ELSEVIER

Experimental Gerontology 38 (2003) 207–216

Experimental Gerontology

www.elsevier.com/locate/expgero

Dawn–dusk simulation light therapy of disturbed circadian rest–activity cycles in demented elderly

Paola Fontana Gasio[a], Kurt Kräuchi[a], Christian Cajochen[a], Eus van Someren[b], Isabelle Amrhein[a], Mona Pache[c], Egemen Savaskan[d], Anna Wirz-Justice[a,*]

[a]*Centre for Chronobiology, Psychiatric University Clinic, Basel, Switzerland*
[b]*Netherlands Institute for Brain Research, Amsterdam, The Netherlands*
[c]*University Eye Clinic, Basel, Switzerland*
[d]*Department of Psychogeriatry, Psychiatric University Clinic, Basel, Switzerland*

Received 17 May 2002; accepted 2 July 2002

Abstract

We investigated whether low intensity dawn–dusk simulation (DDS), a 'naturalistic' form of light therapy designed to embed sleep in its accustomed phase, could improve the disturbed circadian rest–activity cycle, nocturnal sleep and and/or cognitive functions in dementia. A protocol of 3 weeks each of baseline, treatment and follow-up was completed by 13 patients (85 yr old ± 5 yr, MMSE 14 ± 5; $n = 9$ DDS versus $n = 4$ 'placebo' dim red light) who wore an activity/lux monitor throughout. There were no significant changes in clinical or cognitive status, nor modification of circadian stability or amplitude characteristics of the rest–activity cycle. However, two aspects of sleep responded to DDS but not to dim red light. The main sleep episode was 1:14 h earlier during treatment ($p = 0.03$) compared with before and after DDS. With respect to actimetry-determined sleep variables, the DDS group tended to have shortened 'sleep latency', longer 'sleep duration', more nocturnal immobility and less nocturnal activity than the dim red group ($p < 0.1$). In parallel, nighttime light exposure tended to be reduced ($p = 0.07$). These promising findings—after only 3 weeks of light treatment in elderly patients with advanced dementia—suggest that the circadian timing system remains functionally responsive even to low intensity DDS light. Increasing zeitgeber strength is an important strategy for improving sleep quality and timing in dementia, and DDS light therapy may provide one of the appropriate means to do so.
© 2002 Elsevier Science Inc. All rights reserved.

Keywords: Circadian rest–activity cycle; Sleep disturbances; Dawn–dusk simulation; Light therapy; Alzheimer's disease; Dementia

1. Introduction

Sleep disturbances increase with age. Sleep is delayed in onset, more superficial and fragmented, and often followed by early morning awakening (Bliwise, 1993). This age-related reduction of sleep consolidation is primarily related to a reduction in the consolidation of non-rapid-eye-movement sleep (Dijk et al., 2001). Elderly patients suffering from dementia often have disturbed sleep–wake behavior and in some cases the rest–activity cycle becomes totally disrupted (Van Someren et al., 1996; Werth et al., 2002). In Alzheimer's dementia (AD) it has been hypothesized that the disrupted rest–activity cycle is caused by deterioration of neurons of the suprachiasmatic nucleus (SCN), the biological clock (Stopa et al., 1999; Swaab et al., 1985; Witting et al., 1990). Support for this hypothesis comes from changes in the characteristics of circadian rhythms such as core body temperature and melatonin secretion in AD patients (Satlin et al., 1995; Harper et al., 2001). In addition, the finding of up-regulated melatonin-1a receptors in hippocampus, retina and vascular tissue of AD patients suggests a widespread compensatory response to the markedly diminished melatonin levels (Savaskan et al., 2001, 2002a,b).

