NeuroRehabilitation 44 (2019) 341–351
DOI:10.3233/NRE-182565
IOS Press

Original Research

An exploratory investigation of the effect of naturalistic light on depression, anxiety, and cognitive outcomes in stroke patients during admission for rehabilitation: A randomized controlled trial

Anders West[a,b,*], Sofie Amalie Simonsen[a], Alexander Zielinski[a], Niklas Cyril[a], Marie Schønsted[a], Poul Jennum[b,c], Birgit Sander[b,d] and Helle K. Iversen[a,b]
[a]*Department of Neurology, Clinical Stroke Research Unit, Rigshospitalet Glostrup, Glostrup, Denmark*
[b]*Faculty of Health Sciences, University of Copenhagen, Denmark*
[c]*Department of Neurophysiology, Danish Center for Sleep Medicine, Rigshospitalet Glostrup, Glostrup, Denmark*
[d]*Department of Ophthalmology, Rigshospitalet Glostrup, Glostrup, Denmark*

Abstract.
BACKGROUND: Patients admitted for rehabilitation often lack sufficient natural light to entrain their circadian rhythm.
OBJECTIVE: Installed diurnal naturalistic light may positively influence the outcome of depressive mood, anxiety, and cognition in such patients.
METHODS: A quasi-randomized controlled trial. Ninety stroke patients in need of rehabilitation were randomized between May 1, 2014, and June 1, 2015 to either a rehabilitation unit equipped entirely with always on naturalistic lighting (IU), or to a rehabilitation unit with standard indoor lighting (CU).

Examinations were performed at inclusion and discharge. The following changes were investigated: depressive mood based on the Hamilton Depression scale (HAM-D_6) and Major Depression Inventory scale (MDI), anxiety based on the Hospital Anxiety and Depression Scale (HADS), cognition based on the Montreal Cognitive Assessment (MoCA) and well-being based on the Well-being Index (WHO-5).
RESULTS: Depressive mood (MDI $p = 0.0005$, HAM-D6 $p = 0.011$) and anxiety (HADS anxiety $p = 0.045$) was reduced, and well-being (WHO-5 $p = 0.046$) was increased, in the IU at discharge compared to the CU. No difference was found in cognition (MoCA $p = 0.969$).
CONCLUSIONS: This study is the first to demonstrate that exposure to naturalistic light during admission may significantly improve mental health in rehabilitation patients. Further studies are needed to confirm these findings.

Keyword: Circadian rhythm, stroke, clinical trial, depression, anxiety, cognitive, light

1. Introduction

Stroke patients often have, in addition to physical disabilities, cognitive impairments, depression, and anxiety, all of which reduce their quality of life.

*Address for correspondence: Anders Sode West, Department of Neurology, Clinical Stroke Research Unit, Rigshospitalet Glostrup, Valdemar Hansens Vej 1-23, 2600 Glostrup, Denmark. Tel.: +4521748587; E-mail: anders.sode.west@regionh.dk.

Improving the rehabilitation process is essential for increasing quality of life and reducing the socioeconomic costs in relation to stroke.

The circadian response is especially sensitive for short-wavelength blue light because of the blue light-sensitive photopigment melanopsin, which communicates with the suprachiasmatic nucleus (SCN) through the retinohypothalamic tract (RHT) (Thapan, Arendt, & Skene, 2001). As sunlight contains blue light, it is essential to imitate the stimulation during the day to entrain the circadian rhythm.

The circadian rhythm is responsible for the circadian expression and activity of several neurotransmitters and circadian-controlled genes known as clock genes. These genes are expressed in many areas of the brain and have a substantial influence on mood (Kim et al., 2015). Whether circadian influence stands alone regarding the prevention of mood disorders or the blue spectrum of light has a more direct physical impact on mood behavior is unclear (Alkozei, Smith, & Killgore, 2016). However, a circadian influence on depressive mood is becoming clear (McClung, 2007).

Post-stroke depression (PSD) occurs in 30–40% of patients and is significantly associated with increased mortality, new stroke incidence, and decreased activity of daily living (Everson, Roberts, Goldberg, & Kaplan, 1998). PSD has been associated with lesion location, infarct size, neurotransmitter disturbances, reduced hippocampal neurogenesis, immune dysfunction, and hypothalamic-pituitary-adrenal axis activation, but anatomically and psychologically there is no clear evidence linking brain lesions to PSD (Feng, Fang, & Liu, 2014).

Mood is well known to change seasonally in healthy people, and light has a therapeutic effect on this mood behavior. The activity in the mood-related brain areas is affected by dose-dependent bright light and blue wavelength light (Alkozei et al., 2016). Studies imply that bright light can decrease non-seasonal depression and elevate serotonin turnover in the brain (Lam et al., 2016). This is also supported by the few published clinical trials in which light interventions (i.e., exposure to bright light) in combination with antidepressants were reported to decrease depressive mood in hospitalized patients. Only four prior studies have had depressive mood as the primary outcome and light as the only intervention. Of these studies, only Kopp et al. demonstrated significantly reduced depressive mood after light intervention (Giménez et al., 2016; Hickman et al., 2007; Kopp et al., 2016; Leichtfried et al., 2014).

Post stroke anxiety (PSA) is frequent after stroke like depression, and a meta-analysis reported that 18% of stroke survivors meet the diagnostic criteria for a PSA disorder (Campbell Burton et al., 2012), with decreased quality of life (Ayerbe, Ayis, Crichton, Wolfe, & Rudd, 2014), There are a range of treatments for PSA in the general population, but whether they are effective for PSA is uncertain. Even though proper treatment and suitable interventions are lacking (Campbell Burton et al., 2012), light seems to reduce the activity in anxiety-related brain areas (Fisher et al., 2014). However, we found no studies that investigated the effect of light intervention on anxiety outcome alone in hospitalized patients.

