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Effects of a dawn-dusk simulation on circadian rest-activity cycles, sleep, mood and well-being in dementia patients

Vivien Bromundt[a], Anna Wirz-Justice[b], Marc Boutellier[c], Seraina Winter[c], Markus Haberstroh[d], Michael Terman[e], Mirjam Münch[f,*,1]

[a] Sleep-Wake-Epilepsy-Center, Dept. of Neurology, Inselspital, Bern University Hospital, Bern, Switzerland
[b] Centre for Chronobiology, Transfaculty Research Platform Molecular and Cognitive Neurosciences, Psychiatric Hospital of the University of Basel, Basel, Switzerland
[c] Nursing Home Hofmatt, Münchenstein, BL, Switzerland
[d] Haberstroh Architects, Basel, Switzerland
[e] Columbia University, New York, USA
[f] Charité, University Medicine Berlin, Institute of Physiology and Institute of Medical Immunology, Berlin, Germany

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ABSTRACT

Light is the most powerful "zeitgeber" signal to synchronize circadian sleep-wake cycles. In dementia, these rhythms are often fragmented — probably due to loss of neuronal function of the suprachiasmatic nuclei (the biological "master clock" in the brain) and/or weakness of external zeitgebers. We investigated the effects of a prototype dawn-dusk simulator (DDS) on circadian rest-activity cycles, sleep, mood and well-being in a balanced crossover design during fall and winter in 20 institutionalized patients with dementia (86 ± 6 y, 17 f).

All participants had one baseline week followed by exposure to individually timed DDS over their beds for 7–8 weeks. They spent 8 weeks without DDS as a control. Mood, self-reliant daily activity, social behavior, agitation, and quality of life were assessed by standardized questionnaires and visual analogue scales, regularly rated by trained caregivers. Circadian and sleep characteristics of their rest-activity cycles were analyzed by actimetry over 17 weeks.

DDS exposure led to significantly better mood in the morning hours after waking. The effects were most pronounced in the second 4 weeks with DDS, indicating that positive effects emerged gradually. Differences in circadian rest-activity cycles and sleep were mainly age-dependent. We found statistically significant correlations between measures of higher quality of life and better mood, greater alertness and circadian rhythm stability. We conclude that continuous, long-term application of dawn-dusk simulation at the sleep-wake transitions appears to increase external zeitgeber strength in institutionalized patients with dementia. The DDS may provide an effective, non-invasive tool to improve mood and ameliorate patients' quality of life.

1. Introduction

Daylight is not only important for vision, but also for a wide variety of so-called "non-visual" effects such as synchronizing the biological clock, modifying alertness, mood, performance and pupillary size. The 24-h light-dark (day-night) cycle is the most important signal ("zeitgeber") for entraining circadian rhythms. Regular sleep-wake cycles that are well synchronized with multiple somatic functions promote positive mood, and better cognition and performance (for recent reviews see Abbott et al., 2018; Fisk et al., 2018). In dementia, many behaviors are negatively impacted by the progressive functional loss of CNS neurons. These neurodegenerative processes also directly affect the functionality of the suprachiasmatic nuclei (SCN), the "master clock" in the anterior hypothalamus (Swaab et al., 1985; Zhou et al., 1995), as well as other nuclei and pathways involved in circadian sleep-wake regulation and alterations in clock gene RNA expression (Bellanti et al.,

Abbreviations: BL, baseline; DDS, dawn-dusk simulation; noDDS, time without exposure to DDS; SCN, suprachiasmatic nuclei; S-MMSE, Severe Mini-Mental State Examination; VAS, visual analogue scale; NOSGER, Nurses' Observation Scale for Geriatric Patients; ADL, Activities of daily living; CADS, Changes in Advanced Dementia Care Scale; CMAI, Cohen-Mansfield Agitation Inventory; QUALID, Quality of Life Scale for Severe Dementia; IS, inter-daily stability of rest-activity patterns; IV, intra-daily variability of rest-activity patterns

* Corresponding author at: Sleep/Wake Research Centre, Massey University, Wellington Campus, PO Box 756, Wellington, NZ 6140, New Zealand.
E-mail address: m.munch@massey.ac.nz (M. Münch).
[1] Current address: Sleep/Wake Research Centre, Massey University, Wellington, New Zealand.

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Table 1
Demographics of the study participants (n = 20) with sex, age, diagnosis, years since diagnosis (related to the entry in the nursing home), average of S-MMSE score before and at the end of the study as well as medications. Prn = pro re nata, as needed, VD = vascular dementia, AD = Alzheimer's disease.