The circadian pacemaker in the SCN is synchronized with the 24 h day by so-called 'zeitgebers', of which light is the most important. In elderly demented patients most zeitgebers are reduced: social input is diminished, motor activity decreases, and in particular, there is less exposure to sufficient outdoor or bright light (Ancoli-Israel et al., 1997b; Martin et al., 2000; Mishima et al., 2001). In addition to

* Corresponding author. Tel.: +41-61-325-5473; fax: +41-61-325-5577.
E-mail address: anna.wirz-justice@pukbasel.ch (A. Wirz-Justice).

0531-5565/03/$ - see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0531-5565(02)00164-X

degeneration of SCN function with age, ocular light transmission may be impaired by different age-related deficiencies in the eye (i.e. macula degeneration, clouding of the ocular media, retinopathies, cataracts, etc.) or optic nerve degeneration. Thus, even if patients were exposed to adequate light intensities during the day, less light would actually reach the circadian clock.

Increasing zeitgeber strength by augmenting light intensity has been suggested as a possible treatment for stabilizing disrupted sleep–wake rhythms (Campbell et al., 1995), and in recent years a number of studies have tested the effects of light in patients with dementia (Satlin et al., 1992; Van Someren et al., 1997; Okumoto et al., 1998; Mishima et al., 1998; Haffmans et al., 2001; Ancoli-Israel et al., 2002).

Light therapy was developed as a treatment for seasonal affective disorder (SAD) (Partonen and Magnusson, 2001). Depressive symptoms are also found in early stages of dementia of the elderly. The sleep disturbance can be a direct consequence of dementia or related to the depressive symptoms. Although plausible, there is no direct evidence that light therapy can improve depressive symptoms in dementia. The chronobiological treatment could improve the disrupted sleep–wake cycle, diminish the intake of hypnotics, improve cognitive function and/or reduce depressive symptoms.

Conventional light therapy is administered by sitting for a minimum of 30 min per day in front of a light box. This procedure is difficult for patients with dementia and requires supervision (Colenda et al., 1997). Thus, an alternative has been developed, to augment light intensity in the ambient surroundings of the main room where patients spend their days (Van Someren et al., 1997; Riemersma et al., 2001). Another possibility is the use of dawn–dusk simulation (DDS) mimicking outdoor twilight transitions. Here a gradual dusk and dawn is fitted to the patient's sleep time and does not require daily lightbox sessions or care-giver presence. DDS can be considered as a 'naturalistic' light therapy, using lower and gradual changes in light intensity (Terman et al., 1989). It has been successfully used to treat SAD patients (Terman et al., 1989; Avery et al., 2001) and for patients suffering circadian sleep–wake cycle disorders (Terman and Terman, 2000). Low intensity dawn simulation has been shown to phase advance or prevent a delay drift in the circadian rhythm of melatonin secretion (Terman et al., 1989; Danilenko et al., 2000a,b).

Although the gold standard for evaluating sleep–wake status is the electroencephalogram (EEG), it is not easily applicable in many clinical conditions, particularly in demented patients. EEG records of demented patients show many diffuse delays, which makes discrimination between sleep and wakefulness difficult (Bliwise, 1993).

Twenty-four-hour around-the-clock observation has been used as an heroic method to gain the needed information (Martin et al., 2000), however, actimetry has become more practicable for objective documentation of rest–activity rhythms in dementia populations (Ancoli-Israel et al., 1997a). Actimetry consists of a small computerized device, usually worn on the non-dominant arm, that continuously measures movements per time interval selected. Thus, activity counts can be collected over days, weeks or longer, is non-invasive and the method is well tolerated by patients (though requiring not a few innovative techniques to convince them to wear it or conversely, to not lose the apparatus!).

We report here a pilot study of the feasibility of DDS light therapy in a Swiss population of patients with different degrees of dementia, using actimetry to investigate their circadian rest–activity cycle and to quantify sleep disturbances. The aim of the study was to document and ameliorate the condition of elderly, demented patients with disrupted rest–activity cycles. DDS was delivered at the bedside and timed to embed sleep in its accustomed phase for each individual.