The prevalence of post-stroke cognitive impairment varies depending on the diagnostic criteria but ranges from 7.5% to 72% (Mohd Zulkifly, Ghazali, Che Din, Singh, & Subramaniam, 2016). The impaired cognition levels among rehabilitation patients could be associated with circadian desynchronization (Paradee, Rapport, Hanks, & Levy, 2005), and improvements in cognition may be under the influence of light (Riemersma-van der Lek et al., 2008) and physiological modulation in areas controlling cognition (Perrin et al., 2004). The physiology underlying circadian disturbance and cognitive dysfunction is not completely understood, but a link exists between genes involved in the generation of circadian oscillations and the recall of learned behavior (Wang et al., 2009).

Despite the presumed positive effects of light and the increasing financial and scientific interests in light and health, we have found no studies investigating the clinical effect of light interventions during long-term hospitalization (not including delirium patients). We initiated this study based on the absence of knowledge in this field. The aims of this randomized controlled trial were to identify the effect of naturalistic lighting (i.e., artificial light imitating the sunlight rhythm and spectrum) on depression, anxiety, and cognition in a hospital setting among patients admitted for post-stroke rehabilitation.

2. Methods

2.1. Evidence before this study

The PubMed database was systematically searched for studies published until April 2018 using the following search string: (“light therapy” or “lighting” or “dynamic light” or “naturalistic light” or

"bright light") AND (hospitalization OR inpatients OR admission OR hospital) NOT (infants OR "shift work" OR child OR laser OR chain OR skin). Clinical trials and humans were chosen. The search demonstrated a well-known understanding of entrainment of the circadian rhythm by light and the influence on various biological mechanisms. A meta-analysis from 2005 concerning light therapy for non-seasonal depression presented evidence for the efficacy of light, but also a request for rigorous designs (Golden et al., 2005).

Only one study investigated the effect of bright light on PSD and found a positive effect in combination with antidepressants (Søndergaard, Jarden, Martiny, Andersen, & Bech, 2006). No studies investigated the effect of light intervention on PSA alone. One study investigated the effect of light on cognition in hospitalized patients (Chong, Tan, Tay, Wong, & Ancoli-Israel, 2013). However, cognition was measured as part of a delirium spectrum and not as a separate outcome.

No studies were found when naturalistic light (sun-imitating light) was included as a criterion in any database.

2.2. *Study design and participants*

The study is a quasi-randomized controlled trial with two arms. The intervention group (IU) was randomized to a rehabilitation unit equipped with naturalistic light and the control group (CU) to a rehabilitation unit with standard indoor lighting. From May 1, 2014, to June 1, 2015, stroke patients who needed in-hospital neuro-rehabilitation for more than 2 weeks were recruited from the acute stroke unit at the Department of Neurology, Rigshospitalet, Denmark, after obtaining informed consent. Patients were excluded if they were unable to give consent due to their awareness status, severe aphasia, or less than 2 weeks of hospitalization in the rehabilitation unit. A thoroughly detailed description of the methods were published elsewhere (West et al., 2017). No safety precautions were necessary regarding assessments and interventions. The study was approved by the Danish scientific ethics committee (H-4-2013-114) and Danish Data Protection Agency (2007-58-0015). ClinicalTrials.gov Identifier: NCT02186392.

2.2.1 *Randomization*

Randomization was performed by non-blinded stroke nurses (quasi-randomization). The nurses were not involved in the study and were simply following normal procedure regarding the relocation of patients to the two rehabilitation units.

2.2.2 *Procedures*

A 24-hour naturalistic lighting scheme was implemented in all areas and rooms in the IU using multi-colored LED-based luminaires (lamps) with a centralized lighting controller to manage all luminaires according to the computer-controlled lighting scheme (ChromaViso, Denmark). The naturalistic lighting scheme was constantly running during the inclusion period.

The lighting started as dim in the morning with low blue light content. The blue light increased from 7 am to reach maximum illuminance around noon, and then dimmed again from 3 pm across the evening, changing to an amber color with minimal blue light content, and turn of at 10 pm, imitating the sunlight rhythm. The amber color was running during the night at hallways and toilets. The technical light setup is produced in accordance with the CIE TN 003 following the principles of Lucas et al. (Lucas et al., 2014). The technical description is complex and acquires appropriate explanation why it was necessary to present the light intervention in detail in a method description paper. Thus, the technical light description regarding the irradiance profiles for the IU and CU can therefore be found in Fig. 3a and 3b in West et al. (West et al., 2017). All normal ceiling luminaries in the CU had new fluorescent tubes installed prior to the inclusion in order to stabilize the light in all areas of the unit.

The assessments were questionnaires/tests scoring depression, well-being, anxiety, and cognition. The questionnaires and tests were self-administered, but the examiner did the reading or writing if the patient had difficulties filling out the questionnaire due to visual or mobile disabilities. The questionnaires were administered at inclusion and discharge between 9:00 am and 3:00 pm.

Missing data regarding single questions in the questionnaires were replaced by the patient's own answer from either the inclusion or discharge questionnaire. Questionnaires with more than three missing questions were excluded. Because missing data were related to neglected questions, it was not a continuous issue (<10% of patients), as other reasons for the missing data (unable to fill out the questionnaire) resulted in exclusion.