Subjects	Sex	Age	Neurodegen. dignosis	Time since diagnosis	Mean S-MMSE	Hypnotics	Anxiolytics; neuroleptics	Cardiovascular drugs	Analgesics	Antidementia drugs
DDS_01	f	85	VD	1	29.5	prn	+	−	+	−
DDS_02	m	68	AD	4	0	−	+	−	prn	−
DDS_03	f	90	suspected AD	4	0	−	+	−	prn	−
DDS_04	f	86	AD	4	0.5	−	+	+	prn	−
DDS_05	f	84	AD	4	0	+	−	−	prn	−
DDS_06	f	93	suspected Lewy-body dementia; Parkinson syndrome	4	0	−	prn	prn	prn	−
DDS_07	f	85	suspected VD	4	8.5	prn	prn	+	prn	−
DDS_08	f	87	VD; AD	0.5	30	prn	+	+	prn	+
DDS_09	f	87	AD	0.5	13	prn	+	+	prn	−
DDS_11	f	89	VD	1	14.5	−	prn	+	prn	−
DDS_12	m	83	frontotemporal dementia	0.5	12	+	+	+	+	−
DDS_13	m	88	suspected VD	4	19	+	+	+	+	−
DDS_14	f	82	AD; Korsakoff's syndrome	3	23	prn	+	−	+	−
DDS_15	f	78	VD	3	13.5	−	+	−	+	−
DDS_16	f	91	AD	2	22	−	+	+	+	+
DDS_17	f	95	VD; AD	2	10.5	+	+	−	prn	−
DDS_18	f	86	VD; AD	2	3.5	−	+	−	prn	−
DDS_19	f	81	suspected AD	1	16	+	+	−	prn	−
DDS_20	f	84	suspected AD	4	28.5	prn	−	+	prn	+
DDS_22	f	89	AD	5	19	prn	−	+	prn	+

2017). Daytime napping and fragmented night-time sleep have been attributed to weakened circadian rhythm regulation (Ancoli-Israel et al., 1997). This circadian rhythm sleep disorder with irregular sleep-wake pattern is most commonly seen in institutionalized patients with neurodegenerative diseases. Nocturnal agitation, so-called "sun-downing", including symptoms such as mood swings, suspicious, agitated or disoriented behavior which typically occurs during the late afternoon and evening, has a prevalence up to 66% in people with Alzheimer's disease and is a primary reason for patient institutionalization (Bachman and Rabins, 2006; Vitiello et al., 1992). Reduced light input may be another factor contributing to reduced circadian rhythm stability arising from less time outdoors, age-related opacity of the lens, and age-related miosis (Turner and Mainster, 2008). These factors often occur together with medical and psychiatric co-morbidities (Satlin et al., 1992).

Ambient daytime lighting in nursing homes is usually sufficient for vision, but often not for non-visual effects such as stabilizing circadian rhythms and sleep, and improving mood and cognitive behavior. Enhanced indoor lighting helps individuals with dementia who cannot regularly go outdoors (Ancoli-Israel et al., 2002; Burns et al., 2009; Figueiro et al., 2014; Hickman et al., 2007; Konis et al., 2018; Mishima et al., 1994; Skjerve et al., 2004; Van Someren et al., 1997; Wahnschaffe et al., 2017a; Wahnschaffe et al., 2017b). The beneficial effect of light on mood might be conveyed via melanopsin-expressing retinal ganglion cells (M4 type) to the lateral habenula, which is a relay site between limbic and striatal regions and the midbrain, as was recently described in nocturnal animals (Huang et al., 2019). The effects of light also impact many hormones and neurotransmitters, such as serotonin (5-HT). Higher serotonin availability in the brain is involved in the regulation of mood and emotions and has been found to be light-dependent (Lambert et al., 2002). Indeed, a pioneering long-term study demonstrated that higher light intensity in the day room slowed cognitive decline, and improved sleep and mood (Riemersma-van der Lek et al., 2008). Both short- and long-term dynamic illuminance patterns mimicking a natural change of intensity and spectral composition of light can reduce nighttime agitation (van Hoof et al., 2009; Wahnschaffe et al., 2017a). Higher daytime illuminance in general (including daylight) also has a positive impact on mood, alertness, and quality of life in patients suffering from severe dementia (Münch et al. 2017).

The geophysical daylight signal is complex, changing in intensity, spectral composition and cloud pattern throughout the day, and in day length throughout the year, dependent on latitude. These changes are also determined by rural vs. urban locations (Spitschan et al., 2016). The mammalian biological clock is particularly sensitive to the gradual changes at twilight (Walmsley et al., 2015), and there is also evidence in humans that color and intensity of light can affect the circadian clock (Woelders et al., 2018). Dawn signals have been shown to improve mood, well-being and cognitive performance in healthy young subjects, as well as increasing salivary cortisol concentration upon wake-up (Gabel et al., 2013). The circadian time course of endogenous cortisol secretion follows a 24-h rhythm with highest concentrations shortly before habitual wake time that is considered as a hormonal wake-up signal (Wüst et al., 2000). This awakening cortisol response is enhanced by dawn simulation (Gabel et al., 2013). Dawn simulation also accelerates the morning decline in the distal-to-proximal skin temperature gradient, thus reducing sleep inertia upon waking (Kondo et al., 2009; Van De Werken et al., 2010). In a small group of demented patients, dawn and dusk simulation advanced sleep timing, with a trend for longer sleep duration and shortened sleep latency (Fontana Gasio et al., 2003).

Here we investigated a newly designed dawn-dusk simulator (DDS) installed over the bed-head, which provided naturalistically contoured twilight signals for institutionalized patients with dementia. We studied effects on circadian rest-activity cycles, sleep, mood, agitation, and well-being during fall and winter.

2. Material and methods

2.1. Participants

Twenty patients with dementia (85.6 ± 5.8 y, range 68–95 y; 17 f; Table 1), who resided in the Nursing Home Hofmatt, Münchenstein BL, Switzerland, were studied during fall/winter months from November to March. The patients were heterogeneous with respect to medication and other illnesses, but none had major ophthalmological involvement such as glaucoma, blindness or cataract.