2. Material and methods

2.1. Subjects

Subjects were recruited from two nursing homes (A, W) or the nursing wing (E) for demented patients in the Psychiatric University Clinic, Basel, Switzerland. Selection criteria were: men or women over 65 yr of age, symptoms/diagnosis of dementia, sleep disturbances (validated by health professionals). Patients with medical illness or other problems were excluded. Medication was kept as constant as possible. Informed consent was signed for every subject by themselves or their relatives, their physicians and their caregivers. The study was approved by the ethics committee of the Medical Faculty, University of Basel. All subjects had an ophthalmologic examination to screen for visual problems. Neither blind subjects nor individuals with severely impaired vision were included.

Thirteen patients completed the study and seven dropped out (non-compliance with wearing the actimeter [5], fear of the DDS installation [1], illness [1]). Details in Table 1.

2.2. Neuropsychiatric status

The mini-mental-state-examination (MMSE) was used to evaluate the grade of dementia severity (Folstein et al., 1975). A short form of the neuropsychiatric inventory was used in the nursing home version (NPI-NH) (Cummings et al., 1994). This test evaluates neuropsychiatric symptoms and the additional work for nurses caused by the management of these symptoms. For the evaluation of mood or diagnosis of depression, respectively, the geriatric depression scale (GDS) was used (Sheikh and Yesvage, 1986). With neuropsychological tests developed for the Consortium to Establish a Registry for Alzheimer's Disease

Table 1
Study participants

Group	#	Age	MMS-E	Psychiatric diagnoses	Major medication (daily dose)
DDS	1	95	16	Probable AD	Clozapine (37.5 mg/d)
	3	83	21	Dementia, probably vascular	Digoxine (0.25 mg/d), Enalapril (20 mg/d)
	4	83	21	Probable AD with psychotic symptoms, depression	Haloperidol (8 Drp/d), Citalopram (10 mg/d),Oxazepam (15 mg/d), Ramipril (1.25 mg/d), Amiloride (2.5 mg/d), Hydrochlorothiazide (25 mg/d), Nitroglycerine (25 mg TTS 20–8°°), ASS (100 mg/d)
	5	89	14	Probable AD with psychotic symptoms	Haloperidol (1–2 mg/d), Olanzapine (after 1 month 7.5 mg/d), Pipamperone (only first 2 months 20–40 mg/d), Carbamazepine (after 2 months 100–200 mg/d), Zolpidem (10 mg/d), Melperon (after 2 months 50 mg/d)
	7	82	11	Probable AD with hydrocephalus	Valproate (600 mg/d), Amlodipine (5 mg/d) Tolterodin (2 mg/d), Celecoxib (400 mg/d)
	9	88	15	Probable AD	Pipamperone (min 20 mg/d), Moclobemide (450 mg/d)
	11	83	15	Probable AD	Enalapril (40 mg/d)
	12	90	2	Dementia, probably vascular	Trimipramine (50 mg/d), Bromazepam (0.75 mg/d)
	13	88	9	Probable AD	Clomipramine (25 mg/d), Amlodipine (5 mg/d), Paracetamol (1500 mg/d), Phenprocoumon
Dim red light	2	87	14	Lewy body dementia	Haloperidol (10 Drp/d), ASS (100 mg/d)
	6	88	9	Probable AD	Clomipramine (25 mg/d), Amlodipine (5 mg/d), Paracetamol (1500 mg/d)
	8	78	19	Probable AD	Haloperidol (10 mg/d), Trimipramine (25 mg/d), Oxazepam (15 mg/d), ASS (100 mg/d)
	10	79	15	Probable AD, Parkinson's disease	Donepezil (5 mg/d), Citalopram (30 mg/d), Levadopa + Benserazid (750 mg/d), Oxazepam (15 mg/d), Amiloride (2.5 mg/d), Hydrochlorothiazide (25 mg/d)

(CERAD) we measured memory, cognitive impairment and the progression of dementia (Morris et al., 1989).