The chosen questionnaires and cut-off values are described in Table 1. The reasoning behind the chosen questionnaires is provided elsewhere (West et al., 2017). In addition to the initial examinations,

Table 1
Questionnaire descriptions

Topic	Questionnaire	Cut-off and description
Depression	Hamilton Depression Scale (HAM-D_6)	Standardized depression cut-off levels according to ICD-10: questionable (5-6), light (7-8), moderate (9–11), moderately severe to severe depression (12–22).(Beck et al., 2005)
	Major Depression Inventory (MDI)	A cut-off score $\geq$ 20 implies a diagnostic depression.(Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001)
Well-being	WHO-Five Well-being Index (WHO-5)	A cut-off score $\leq$ 13 (converted $\leq$ 52) indicates no well-being and has been recommended by the latest version (1998) and shown to be valid in neurological patients.(Schneider et al., 2010)
Anxiety	Hospital Anxiety and Depression Scale (HADS)	Pathological HADS-Depression > 7, and HADS-Anxiety > 4 based on stroke patients.(Burton & Tyson, 2014)
Cognition	Montreal Cognitive Assessment (MoCA)	Mild cognitive impairment when MoCA-total < 25.(Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012)

the Morningness-Eveningness Questionnaire (MEQ) was completed in order to divide the participants into morning or evening types.

Use of anxiety and/or antidepressant prescriptions was recorded at inclusion and discharge. Use over a short interim period (days) during admission was not categorized as use of these medications. The indication for anxiety and/or antidepressant medication was assessed by the attending physicians on the ward rounds. The indication for these medications was not based on tests, but solely on the physician's own assessments.

2.2.3. Outcomes

The study was part of a larger project investigating the effect of light on human health measured by psychological parameters, biochemical parameters, fatigue, and sleep. The present study regards a relatively new scientific area and was defined as an exploratory investigational study. We chose five primary endpoints, including depression, well-being, and anxiety. Cognition was defined as a secondary endpoint.

2.2.4. Power calculation

A power analysis was performed using $N = (Z_a + Z_b)^2 \times s^2/\text{MIREDIF}^2$ to calculate population size, where Z_a and Z_b were set to 1.96 and 0.84 because of the two-sided 5% cut-off point and 80% power. A scale of 0 to 22 for the HAM-D_6 was assumed to have clinical significance with a difference of 3 based on validation studies of HAM-D17 with the standard deviation (SD) set at 5 (Naarding, Leentjens, van Kooten, & Verhey, 2002). The power calculation for a two-sided test showed that 22 subjects should be included in each group. The MoCA is a scale between 0 and 30, and we assumed a difference of 3 based on validation studies of MoCA with the SD set to 3.6 for stroke patients (Pendlebury et al., 2012). The power analysis showed that 12 subjects should be included in each group. Based on validation studies of the WHO scales with the SD set at 4.9 for elderly subjects (Heun, Burkart, Maier, & Bech, 1999), we assumed a difference of 3, and the power calculation showed that 21 subjects should be included in each group. Power analysis was not performed for the HADS and MDI.

2.2.5. Statistical analysis

Continuous variables were expressed as means $\pm$ SD when normally distributed. Variables that were not normally distributed were expressed as medians and interquartile ranges (IQRs). Differences between groups were assessed by analysis of covariance (ANCOVA, SAS) in order to integrate the baseline values, taking into account individual differences between these values. To avoid interaction and confounding effects of antidepressant medications (medicine codes AB-, AA-, AX-, AF-, AG-N06A) and sleep inducing/anxiety preventive medicine (N05 C), the use of these medications was integrated into the covariance analysis as a confounding variable. The significant difference in inclusion period between the two groups made it necessary to adjust for the length of inclusion in all analyzes.

Scores were, due the lack of normal distribution or/and skewed linearity, logarithmically transformed before analysis of covariance. The results were back-transformed from log to empirical fractiles and differences in scores presented as percentages ((x-1)*100).

The *T*-test was used to calculate differences in basic demographic parameters between groups.

All analyses were performed in SAS (SAS Inst. Inc., Cary, NC USA, 9.4). A p-value < 0.05 was considered significant.

3. Results

3.1. Inclusion

Between May 1, 2014, June 1, 2015, 256 patients who needed in-hospital neuro-rehabilitation were screened, 90 of which met the inclusion criteria and agreed to participate. Seventy-one patients completed the study (44 males (62%) and 27 females (38%), mean age 73 (range 51–96) years; Fig. 1). Because of an inability to complete the questionnaires due to severe illness or reduced awareness, 9–30 patients in the IU and 3–22 patients in the CU were excluded or dropped out depending on the questionnaire (Fig. 1).

Because of the comparability between the participants regarding MEQ subtypes (Table 2), the MEQ results were not included as a confounding element.

Demographic data are presented in Table 2. The demographics were well balanced, but the two groups differed significantly regarding length of inclusion (mean 45.3 ± 22.1 days in the IU vs. mean 33.7 ± 12.7 days in the CU; $p = 0.02$). However, no significant correlation was found regarding length of inclusion and depression, anxiety, or cognition