One participant was excluded in the fourth week after refusing to wear an activity monitor, and was replaced by another patient who started the study in week 4. Severity of dementia was assessed at the beginning and end of the study using the Severe Mini-Mental State Examination [S-MMSE; 0–30 points, where 0 points indicates "most severe" and 30 points "least severe cognitive impairment" (Harrell

et al., 2000)]. The mean S-MMSE score (± SD) of all participants was 13.15 ± 10.30, with no significant difference between pre- and post-treatment assessments (S-MMSE at baseline, 14.35 ± 10.51; S-MMSE at termination, 11.95 ± 11.56; p = 0.19; two-sided *t*-test).

Primary family members and/or legal representatives were comprehensively informed about the study and completed written informed consent. As far as possible, the study was also explained to the participants. The protocol and all study procedures were approved by the local ethical review board (Ethics Committee Northwest/Central Switzerland).

2.2. Study design

The 17-week trial was a balanced crossover, within-subject study. After one baseline week, participants were exposed to an individually timed DDS schedule for 8 weeks, followed by another 8 weeks without the DDS (7 weeks for 10 patients, due to technical problems with some of the lamps). The order of DDS exposure was semi-randomized between subjects (yielding two groups of 10 participants). The two groups did not differ in age or cognitive impairment ($p > 0.12$; two-sided *t*-tests).

The main outcome measures were cognitive functioning, mood, agitation, self-reliance in activities of daily living, social behavior, and well-being. These endpoints were assessed by standardized questionnaires and visual analogue scales rated by the nurses. Rest-activity cycles were analyzed from continuous wrist actimetry over 17 weeks (Motion Watch 8; CamNtech, Cambridge UK) for circadian and sleep parameters.

2.3. Dawn-dusk simulation

The design and characteristics of the DDS luminaire can be found in Appendix A of the supplementary material. During DDS, a polychromatic white lighting from light emitting diodes (LED) gradually changed illuminance (but not spectral composition; producing a color temperature of 4000 K), driven by the programmed simulation. We used the MacLite algorithm (Terman et al., 1989) for equatorial dawn and dusk transitions to keep the duration of dawn and dusk twilights constant throughout the study (Supplementary Fig. A1). The timing of dawn and dusk segments was separately determined based on each patient's bedtimes and get-up times during the first study week (baseline) as estimated by actimetry and nurses' logs. After the first and second week of DDS presentation, the procedure was repeated and some DDS times were slightly adjusted to better fit the patients' bedtimes and get-up times. This was repeated after 8 weeks for the group who received the DDS in the second half of the study. Caregivers were instructed to close blinds and curtains at bedtime. Unlike commercial dawn “alarm clocks” that jump from darkness to an intermediate intensity at the start of the dawn signal, the DDS initiated the rise at ~0.35 lx (close to the lower limit of civil twilight, sun 6° below the horizon). The curve followed a nonlinear, smooth progression over ~30 min preceding usual wake-up time, rising to 130 lx, which was maintained for another 60 min. Although variable head position affected proximal illuminance, the DDS curve shape retained its naturalistic contour. The dusk signal began automatically with 60 min at 80 lx, followed by approximately 30 min of gradual progression downward to 0.35 lx, when individual sleep onset was expected. Thereafter, the device turned off automatically for the night until the start of the dawn signal.

2.4. Questionnaires and nurses' assessments

Standardized questionnaires and assessments were carried out by trained caregivers, supported by an on-site psychologist (SW) for data management. Caregivers assessed the current status of a patient between two extremes on five continuous visual analogue scales (VAS; 0–100 mm) every morning approximately 1 h after wake-up: alertness (extremely alert / extremely tired); mood (very good mood / very poor mood); verbal interaction (very talkative / not talkative at all); well-being (very well / not well at all); cheerfulness (very cheerful / very sad). In addition, the Nurses' Observation Scale for Geriatric Patients [NOSGER; (Wahle et al., 1996)] was assessed at baseline and every 4 weeks (2 ratings during the condition with DDS and 2 ratings without DDS). This scale estimates six dimensions including memory, instrumental activities of daily living (IADL), activities of daily living (ADL), mood, social behavior, and disturbing behavior, with scores ranging from 5 to 25 points and higher scores indicating more impairment. IADL and disturbing behavior were excluded from analysis due to very skewed, non-normally distributed data. The Changes in Advanced Dementia Care Scale [CADS; (Haubner, 2002)], the Cohen-Mansfield Agitation Inventory [CMAI; (Cohen-Mansfield et al., 1989)] and the Quality of Life Scale for Severe Dementia [QUALID; (Weiner et al., 2000)] were assessed at baseline and every two weeks (4 ratings during the condition with DDS and 4 ratings without DDS). The CADS estimates the status of independence in daily life activities. It contains eight categories such as eating/drinking and self-body care with higher scores indicating greater independence in these activities. The CMAI contains 29 different behaviors related to agitation of three categories: aggressive behavior, physically non-aggressive behavior, and verbally agitated behavior. Each behavior was rated according to frequency of occurrence, from never to several times per hour, with higher scores indicating greater agitation. The QUALID assesses quality of life in dementia patients. Higher scores indicate lower quality of life.

For analysis, graphs and tables, the mean outcomes from VAS, NOSGER, CMAI and QUALID were subtracted from the sum of minimal and maximal possible scores in order to have the same direction of all assessments, i.e., the higher the better.