2.3. Ophthalmological screening

Each patient was screened by an experienced ophthalmologist. The ophthalmologic examination included: best corrected visual acuity, pupillary reaction, random dot test for stereoscopic vision (Lang I test), motility, saccades confrontation visual field, slit-lamp biomicroscopy, and Goldmann applanation tonometry. In order to avoid problems due to cognitive decline, visual acuity was tested using the Lea Hyvärinen test, a symbolic chart test especially designed for children.

2.4. Design

Thirteen inpatients with the diagnosis of dementia and with nurse-reported sleep disturbances were randomly assigned to a regimen of DDS ($n = 9$ women, aged 86.8 ± 4.5 yr, MMS: 13.8 ± 5.9) or 'placebo' dim red light (<5 lux; $n = 4$, 3 women and 1 man, aged 83.0 ± 5.2, MMS: 14.3 ± 4.1). The low number in the second group arose by chance from the original randomization scheme for 40 patients. The group size was not balanced by the time we realized that the required number of patients could not be recruited. All wore an activity/lux monitor continuously during 3 weeks each of baseline, DDS or dim red light treatment, and follow-up, and received neuropsychological testing at each of these phases.

2.5. Dawn–dusk simulation

The dawn–dusk simulator (DDS)™ includes a computer algorithm which drives an electronic controller connected to an overhead halogen lamp placed behind a diffusing membrane behind the subject's bed (Terman et al., 1989). The DDS accurately specifies outdoor illumination level as a continuous function of time, for latitude and longitude at any day of the year. Thus, the rate of change of dusk before sleep and dawn during sleep can be chosen to fit the individual's habitual sleep times.

For our patients, two dates/latitudes were chosen to provide DDS parameters based on time in bed during baseline. Dusk on 10th April at 38°N lasted 44 min, the dark period 10 h, the dawn 34 min. Dusk on 1st July at 29°N lasted 30 min, the dark period 9 h 16 min, the dawn 30 min. The signal was truncated at 0.001 lux and at 70% of maximum 400 lux. The post-dawn signal remained on for 15 min, the pre-dusk signal for 45 min (to give patients time to be in bed). The placebo condition used the same simulation parameters but replaced the white light with a 15 W red-light bulb yielding <5 lux. An example of the light signal for subject #1 is shown in Fig. 1. This is a calibration signal measured 30 cm from the lamp screen. The maximum light intensity measured was ~210 lux,

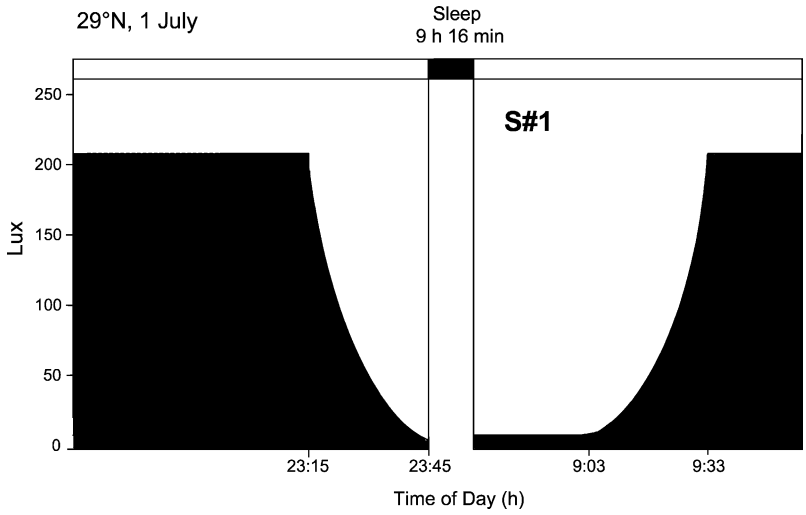

Fig. 1. Illuminance at 30 cm from diffusing screen measured at 1 min intervals over the period of dusk and dawn illumination (29°N 1 July) as administered to Patient #1. The timing of this 9 h 16 min dark period for sleep was fitted to the patient's average 'sleep' time (from actimetry) in baseline. Light during the day was not controlled (natural conditions). The treatment at ca. 200 lux began for 45 min in the evening (to allow time to go to bed), then declined exponentially as defined by this latitude to 0.001 lux where the signal was truncated. Dawn began at 0.001 lux, rose to ca. 200 lux, and remained on for 15 min.