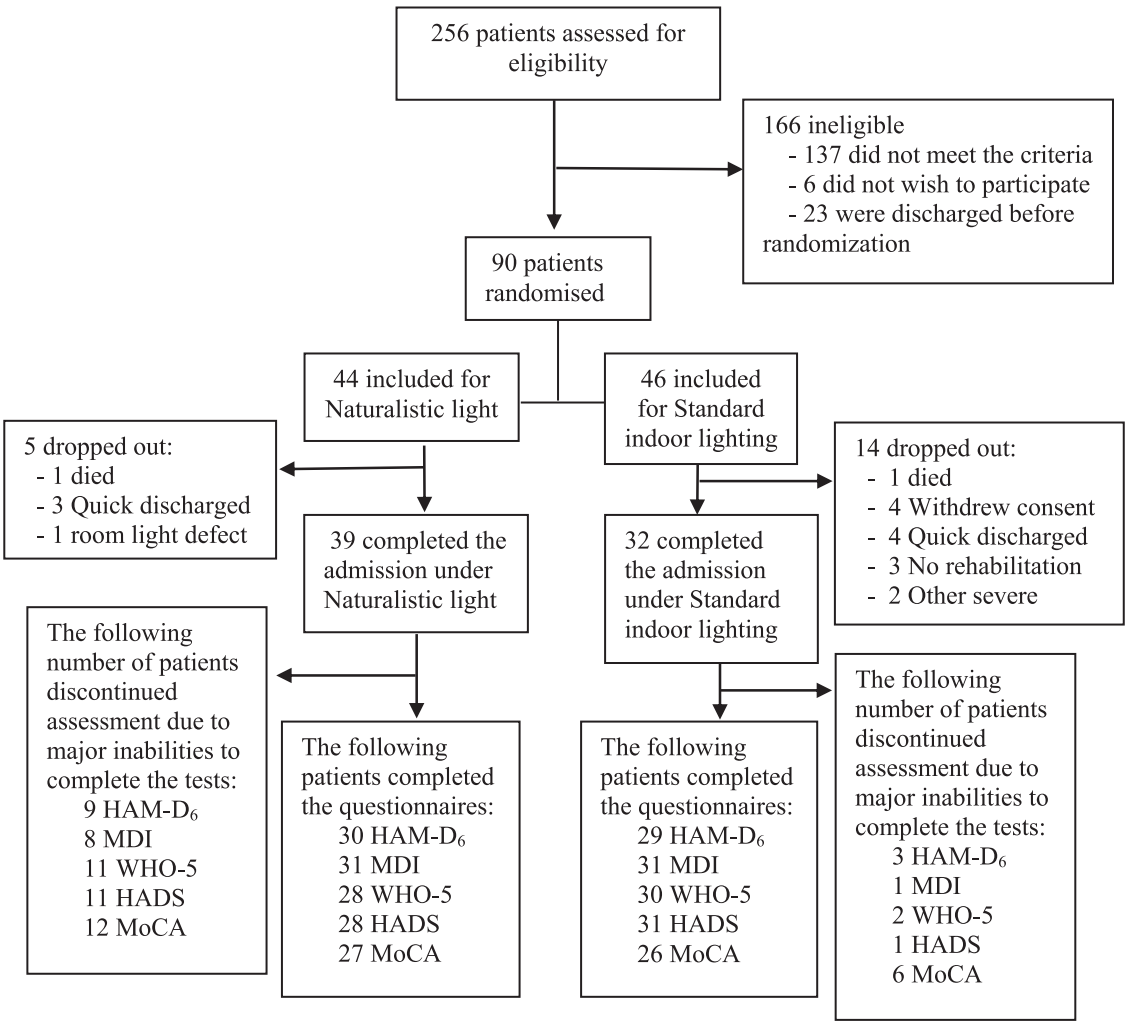

Fig. 1. Trial profile.

Table 2
Basic demographics

Characteristic	Intervention unit (N = 39)	Control unit (N = 32)	*P*-value
Mean age, years (range)	72.7 (55–96)	72.8 (51–89)	0.96
Sex			0.93
Male	24 (62)	20 (63)	
Female	15 (38)	12 (38)	
Time from ictus to inclusion, days	7.6 ± 8.3	6.0 ± 4.4	0.55
Inclusion period, days	45.3 ± 22.1	33.7 ± 12.7	**0.02**
Smoker	26 (67)	26 (84)	0.10
Hypertension*	29 (74)	19 (59)	0.18
Diabetes			
Type 1	0 (0)	2 (6)	0.11
Type 2	7 (18)	6 (19)	0.93
Hypercholesterol	13 (33)	7 (22)	0.29
Atrial fibrillation	5 (13)	7 (22)	0.31
Depression**	2 (5)	3 (9)	0.49
Barthel score	47.6 ± 34.0	51.7 ± 28.9	0.65
NIHSS score	7.0 ± 6.4	5.4 ± 4.2	0.34
MEQ total score	60.1 ± 12.0	60.4 ± 10.7	0.93
*Definitely Evening Type****	1 (3.7)	0 (0)	
*Moderately Evening Type****	7 (25.9)	5 (17.2)	
*Neither Type****	2 (7.4)	2 (6.9)	
*Moderately Morning Type****	10 (37.0)	16 (55.2)	
*Definitely Morning Type****	7 (25.9)	6 (20.7)	

Data are presented as mean ± SD or n (%) unless otherwise noted. *Hypertension defined as under medical treatment for hypertension at study inclusion. **History of depression. ***Percentage of 27 respondents in the IU and 29 in the CU.

Table 3
Difference in scores between the IU and CU groups

Questionnaire	Difference in favor of IU	Standard Error	95% CI	*P*-value
Depression questionnaire				
HAM-D_6[A]	–42.1%	0.3	–61.8% to –12.3%	**0.011**
MDI[A]	–51.9%	0.3	–67.8% to –28.3%	**0.0005**
WHO-5[A]	+46.5%	0.3	0.6% to 113.3%	**0.046**
HADS depression[A]	–8.4%	0.3	–38.2% to 35.9%	0.657
Anxiety questionnaire				
HADS anxiety[B]	–28.6%	0.2	–48.6% to –0.8%	**0.045**
Cognition questionnaire				
MoCA	0.18%	0.1	–8.7% to 9.9%	0.969

Differences determined (IU – CU) from the analysis of covariance. [A]Antidepressant medicine included as a confounder. [B]Anxiety medicine included as a confounder. Length of inclusion was included in all analyzes as a confounder. Due to non-parametric distribution, the scores were log2 transformed before calculation. The calculated estimate was back-transformed from log2 to empirical fractiles to achieve a parametric distribution, which was converted to the percent difference in score ((x-1)*100). Outcome specification: HAM-D_6, MDI, HADS: high scores indicate a high degree of depression; WHO-5: high scores indicates a high degree of well-being; MoCA: high scores indicate a high degree of cognitive function.

measured by regression analysis. No other significant differences were found between the two groups.

