel days 4 ($P = 0.0120$) and 6 ($P = 0.0266$), a trend toward less inertia on post-travel day 5 ($P = 0.0678$), and less forgetfulness on post-travel day 4 ($P = 0.0410$). In addition, a trend toward less forgetfulness was observed on post-travel days 5 ($P = 0.0720$) and 6 ($P = 0.0770$). There were no significant differences between the TBL and placebo groups for the tension, depression, irritability, confusion, or vigor subscales (details not shown).

No significant differences between the TBL and placebo groups were observed for any of the sleep diary parameters (e.g., sleep duration, sleep quality, caffeine or alcohol use, number or duration of naps)(details not shown). None of the 55 subjects reported any adverse effects as a result of the treatment. According to the recovery analysis, more subjects in the TBL group had recovered, i.e., normalized VAS score was less than 2 by post-travel day 6 compared with the placebo group [Fisher's Exact Test, Mantel-Haenszel $\chi^2(1) = 4.3036$, $P = 0.0380$; see Fig. 3].

DISCUSSION

This randomized, double-blind, placebo-controlled field study demonstrates that intermittent transcranial bright light

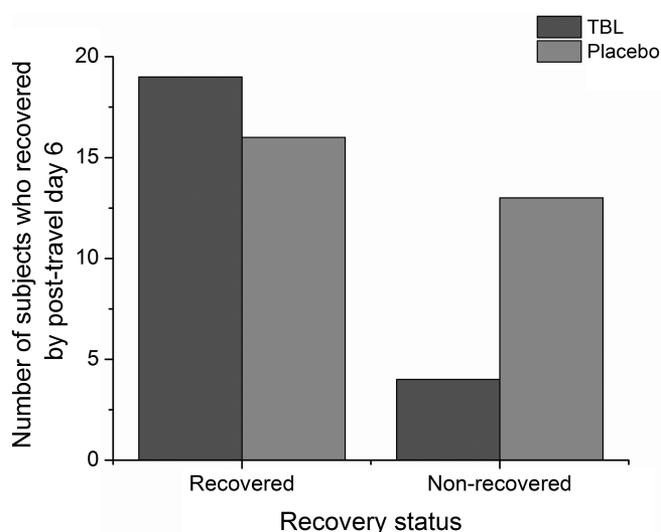


Fig. 3. Recovery analysis. Results of the number of subjects who recovered by the end of the treatment period based on the Visual Analog Scale (VAS) for jet lag symptoms (Fisher's Exact Test). TBL, transcranial bright light.

exposure via the ear canals alleviates jet lag symptoms. Up to four doses of TBL per day significantly reduced overall post-travel jet lag symptoms as well as subjective feelings of fatigue, inertia, and forgetfulness. On average, subjects in the TBL group showed a greater rate of overall recovery based on their VAS scores than subjects in the placebo group. Interestingly, a significant effect of TBL was not observed until post-travel day 4, which may indicate a cumulative effect of the TBL treatment.

The exact underlying neurophysiological mechanisms of transcranial bright light treatment are not fully understood at this point. Recently published studies have shown that transcranial bright light does not suppress melatonin secretion.^{4,12} However, there is evidence that the effect may be mediated by photosensitive opsins similar to the intrinsically photosensitive retinal ganglion cells that recently have been found in extraretinal tissue in the human brain.²⁶ Given that external light can also penetrate the human brain transcranially,^{15,29} these results suggest a general light sensitivity of the brain, which is supported by the findings of TBL exposure modulating brain function^{15,23} and improving psychomotor function.²⁸

The observed effects on the subjective measures of jet lag in the present study are more promising than the findings in earlier bright light field-based studies conducted with considerably small subject groups, such as 20,³ 15,¹³ 4,²¹ and 22²⁷ subjects, and in line with findings in corresponding field-based studies that have used pharmacological aids such as melatonin and sleeping aids which report significantly decreased sleepiness and overall symptoms of jet lag and increased sleep quality and mood with cohorts of 20,¹⁶ 52,¹⁷ 137,²⁴ and 320²⁵ subjects.

The effect of intermittent transcranial light treatment on jet lag symptoms was measured after traveling eastwards. The intensity and duration of a single dose of TBL was based on the earlier TBL studies.^{23,28} Intermittent light exposure has been found to be effective in resetting the human circadian system,

and it is a more feasible and convenient method of administering bright light.⁵ The individual light exposure timing is critical because the direction of the shift is dependent on circadian phase, e.g., the core body temperature minimum, a marker of the phase of the endogenous circadian rhythm. Eastward travelers are usually recommended to avoid light before the body temperature minimum (T_{\min}) and seek light following their T_{\min} in order to facilitate a phase advance.³⁰ However, when traveling east, the avoidance of ambient light exposure prior to the T_{\min} is challenging under field conditions as the number of time zones crossed grows, especially across eight or more time zones.⁵ Thus, in this field study, we chose a protocol developed for phase shift studies with ocular light treatment that used delays instead of advances. The model in this study was based on the delaying model for travelers crossing more than seven time zones eastward introduced by Eastman & Burgess.⁷ Post-travel day 0 was the day of travel back to Finland. Depending on the timing of the flight, the subjects started their treatment on the plane and in some cases also completed all four TBL doses for post-travel day 0 on the plane.

One of the limitations of this study is that we did not measure the underlying circadian rhythm of the subject. In addition, the amount of ambient light the subjects were exposed to during the study period was not controlled. Further studies on the effect of TBL on phase shifting and after westward travel are needed.

This randomized, double-blind, placebo-controlled TBL study conducted under field conditions shows that an alternative route of light administration, i.e., transcranially, significantly reduces jet lag symptoms. Subjects who received transcranial bright light via the ear canals reported significantly less sleepiness, fatigue, inertia, and forgetfulness during the post-travel period than those who were in the placebo group. Intermittent transcranial bright light administered via the ear canals is, therefore, able to alleviate measurable symptoms of jet lag.

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H. Jurvelin works for Valkee Ltd., the company that markets the transcranial bright light device, and T. Takala is a minor shareholder. J. Jokelainen declares no conflicts of interest.

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