the amount received by the patient at the level of the pillow would be somewhat less.

2.6. Actimetry

The rest–activity cycle was documented over the 9 weeks of the study with a small activity monitor (Actiwatch®, Cambridge Neurotechnologies, UK) worn on the non-dominant wrist. The monitor contains a piezo-electric linear accelerometer; activity counts are accumulated at selected time intervals and data are downloaded into a computer. Concurrently, light exposure is measured by an integrated light sensor.

2.7. Data analyses

2.7.1. Psychometric tests

MMS-E, NPI-NH, GDS and CERAD scores were subjected to an ANOVA for repeated measures (rANOVA).

2.7.2. Actimetry and lux data

Data were recorded in 1 min epochs. Daily records were checked for artifacts or lost data and compared with the logbook kept by the nurses. Missing activity or light data were replaced with the average of the mean of the 3 previous days at that time of day. Examples of raw data for activity and light exposure over 24 h are presented in raster format (Fig. 2). The following analyses were carried out to compare treatments.

2.7.2.1. Mean activity and light exposure. To test for effects of DDS or dim red light on the rest–activity cycle, motor activity for each patient was averaged into 1 h bins over the 24 h cycle, and averaged for each 3-week period (Fig. 3). In addition, activity was averaged separately for each institution (Fig. 5). The same calculations were carried out for light exposure: light data were averaged into 1 h bins, over each 3-week period, separated for the group DDS and dim red and for each institution.

2.7.2.2. Circadian rhythm organization. Activity data from 7 consecutive days were used for calculation of circadian rhythm variables. The baseline data set was chosen not to be close to the date of hospitalization (the first week was often particularly restless); light and follow-up periods as close to the end of the 3-week period as possible.

Circadian rhythm organization can be defined by non-parametric variables (Van Someren et al., 1999). Intradaily stability (IS) is inversely proportional to the day-to-day variation of the activity pattern, and gives an indication of the strength of coupling between the rest–activity rhythm and zeitgebers. Interdaily variability (IV) is a measure of the fragmentation of the rhythm. IS and IV variables were calculated on the number of min containing any activity per hour (i.e. compressing and limiting the range of hourly values to 0–60), using software written by EvS. Non-parametric indices of the amplitude and phase of the rhythm were generated by calculating the relative amplitude (RA) of the rest–activity cycle from the difference between the means of the most active 10 h period (M10) and the least active 5 h period (L5) in the average 24 h pattern. The onset time of both L5 and M10 can be used to quantify the onset of the most restful and most active period. In order to increase time resolution these variables were calculated on the number of min containing activity in 6 min rather than 1 h intervals.