3.2. Changes in response to the naturalistic light intervention

The main findings determined by analysis of covariance (Table 3) were a significant reduction in PSD scores and significant increased well-being scores at discharge in the IU compared to the CU (HAM-D_6, MDI and WHO-5). PSA was also significantly reduced in the IU compared to the CU (HADS anxiety). However, no significant difference was found in cognition (MoCA).

The overall median scores for each unit at inclusion and discharge are presented in Table 4.

3.3. Effect of antidepressants and anxiety medication

Patients without antidepressant prescriptions had a significantly lower degree of depressive mood than

Table 4
Median scores at inclusion and discharge in each unit.

	Inclusion	Discharge
Depression questionnaire		
HAM-D_6		
Control Unit (N = 29)	6.0 (1.0–11.0)	4.0 (0.0–7.0)
Intervention Unit (N = 30)	6.0 (0.0–9.0)	1.0 (0.0–3.0)
MDI		
Control Unit (N = 31)	14.0 (0.0–24.0)	13.0 (2.0–21.0)
Intervention Unit (N = 31)	8.0 (1.0–16.0)	8.0 (0.0–14.0)
WHO-5		
Control Unit (N = 30)	52.0 (4.0–76.0)	52.0 (4.0–68.0)
Intervention Unit (N = 28)	62.0 (0.0–80.0)	58.0 (12.0–76.0)
HADS depression		
Control Unit (N = 31)	5.0 (0.0–10.0)	4.0 (0.0–8.0)
Intervention Unit (N = 28)	2.0 (0.0–6.5)	3.0 (0.0–7.5)
Anxiety questionnaire		
HADS anxiety		
Control Unit (N = 31)	5.0 (0.0–8.0)	5.0 (0.0–6.0)
Intervention Unit (N = 28)	4.5 (0.0–7.0)	3.0 (0.0–6.5)
Cognition questionnaire		
MoCA		
Control Unit (N = 26)	20.5 (15.0–22.0)	24.0 (11.0–25.0)
Intervention Unit (N = 27)	22.0 (12.0–25.0)	24.0 (12.0–26.0)

Data are presented as median (interquartile range).

patients treated with antidepressants according to the HAM-D_6 (difference –45.6%, 95% CI –65.7% to –13.8%, $p = 0.011$), MDI (difference –57.2%, 95% CI –71.8% to –35.0%, $p = 0.0001$), and WHO-5 (difference +56.3, 95% CI +3.6 to 135.7%, $p = 0.034$). No significant difference was found in HADS depression or anxiety scores between treated and untreated patients. Overall, 16 and 9 patients in the IU and CU, respectively, were treated with antidepressants, and 11 and 7 in the IU and CU, respectively, were treated with anxiety medication.

3.4. Interactions

No significant interactions of antidepressants and anxiety medication were detected.

4. Discussion

4.1. Discussion of the results

This study is the first to investigate the clinical effect of naturalistic light on mental health in stroke patients undergoing long-term hospitalization.

4.1.1. Depression

We demonstrated a significant decrease in depressive mood and anxiety symptoms along with improved well-being in stroke patients exposed to naturalistic light over at least 14 days of admission for neuro-rehabilitation. These results may be explained by the naturalistic light having a stabilizing effect on the circadian rhythm. However, the results could also be caused by a direct effect of accumulated blue light stimulation, or both. The patients treated with antidepressants scored significantly higher on the HAM-D_6 and MDI and lower on the WHO-5 than patients not treated with antidepressants. Consequently, the use of antidepressants was included in the statistical calculation as a confounder due to this difference in scores. A meta-analysis of the effect of antidepressants on PSD revealed a significant effect (Xu et al., 2016). In a review by Xiao-min Xu et al. (Xu et al., 2016) the effect on HAM-D_{17} score percentage of antidepressants vs. placebo was 18.0–91.4% in favor of antidepressants. The calculated percentage effect in our study between naturalistic and standard indoor lighting was 49.2% (HAM-D_6) and 44.0% (MDI). Therefore, naturalistic lighting could be within the present treatment effect range of antidepressants. However, further studies need to elucidate this.

HADS was the only measurement for depression that did not decrease significantly in the IU group compared with the CU group. As the cognitive tests revealed, the patients were highly cognitive challenged, hence questions requiring reflection, which is frequent in HADS, may have been difficult to answer correctly. This may relate to the low detections rate of depression in our cohort (Table 4) as in previous studies (Meader, Moe-Byrne, Llewellyn, & Mitchell, 2014).

In a recent study with 63 acute stroke patients, bright light intervention (high or medium white light intensity) had a cumulative effect on depression in combination with antidepressants (Søndergaard et al., 2006). We found no significant effect in the group prescribed antidepressants, but this may be explained by a power problem due to the low number of treated patients. In addition, SSRIs are known to have a latency in effect of 1-2 weeks, which could have influenced the results. However, our calculations present a significant positive effect of naturalistic light in the group not given antidepressants. Therefore, the difference between groups regarding number of patients prescribed antidepressants, with more prescriptions in the IU, could not have affected our conclusion.