2.5. Actimetric measured rest-activity cycles and sleep

The rest-activity rhythms were recorded by wrist actimetry (MotionWatch 8, CamNtech, UK) and analyzed with the Sleep Analysis Software v7.23 (Cambridge Neurotechnology Ltd., Cambridge, UK). Actimetry recordings were downloaded weekly and all files were visually inspected for data losses. Activity data were interpolated with the mean 24-h activity if the data loss lasted for < 3 h and > 10 min per 24-h day. For data loss of > 3 h per 24 h, the respective day was excluded from circadian rhythm analysis (Bromundt et al., 2011). Data loss was on average 7.4% for the DDS and 7.6% for the condition without DDS. Sleep periods derived from actimetry recordings without any data loss were used for sleep analysis, on average 6.35 ± 1.23 (mean ± SD) nights of baseline, 50.2 ± 5.23 nights with DDS, and 51.75 ± 6.50 nights without DDS.

Nonparametric circadian rhythm analysis (Van Someren et al., 1997) was applied for weekly epoch lengths of 2–7 days, with assessments of: circadian activity amplitude as the absolute count of 24-h oscillations; inter-daily stability (IS) and intra-daily variability (IV), as indicators for the degree of day-to-day and intra-daily fragmentation of rest-activity patterns; and relative amplitude (RA), as the ratio of the 10 h with highest activity (M10) per 24 h, and the 5 h with lowest activity (L5). L5on was defined as the onset clock time for L5, and M10on as the onset clock time for M10.

The sleep analysis was conducted at a high sensitivity level and assessed time in bed (interval between bedtime and get-up time), sleep duration (interval between sleep onset and wake-up time), sleep efficiency (actual sleep time expressed as a percentage of time in bed), mean wake bout time (average length of each wake bout in the epoch-by-epoch wake/sleep categorization), and the fragmentation index, as measure of restlessness during sleep episodes [sum of mobile time (%) plus immobile bouts ≤ 1 min (%)].

2.6. Statistical analysis

Repeated analysis of variance (rANOVA; general linear model; GLM) with Huynh-Feldt's statistics was applied, and two-sided *t*-tests were used for post-hoc tests. To determine the effects of DDS, the within-subject factors "condition" (with DDS vs. without DDS), and "time" (first vs. second half of "condition", 4 weeks each) were included in the analysis. DDS1 indicates the first study half with DDS whereas noDDS1 indicates the first 4 weeks without DDS. Similarly, for the second 4 weeks of each condition: DDS2 indicates the second 4 weeks with DDS whereas noDDS2 indicates the second half without DDS. For the comparisons with the baseline week (BL) and for testing effects after several weeks of DDS exposure, we additionally analyzed a main effect of "condition" with three levels (BL, DDS2 and noDDS2). The variables "age" and "cognitive functioning" (mean S-MMSE scores) were added to the analysis as dichotomized covariates after applying a median split on both data sets (median value for age = 86 y, and median for S-MMSE = 13.5).

A potential order effect of DDS administration was determined for each variable separately. Pearson's correlations were used and non-normally distributed data were $\log_{10}$-transformed prior to analysis. For one participant, missing data from weeks 5–8 (without DDS; see Participants) was replaced by the values for the first 4 weeks of the same condition. SPSS (IBM Corporation, Armonk, NY, USA; v 25) was used for statistical analyses with the alpha criterion set at a significance level of $p < 0.05$. Cohen's d was calculated for the effect sizes.

3. Results

3.1. Timing of DDS

The DDS was well tolerated by all participants, based on quantitative analysis from activity watches and questionnaires as well as caregiver's observations. The timing of dawn and dusk was adjusted to the individual bed- and get-up times and kept fixed for the remainder of the study. The participants received the dusk signal on 63.9 ± 20.7% of all evenings, and the dawn signal on 63.5 ± 18.3% of all mornings. For the remaining evenings and mornings, participants either went to bed later (i.e., after the DDS signal) or got up earlier (i.e., before the DDS signal). Additionally, the DDS did not properly function due to technical reasons on 0.74% of all evenings and 2.8% of all mornings of the weeks with scheduled DDS.

3.2. Questionnaires and nurses' assessments

Participants expressed significantly better mood and greater cheerfulness upon awakening during DDS2, when compared to noDDS2 (VAS mood: "condition x time" $F_{117} = 12.79$, $p = 0.002$; $d = 0.37$, Fig. 1a; VAS cheerfulness: "condition x time" $F_{1,\ 17} = 11.30$; $p = 0.004$; $d = 0.42$; Fig. 1b).

The positive DDS effects on mood appeared stronger in the younger subgroup (< 86 years; n = 10), since their mood was better during both parts of the study, i.e. DDS1 and DDS2, when compared to noDDS2 ("condition x time x age" $F_{1,\ 17} = 9.25$, $p = 0.007$; DDS1 vs. noDDS2: $d = 0.55$; DDS2 vs. noDDS2: $d = 1.06$).

For the VAS alertness item, only those patients who had the DDS in the second half of the study showed improved alertness compared to the time without DDS (VAS alertness; interaction "condition x DDS order"; $F_{1,\ 18} = 12.79$, $p = 0.002$), whereas patients with DDS exposure in the first half showed no significant change in alertness (Table 2).

We found no statistically significant impact of the DDS on any of the standardized questionnaires (NOSGER, CADS, CMAI, QUALID). However, there was an influence of the covariate "cognitive functioning" indicating that participants with better cognitive functioning (i.e., S-MMSE score > 13.5; n = 10) were more self-reliant in daily activities (main effect of "cognitive functioning": NOSGER ADL: $F_{1,\ 17} = 5.37$, $p = 0.033$; CADS: $F_{1,\ 17} = 16.07$, $p = 0.001$), and also expressed more agitation (main effect of "cognitive functioning" CMAI: $F_{1,\ 17} = 4.53$, $p = 0.048$) than patients with lower cognitive functioning (Table 3).