The findings from the previous studies investigating light intervention on depressive outcome in patients during hospitalization were inconclusive (Giménez et al., 2016; Hickman et al., 2007; Leicht-

fried et al., 2014), as only one study could present a significant effect (Kopp et al., 2016). Our study showed an evident effect of light on depressive outcome. The explanations behind the different findings may relate to the differences in study design and choice of questionnaires. In our understanding, naturalistic light as the light intervention and a cohort of long-term admitted patients are two essential parameters for a sufficient effect on the circadian system and may explain the absence of an effect in prior studies.

4.1.2. Well-being

Suffering from stroke and dealing with deficits negatively influences well-being. Nevertheless, the feeling of well-being improved in favor of the IU between inclusion and discharge. Low well-being is known to be associated with depression, which can explain some of the positive outcome, but it appeared that patients admitted in the CU had a better rested feeling and improved energy measured by WHO-5, which may indicate a reduction in fatigue. However, other questionnaires should elaborate on this.

4.1.3. Anxiety

Our results revealed significant decreased PSA in the IU (Table 3). Since PSA is associated to PSD, some of the anxiety reduction may be found in the reduction of PSD. The shown positive effect of bright light on amygdala and prefrontal brain areas (Fisher et al., 2014) could also be part of the etiology. However, the improvement in anxiety in this study may indicate the first available intervention to treat or prevent PSA. More studies should however explore on this and further bio physical investigations between light and anxiety are needed.

4.1.4. Cognition

MoCA scores increased from inclusion to discharge in all patients, indicating cognitive improvement during the admission period. MoCA was chosen because of its high sensitivity and specificity for mild cognitive impairment compared to the MMSE (Pendlebury et al., 2012). Whether it is a continuously disrupted circadian rhythm that is responsible for the absence of significant cognitive improvement in the IU compared to the CU, or because the cognitive impairments are severe and may persist several years after ictus, is unclear (Patel, Coshall, Rudd, & Wolfe, 2003).

4.2. Strengths and limitations

One of the main limitations of this study was that not all patients were able to answer all the questionnaires. As it was not always possible to identify who would be able to complete the questionnaires in advance, we chose to include all eligible patients regardless of complications that could make them unable to complete all questionnaires, inducing a high risk of drop out. Unawareness was the main reason for dropping out after inclusion. The IU had a higher NIHSS score at discharge, though it was not significant, indicating that stroke severity did not influence drop outs in the IU.

The randomization followed the normal procedure for distributing patients to the two rehabilitation units. Completely blind randomization would be optimal, but this was not feasible in the clinical setting due to the visible intervention. The two groups were well balanced demographically, but there was a significant difference regarding the duration of inclusion period. We speculate that the main explanation for this is that it was not the same rehabilitation team that handled patient discharge in the two units. Furthermore, the patients in the IU had a higher NIHSS at inclusion, which may also have influenced the longer admission time. However, no significant correlation was found between length of inclusion and the scores of depression, anxiety, or cognition calculated by regression analysis. Still, the length of the inclusion period was included as a variable in the analyzes, to exclude the possible influence it may have on the outcome. No other differences were found between the two groups.

The conditions in the two rehabilitation units were equal in regards to size, form, and staff profession. The impact of daylight on the facade of the two units was not completely identical, as the angle to the sun differed between the two wings during all four seasons. However, measurement of the incoming light from the sun between the two units revealed no significant differences as described in West et al. Fig. 4a and 4b (West et al., 2017), assuming that levels above 200 lux would stimulate the circadian center (M. Andersen, Mardaljevic, & Lockley, 2012). Based on that, we assume, that the difference in daylight exposure between the units for the door beds was not significant and did not favor the IU.

The IU had blackout curtains that went up at 8:00 am and down at 8:00 pm for all four seasons. Information on all bed positions (two beds: window-bed and away-from-window-bed) was collected during the study, and all patients were placed at the window

at the end of the stay because of the natural rotation in the units. Thus, no differences were found in bed positions between patients and bed positions were excluded from the calculations. Locations of brain lesion in relation to depression have been discussed in several papers, but also the skepticism of the significance in this influence. MRI scans as part of the verification of infarcts, size and location were included in this study. However, we were only able to MRI scan 31 patients of the enrolled patients, why MRI data were excluded as a confounding element. Since the enrolled patients were randomized, the location of the infarctions should be randomly allocated in the two groups. Further studies are needed to confirm a relation between location of infarctions and depression.

The main strength of this study was that it was performed in a real clinical setting and compared two units at the same institution. We think that our data can be directly transferred to everyday clinical life. However, this study is part of an exploratory investigational study in a relatively new scientific area. More specific studies are required to address the effects of naturalistic light on PSD, PSA, and cognitive function.

5. Conclusion

This study was performed in a real hospital environment and showed for the first time the impact of naturalistic light exposure during long-term hospitalization. After at least 14 days, a significant decrease in PSD and PSA, and significant improved well-being was found in patients exposed to naturalistic light in an adjusted analysis. The effect of the naturalistic light was within the range of the treatment effect of antidepressants on PSD, with no side effects. No clear effect of naturalistic light on cognitive outcomes was found.

PSD has substantial consequences on mortality and activity of daily living after stroke,(Everson et al., 1998; Robinson, Bolduc, & Price, 1987) and the effect of naturalistic light on PSD, and PSA, indicates that naturalistic lighting is a potentially beneficial concept to integrate into the environment for long-term hospitalizations.

5.1. Declaration of interest

All authors have completed the Unified Competing Interest form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted, and no other relationships or activities that could appear to have influenced the submitted work.

ChromaViso delivered the light installation and had no influence on the study design or interpretation of the results.

This study received research grant support from the Market Development Foundation Denmark and support from the involved departments. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing.

Acknowledgments

We are deeply grateful to the stroke patients for participating in this study. We thank Service Manager Svend Morten Christiansson and architect Maj Lis Brunsgård Seligmann from the Service Center Rigshospitalet for their focus on the importance of lighting in hospitals and making it possible to install naturalistic light throughout an entire hospital ward. We thank ChromaViso and especially master in optical engineering, Torben Skov Hansen for always being available for technical support regarding the light setup. The authors also wish to thank to Nina Vindegaard Grønberg, MD, who was a great help during periods of high work pressure. The health staff at the Stroke Department, Rigshospitalet, Glostrup, require gratitude for their engagement and professionalism as they provided support and logistical assistance during the entire project period. The last gratitude goes to The Market Development Foundation Denmark for financing the project.

Conflict of interest

None to report.

References

Alkozei, A., Smith, R., & Killgore, W. D. S. (2016). Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neuroscience Letters*, *616*, 5–10. http://doi.org/10.1016/j.neulet.2016.01.034

Andersen, M., Mardaljevic, J., & Lockley, S. (2012). A framework for predicting the non-visual effects of daylight – Part I: photobiology- based model. *Lighting Research and Technology*, *44*(1), 37–53. http://doi.org/10.1177/1477153511435961

Ayerbe, L., Ayis, S. A., Crichton, S., Wolfe, C. D. A., & Rudd, A. G. (2014). Natural history, predictors and associated outcomes of anxiety up to 10 years after stroke: The South London Stroke Register. *Age and Ageing*, *43*(4), 542–547. http://doi.org/10.1093/ageing/aft208

Bech, P., Rasmussen, N. A., Olsen, L. R., Noerholm, V., & Abildgaard, W. (2001). The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *Journal of Affective Disorders*, *66*(2-3), 159–164.

Beck, P., Licht, R. W., Stage, K. B., Abildgaard, W., Bech-Andersen, G., Søndergaard, S., & Martiny, K. (2005). Den blaa bog – Rating scales for affektive lidelser. In *RATING SCALES FOR AFFEKTIVE LIDELSER* (1st ed., Vol. 1, pp. 1–121).

Burton, L. J., & Tyson, S. (2014). Screening for mood disorders after stroke: A systematic review of psychometric properties and clinical utility. *Psychological Medicine*, *45*(01), 29–49. http://doi.org/10.1017/S0033291714000336

Campbell Burton, C. A., Murray, J., Holmes, J., Astin, F., Greenwood, D., & Knapp, P. (2012). Frequency of anxiety after stroke: A systematic review and meta-analysis of observational studies. *International Journal of Stroke*, *8*(7), 545–559. http://doi.org/10.1111/j.1747-4949.2012.00906.x

Chong, M. S., Tan, K. T., Tay, L., Wong, Y. M., & Ancoli-Israel, S. (2013). Bright light therapy as part of a multicomponent management program improves sleep and functional outcomes in delirious older hospitalized adults. *Clinical Interventions in Aging*, *8*, 565–572. http://doi.org/10.2147/CIA.S44926

Everson, S. A., Roberts, R. E., Goldberg, D. E., & Kaplan, G. A. (1998). Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Archives of Internal Medicine*, *158*(10), 1133–1138.

Feng, C., Fang, M., & Liu, X.-Y. (2014). The Neurobiological Pathogenesis of Poststroke Depression. *The Scientific World Journal*, *2014*(5506), 1–8. http://doi.org/10.1155/2014/521349

Fisher, P. M., Madsen, M. K., Mc Mahon, B., Holst, K. K., Andersen, S. B., Laursen, H. R., et al. (2014). Three-Week Bright-Light Intervention Has Dose-Related Effects on Threat-Related Corticolimbic Reactivity and Functional Coupling. *Biological Psychiatry*, *76*(4), 332–339. http://doi.org/10.1016/j.biopsych.2013.11.031

Giménez, M. C., Geerdinck, L. M., Versteylen, M., Leffers, P., Meekes, G. J. B. M., Herremans, H., et al. (2016). Patient room lighting influences on sleep, appraisal and mood in hospitalized people. *Journal of Sleep Research*, *26*(2), 236–246. http://doi.org/10.1111/jsr.12470

Golden, R. N., Gaynes, B. N., Ekstrom, R. D., Hamer, R. M., Jacobsen, F. M., Suppes, T., et al. (2005). The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. *The American Journal of Psychiatry*, *162*(4), 656–662. http://doi.org/10.1176/appi.ajp.162.4.656

Heun, R., Burkart, M., Maier, W., & Bech, P. (1999). Internal and external validity of the WHO Well-Being Scale in the elderly general population. *Acta Psychiatrica Scandinavica*, *99*(3), 171–178.

Hickman, S. E., Barrick, A. L., Williams, C. S., Zimmerman, S., Connell, B. R., Preisser, J. S., et al. (2007). The Effect of Ambient Bright Light Therapy on Depressive Symptoms in Persons with Dementia. *Journal of the American Geriatrics Society*, *55*(11), 1817–1824. http://doi.org/10.1111/j.1532-5415.2007.01428.x

Kim, H.-I., Lee, H.-J., Cho, C.-H., Kang, S.-G., Yoon, H.-K., Park, Y.-M., et al. (2015). Association of CLOCK, ARNTL, and NPAS2gene polymorphisms and seasonal variations in mood and behavior. *Chronobiology International*, *32*(6), 785–791. http://doi.org/10.3109/07420528.2015.1049613

Kopp, B. T., Hayes, D. Jr, Ghera, P., Patel, A., Kirkby, S., Kowatch, R. A., & Splaingard, M. (2016). Pilot trial of light therapy for depression in hospitalized patients with cystic fibrosis. *Journal of Affective Disorders*, *189*, 164–168. http://doi.org/10.1016/j.jad.2015.08.056