In order to explore whether potential effects of the DDS were revealed only after several weeks, we compared the baseline week with DDS2 and noDDS2, but found no statistically significant effects of the

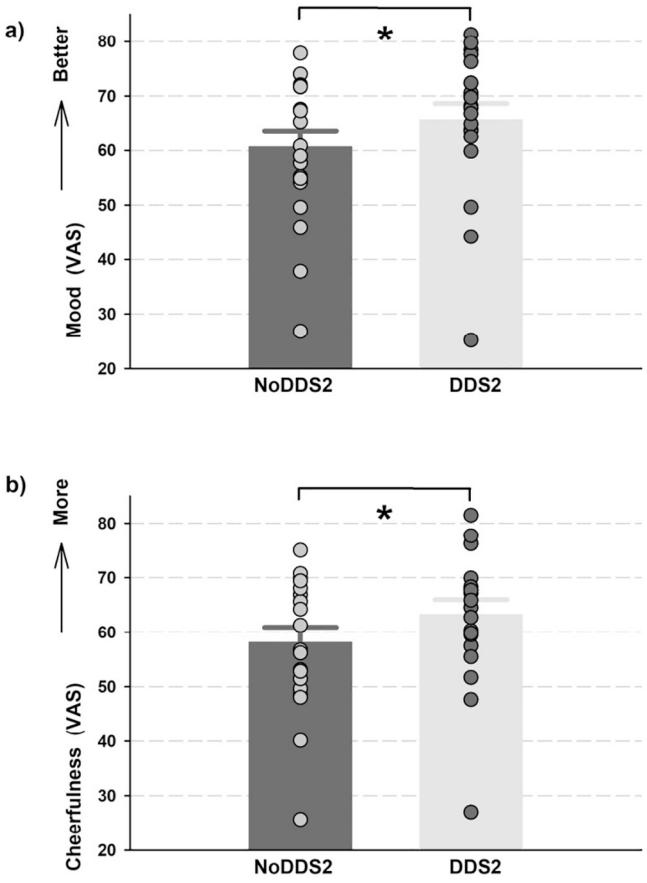

Fig. 1. Significantly a) better mood (* p = 0.036) and b) more cheerfulness (* p = 0.014) upon awakening during DDS2 (light grey bar) compared to noDDS2 (dark grey bar) (mean ± SE, n = 20, individual mean values are overlaid by light and dark grey circles).

Table 2
Order differences for alertness (VAS) between DDS conditions for patients with the DDS exposure in the first half (n = 10) and those in the second half (n = 10) of the study.

	DDS (8 weeks)	noDDS (8 weeks)	p
DDS first (n = 10)	66.3 ± 10.1	68.9 ± 11.6	n.s.
DDS last (n = 10)	69.9 ± 13.8	62.3 ± 14.7	0.01

Table 3
The group with better cognitive functioning (n = 10, S-MMSE > 13.5) showed more self-reliant activities of daily living (CADS, NOSGER ADL) and more agitated behavior (CMAI) than the group with lower cognitive functioning (n = 10, S-MMSE < 13.5; mean ± SD).

	Group with S-MMSE > 13.5	Group with S-MMSE < 13.5	p
NOSGER ADL	15.8 ± 3.9	12.4 ± 2.4	0.033
CADS	29.9 ± 9.1	17.4 ± 4.9	0.001
CMAI	183.3 ± 10.6	192.5 ± 8.0	0.048

Table 4
Mean ± SD of questionnaire and nurses' assessments for visual analogue scales (VAS), NOSGER, CADS, CMAI and QUALID at baseline, during DDS2 and noDDS2 (n = 20); * p < 0.05; significant main effect of the covariate "cognitive functioning" (means not shown).

	Baseline	DDS2	noDDS2
VAS Alertness	61.67 ± 15.85	69.05 ± 11.24	64.84 ± 15.22
VAS Mood	59.32 ± 11.92	65.65 ± 13.35	60.67 ± 13.25
VAS Verbal Interaction	56.89 ± 17.96	54.10 ± 16.88	48.62 ± 15.85
VAS Wellbeing	56.83 ± 12.92	60.61 ± 13.33	57.52 ± 12.83
VAS Cheerfulness	58.49 ± 11.24	63.25 ± 12.21	58.16 ± 12.27
NOSGER Memory	11.95 ± 2.09	10.75 ± 3.50	11.10 ± 3.55
NOSGER ADL *	15.70 ± 4.60	14.45 ± 3.62	12.85 ± 4.07
NOSGER Mood	19.65 ± 3.88	17.80 ± 3.76	19.10 ± 3.91
NOSGER Social Behavior	10.85 ± 3.56	11.40 ± 3.44	12.80 ± 4.79
CADS *	24.15 ± 10.96	23.05 ± 9.36	23.90 ± 10.56
CMAI	184.85 ± 11.60	186.05 ± 11.84	187.35 ± 12.83
QUALID	41.45 ± 8.13	41.15 ± 6.75	42.13 ± 6.45

DDS on the VAS and the standardized questionnaires ($F_{2, 34} < 2.89$, $p > 0.069$; Table 4). The NOSGER ADL and CADS showed an effect of the covariate "cognitive functioning" ($F_{1, 17} = 5.22$, $p = 0.035$; $F_{1, 17} = 15.17$, $p = 0.001$), confirming that the group with higher cognitive functioning was more self-reliant in activities of daily living.

3.3. Rest-activity cycles and sleep

Overall, the rest-activity recordings revealed a heterogeneous pattern with large inter-individual differences (Fig. 2). None of the circadian parameters was significantly influenced by DDS exposure, time, or their interaction ($p > 0.40$). In order to test the effect of DDS after several weeks, we also compared DDS2 and noDDS2 to baseline and found a significant main effect of "condition" for IV ($F_{2, 34} = 4.31$, $p = 0.024$), but post-hoc comparisons were not significant ($p > 0.455$; Table 5a).

However, a main effect of the covariate "age" was found for IV, IS and amplitude, indicating that the older subgroup (> 86 y) showed higher intra-daily variability of activity than the younger subgroup ($F_{1, 17} = 7.33$, $p = 0.015$, $d = 1.2$), reduced inter-daily stability of activity patterns ($F_{1, 17} = 7.49$, $p = 0.014$, $d = 1.2$), and lower amplitude of absolute activity ($F_{1, 17} = 8.49$, $p = 0.010$, $d = 0.9$) (Table 6).

Table 5
Mean ± SD of actimetry derived a) circadian parameters and b) sleep parameters at baseline, during DDS2 and noDDS2 (n = 20). * P < 0.05; main effect of the covariate "age".

	Baseline	DDS2	noDDS2
a) Circadian parameters			
Intra-daily Variability (IV) *	1.36 ± 0.33	1.32 ± 0.39	1.32 ± 0.36
Inter-daily Stability (IS) *	0.51 ± 0.15	0.48 ± 0.14	0.47 ± 0.15
Relative Amplitude	0.73 ± 0.16	0.73 ± 0.19	0.70 ± 0.19
Amplitude *	4962 ± 6287	3871 ± 3961	3885 ± 5204
L5 Onset	22:56 ± 2:40	22:35 ± 1:55	22:27 ± 2:34
b) Sleep parameters			
M10 Onset	8:57 ± 1:37	8:48 ± 1:15	9:36 ± 2:51
Bed time [h] *	19:11 ± 1:16	19:18 ± 1:30	19:13 ± 1:25
Get-up time [h]	8:11 ± 0:36	8:22 ± 0:37	8:27 ± 0:39
Time in bed [h]	12:59 ± 1:37	13:04 ± 1:46	13:15 ± 1:38
Sleep duration [h] *	12:25 ± 1:41	12:40 ± 1:47	12:43 ± 1:44
Sleep efficiency [%]	79.23 ± 11.21	82.64 ± 10.84	81.29 ± 12.24
Mean wake bout time [min]	3:58 ± 2:31	3:29 ± 1:48	4:05 ± 2:20
Fragmentation index	46.15 ± 20.04	42.50 ± 19.16	44.47 ± 19.81

None of the sleep parameters was significantly influenced by DDS exposure ($p > 0.174$; see also Table 5b). However, the older subgroup went to bed earlier than the younger subgroup (main effect of "age"; $F_{1, 17} = 5.29$, $p = 0.035$, $d = 1.16$), slept longer ($F_{1, 17} = 6.82$, $p = 0.018$, $d = 0.99$) and there was a trend for more time in bed ($F_{1, 17} = 4.44$, $p = 0.05$, $d = 0.92$; data not shown). The sleep analysis revealed no significant differences at baseline, or for order of DDS administration, or cognitive functioning ($p > 0.141$).

3.4. Correlations of quality of life, age and cognition with sleep and circadian parameters

In a final step, we correlated quality of life (as indexed by the QUALID), age and cognitive functioning by S-MMSE scores with all other variables of nurse assessments, circadian and sleep parameters by