Lam, R. W., Levitt, A. J., Levitan, R. D., Michalak, E. E., Cheung, A. H., Morehouse, R., et al. (2016). Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients With Nonseasonal Major Depressive Disorder. *JAMA Psychiatry*, *73*(1), 56–58. http://doi.org/10.1001/jamapsychiatry.2015.2235

Leichtfried, V., Matteucci Gothe, R., Kantner-Rumplmair, W., Mair-Raggautz, M., Bartenbach, C., Guggenbichler, H., et al. (2014). Short-term effects of bright light therapy in adults with chronic nonspecific back pain: A randomized controlled trial. *Pain Medicine (Malden, Mass.)*, *15*(12), 2003–2012. http://doi.org/10.1111/pme.12503

Lucas, R. J., Peirson, S. N., Berson, D. M., Brown, T. M., Cooper, H. M., Czeisler, C. A., et al. (2014). Measuring and using light in the melanopsin age. *Trends in Neurosciences*, *37*(1), 1–9. http://doi.org/10.1016/j.tins.2013.10.004

McClung, C. A. (2007). Circadian genes, rhythms and the biology of mood disorders. *Pharmacology & Therapeutics*, *114*(2), 222–232. http://doi.org/10.1016/j.pharmthera.2007.02.003

Meader, N., Moe-Byrne, T., Llewellyn, A., & Mitchell, A. J. (2014). Screening for poststroke major depression: A meta-analysis of diagnostic validity studies. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(2), 198–206. http://doi.org/10.1136/jnnp-2012-304194

Mohd Zulkifly, M. F., Ghazali, S. E., Che Din, N., Singh, D. K. A., & Subramaniam, P. (2016). A Review of Risk Factors for Cognitive Impairment in Stroke Survivors. *The Scientific World Journal*, *2016*(3), 1–16. http://doi.org/10.1155/2016/3456943

Naarding, P., Leentjens, A. F. G., van Kooten, F., & Verhey, F. R. J. (2002). Disease-specific properties of the Rating Scale for Depression in patients with stroke, Alzheimer"s dementia, and Parkinson"s disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(3), 329–334.

Paradee, C. V., Rapport, L. J., Hanks, R. A., & Levy, J. A. (2005). Circadian preference and cognitive functioning among rehabilitation inpatients . *The Clinical Neuropsychologist*, *19*(1), 55–72. http://doi.org/10.1080/13854040490524173

Patel, M., Coshall, C., Rudd, A. G., & Wolfe, C. D. (2003). Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clinical Rehabilitation*, *17*(2), 158–166. http://doi.org/10.1191/0269215503cr596oa

Pendlebury, S. T., Mariz, J., Bull, L., Mehta, Z., & Rothwell, P. M. (2012). MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke. *Stroke*, *43*(2), 464–469. http://doi.org/10.1161/STROKEAHA.111.633586

Perrin, F., Peigneux, P., Fuchs, S., Verhaeghe, S., Laureys, S., Middleton, B., et al. (2004). Nonvisual Responses to Light Exposure in the Human Brain during the Circadian

Night. *Current Biology*, *14*(20), 1842–1846. http://doi.org/10.1016/j.cub.2004.09.082

Riemersma-van der Lek, R. F., Swaab, D. F., Twisk, J., Hol, E. M., Hoogendijk, W. J. G., & Van Someren, E. J. W. (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial. *JAMA : The Journal of the American Medical Association*, *299*(22), 2642–2655. http://doi.org/10.1001/jama.299.22.2642

Robinson, R. G., Bolduc, P. L., & Price, T. R. (1987). Two-year longitudinal study of poststroke mood disorders: Diagnosis and outcome at one and two years. *Stroke*, *18*(5), 837–843.

Schneider, C. B., Pilhatsch, M., Rifati, M., Jost, W. H., Wodarz, F., Ebersbach, G., et al. (2010). Utility of the WHO-Five Well-being Index as a screening tool for depression in Parkinson's disease. *Movement Disorders*, *25*(6), 777–783. http://doi.org/10.1002/mds.22985

Søndergaard, M. P., Jarden, J. O., Martiny, K., Andersen, G., & Bech, P. (2006). Dose Response to Adjunctive Light Therapy in Citalopram-Treated Patients with Post-Stroke Depression. *Psychotherapy and Psychosomatics*, *75*(4), 244–248. http://doi.org/10.1159/000092895

Thapan, K., Arendt, J., & Skene, D. J. (2001). An action spectrum for melatonin suppression: Evidence for a novel non-rod, non-cone photoreceptor system in humans. *The Journal of Physiology*, *535*(Pt 1), 261–267.

Wang, L. M.-C., Dragich, J. M., Kudo, T., Odom, I. H., Welsh, D. K., O'Dell, T. J., & Colwell, C. S. (2009). Expression of the circadian clock gene Period2in the hippocampus: Possible implications for synaptic plasticity and learned behaviour. *ASN Neuro*, *1*(3), 139–152. http://doi.org/10.1042/AN20090020

West, A., Jennum, P., Simonsen, S. A., Sander, B., Pavlova, M., & Iversen, H. K. (2017). Impact of naturalistic lighting on hospitalized stroke patients in a rehabilitation unit: Design and measurement. *Chronobiology International*, *43*, 1–11. http://doi.org/10.1080/07420528.2017.1314300

Xu, X.-M., Zou, D.-Z., Shen, L.-Y., Liu, Y., Zhou, X.-Y., Pu, J.-C., et al. (2016). Efficacy and feasibility of antidepressant treatment in patients with post-stroke depression. *Medicine*, *95*(45), e5349–9. http://doi.org/10.1097/MD.0000000000005349