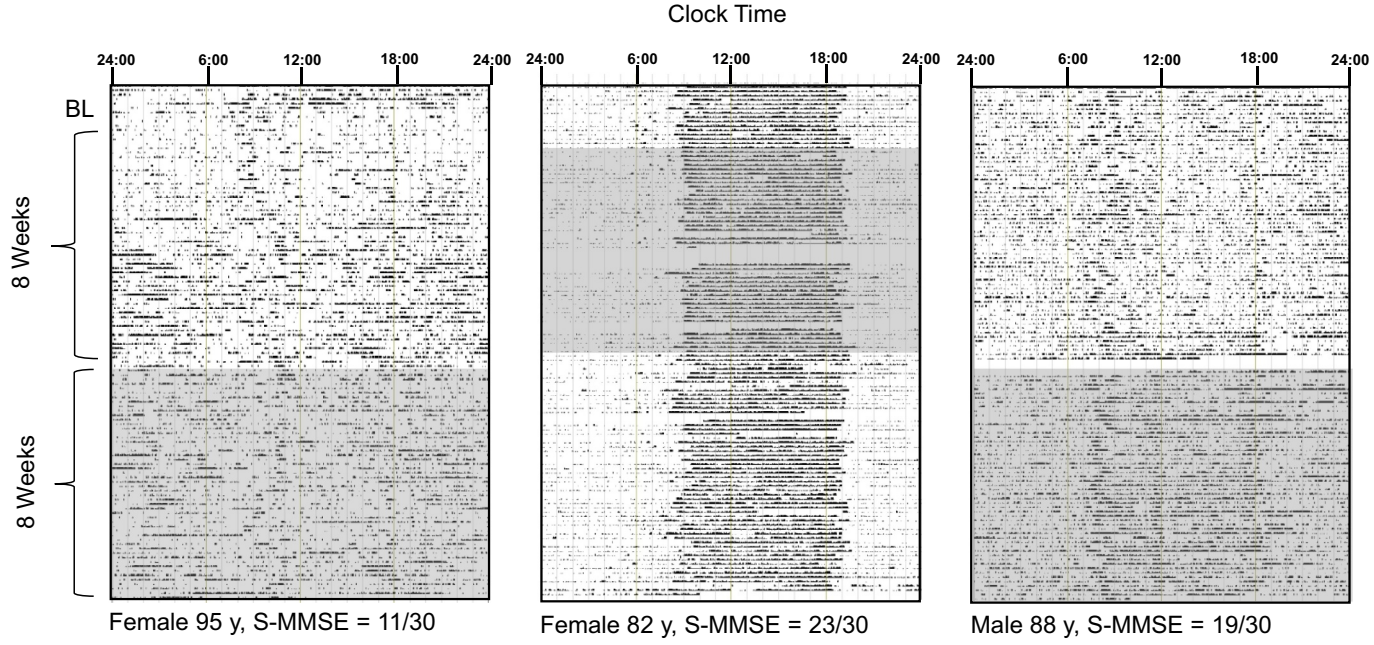

Fig. 2. Three examples of actograms from three patients over 17 weeks (grey overlay = with DDS) showing the high heterogeneity in rest-activity patterns [BL = Baseline week; S-MMSE (range 0–30; a score of 30 = least cognitive impairment)].

Table 6
The younger subgroup (n = 10, < 86 y) showed significantly higher IS and lower IV, and higher absolute amplitude compared to the older subgroup (n = 10, > 86 y; mean ± SD).

	Younger subgroup (< 86 y)	Older subgroup (> 86 y)	p
Inter-daily Stability (IS)	0.56 ± 0.16	0.41 ± 0.12	0.015
Intra-daily Variability (IV)	1.13 ± 0.36	1.51 ± 0.24	0.014
Absolute Amplitude	6223 ± 5907	2058 ± 2224	0.01

using mean values of all 17 weeks per subject. There were significant associations between higher quality of life (QUALID) and: greater alertness ($r^2 = 0.48$, $p = 0.001$), better mood (for both: NOSGER mood: $r^2 = 0.81$, $p < 0.001$; and VAS mood: $r^2 = 0.63$, $p < 0.001$), better well-being ($r^2 = 0.53$, $p < 0.001$), and greater cheerfulness ($r^2 = 0.65$, $p < 0.001$). Higher quality of life was also correlated with a higher stability of activity pattern between days (IS: $r^2 = 0.26$, $p = 0.021$), with a higher relative amplitude of day-night activity (RA: $r^2 = 0.26$, $p = 0.023$), a higher amplitude of absolute activity ($r^2 = 0.32$, $p = 0.009$) and with earlier get-up times ($r^2 = 0.25$, $p = 0.024$).

Older age was significantly correlated with reduced stability of activity patterns across days (IS: $r^2 = 0.38$, $p = 0.004$), higher variability of activity within days (IV: $r^2 = 0.45$, $p = 0.001$), lower amplitude of absolute activity ($r^2 = 0.65$, $p < 0.001$), with earlier bed times ($r^2 = 0.31$, $p = 0.011$), longer time in bed ($r^2 = 0.34$, $p = 0.007$) and longer sleep duration ($r^2 = 0.43$, $p = 0.002$), higher sleep efficiency ($r^2 = 0.36$, $p = 0.005$), and shorter mean wake bout times ($r^2 = 0.36$, $p = 0.005$). Age was not associated with S-MMSE, QUALID, CMAI, CADS ratings or VAS scores (all $p > 0.14$).

Better cognitive functioning according to mean S-MMSE scores was significantly correlated with more self-reliance in activities of daily living (NOSGER ADL: $r^2 = 0.48$, $p = 0.001$, and CADS: $r^2 = 0.75$, $p < 0.001$), and with better social skills (NOSGER social behavior; $r^2 = 0.31$, $p = 0.010$). None of the circadian or sleep parameters was significantly correlated with cognitive functioning ($p > 0.133$).

4. Discussion

We tested a newly developed naturalistic dawn-dusk simulator with dementia patients, in a balanced crossover design for 17 weeks during fall and winter. Several questionnaires were administered by trained caregivers, and rest-activity cycles were continuously recorded. The patients showed better mood and greater cheerfulness upon getting up during weeks with DDS exposure. The status of cognitive functioning per se had an impact on several outcome variables, such as independence in daily activities. Quality of life was significantly correlated with alertness, better mood and circadian stability, indicating that the DDS might be a meaningful, non-invasive tool to alleviate some of the burden, and increase quality of life, in these patients.

The improvement of mood and cheerfulness upon awakening may be directly induced by DDS exposure, since light exposure can lead to a greater serotonergic/dopaminergic signaling, as has been shown in patients with depression (Praschak-Rieder and Willeit, 2012; Tyrer et al., 2016). There is evidence from rodent studies that the impact of light on mood is independent of the SCN, and is conveyed by distinct subpopulations of intrinsically photosensitive retinal ganglion cells (Fernandez et al., 2018). A recent study found the circuit linking the retinal ganglion cells and the lateral habenula as a potential pathway for the positive effect of light in depression (Huang et al., 2019). In patients with seasonal affective disorder, dawn simulation was shown to have an antidepressant effect similar to classic bright light therapy (Danilenko and Ivanova, 2015; Terman and Terman, 2005), or even a superior effect (Avery et al., 2001).

The benefit may also stem from increased cortisol concentration upon awakening, since early morning bright light exposure enhances the cortisol awakening response in young healthy subjects (Scheer and Buijs, 1999; Thorn et al., 2004). Moreover, dawn light exposure in the last 30 min of sleep has been shown to increase subjective alertness and cognitive and physical performance after waking up (Thompson et al., 2015; Tonetti et al., 2015).

A single dawn signal can phase advance circadian timing (Danilenko et al., 2000). Dawn simulation also phase advances rhythms in patients treated for winter depression (Terman and Terman, 2010) suggesting a mechanism for the mood improvement found in the dementia patients. A further, indirect circadian mechanism may contribute to the DDS effect through stabilizing the sleep-wake cycle by increasing external zeitgeber strength compared with standard light on/off signaling. The slow rising glow of light may induce stronger zeitgeber signals than abrupt light switching. Since blinds were closed during DDS exposures and sleep episodes, there was no other dawn or dusk signal available.

We found significant DDS responses on mood within the first 4 weeks of the DDS in the subgroup of patients below age 86, suggesting that the response may need more time to manifest with higher age. Stronger effects in the younger group were also seen in greater inter- and intra-daily stability of activity patterns, greater absolute amplitude of activity, later bedtimes and shorter sleep duration. Higher age leads to greater SCN deterioration, which is accentuated in dementia (Skene and Swaab, 2003; Swaab et al., 1985), although within our advanced age groups there was no difference of cognitive function as assessed by the S-MMSE (younger vs. older subgroups, 13.5 vs.12.8; $p = 0.9$).

The level of cognitive functioning had a significant effect on daily activities and agitation, irrespective of DDS exposure. It is important to note that higher cognitive functioning might indirectly impact behavioral changes related to dementia without a direct connection to the efficacy of external zeitgebers like the DDS. A DDS effect on cognitive functioning might emerge with longer use, as was observed in a large multicenter study of long-term daytime bright light exposure (Riemersma-van der Lek et al., 2008). Those results showed a slowing in disease progression over the course of 3.5 years. A higher daylight exposure regimen might be added to the DDS application as a potential complementary approach.

Our study showed no significant influence of the DDS on circadian sleep-wake cycles or sleep, similar to other studies of bright daytime light exposure for dementia patients (Dowling et al., 2005). In our field study, the patients were free to vary their bed- and get-up times, with inconsistent exposure to the dawn and dusk signal. The 8-week treatment period, in which they experienced only 64% of dawn-dusk simulations, may have been insufficient. The signal was confined to 30-min segments of the algorithmic simulation curves, at the most rapid equatorial transition rate, which might be too fast. The seasonal timing for natural sunrise was between 6:58 am and 8:18 am, and for sunset between 4:37 pm and 6:24 pm (data extracted from https://www.sunrise-and-sunset.com; 47° 33′ N). Beyond the DDS signal, natural dusk and dawn might also have had an effect on the patients if one or both were perceived through the window if their habitual bedtimes with scheduled DDS occurred after sunset, or their habitual get-up time with the DDS occurred before sunrise. The spectral composition varies under natural twilights (Spitschan et al., 2016), which contrasts with the constant color temperature of the DDS. As recently shown, dynamic lighting led to less daytime napping and less fragmented night sleep in people with dementia (van Lieshout-van Dal et al., 2019) and less nighttime agitation (Wahnschaffe et al., 2017a). Lastly, considering the

inter- and intra-individual heterogeneity of sleep patterns, our study may have been underpowered to detect improvement, in contrast to the positive effects on daytime behavior. However, this result may have been influenced by the raters, who were not blinded to the conditions.

Within subjects, better quality of life, mood and higher alertness were associated with higher relative circadian amplitude and more stable rest-activity patterns. Many patients with dementia show blunted melatonin secretion (Münch et al. 2017; Skene and Swaab, 2003; Uchida et al., 1996), suggesting weakened, low-amplitude rhythms. Thus, increasing zeitgeber strength with light exposure (as with the DDS) may be crucial for increasing circadian stability. From our and results from others (Saito et al., 2018) it seems that dementia severity and circadian disruption depend on cognitive function, but also other internal and external functions. The greatest benefit for these patients is that their mood and cheerfulness improved under the DDS condition. Given the fact that there is as yet no cure for dementia, any non-pharmacological approach which alleviates symptoms, increases mood and indirectly improves quality of life without side effects seems essentially important for these patients, their relatives and caregivers.

5. Conclusion

We found positive effects on mood and cheerfulness in patients with dementia, using a naturalistic dawn-dusk simulation within the civil twilight range. The results justify replication in combination with more gradual northerly twilight transitions terminating at higher maximum dawn illuminance, and with a naturalistic progression of spectral composition.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Description of authors' roles

VB, AWJ and MM designed the study; MB, SW and VB performed the study; MH and AWJ designed the luminaire; MH, AWJ and MB tested the luminaire; MT provided the algorithm and software for DDS administration; SW helped with data processing; VB and MM analyzed the data; VB, MM, AWJ and MT wrote the paper and edited and reviewed the final version of the manuscript.

Appendix A. Supplementary data

See supplementary material about the development, design and use of the DDS (Appendix A) with Supplementary Fig. A1 (DDS example) and Fig. A2 (DDS design). Supplementary data to this article can be found online at doi:https://doi.org/10.1016/j.exger.2019.110641.

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