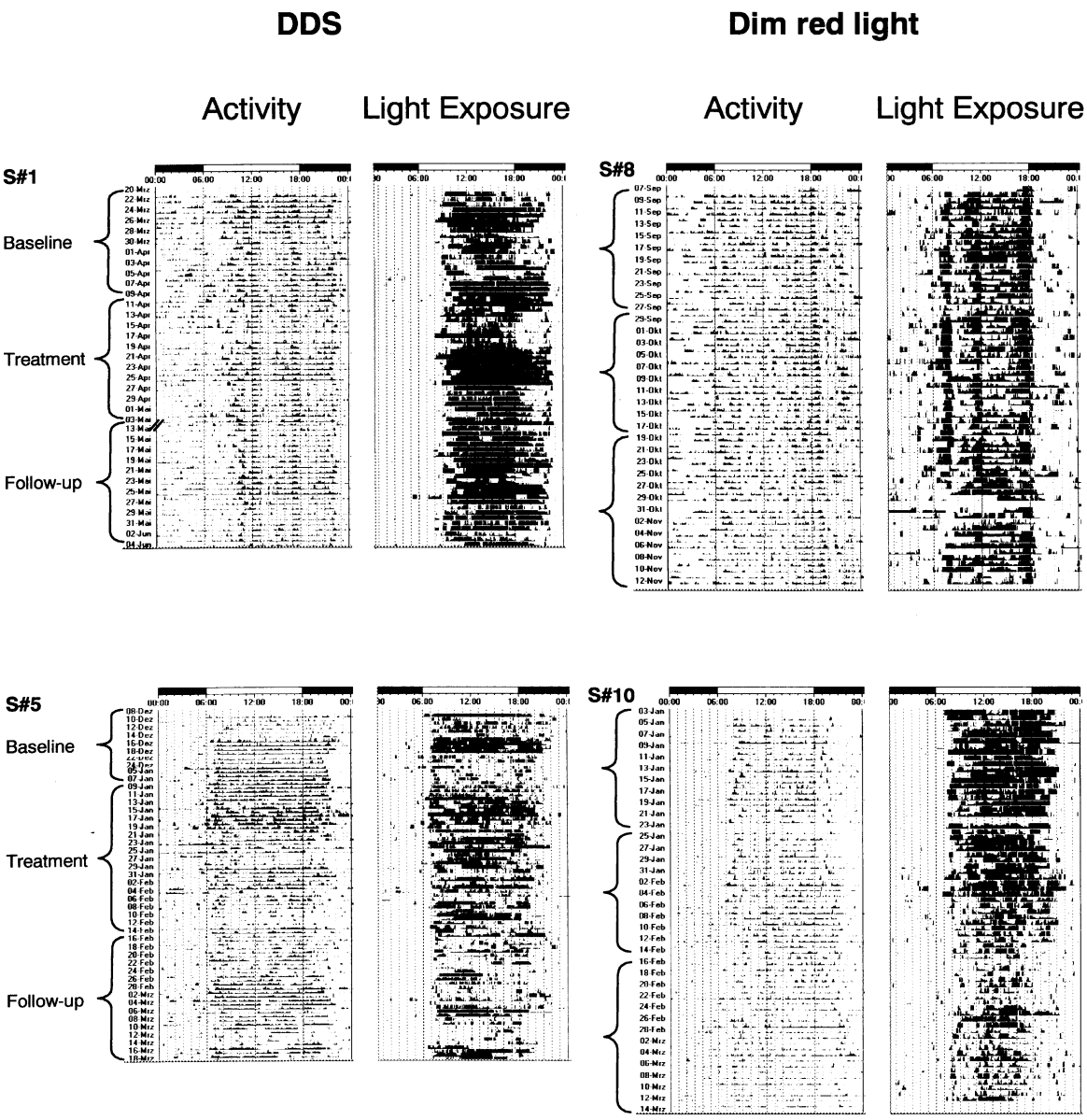

Fig. 2. Examples of raw data over the entire protocol (baseline, treatment, follow-up) from two patients who received DDS (S#1, S#5), and two who received dim red light (S#8, S#10). On the left-hand side, 24 h motor activity is presented in raster format, subsequent days beneath each other, on a condensed scale (maximum activity 1000 counts). On the right-hand side, 24 h light exposure is presented in identical format, except that the threshold is low (50 lux) to visualize the many brief nocturnal episodes of lights on. Social zeitgebers can be seen clearly, e.g. activity in S#1, light exposure in S#8 (more light at breakfast, lunch and dinner). The actograms reveal the degree and timing of disturbed nocturnal activity: in S#1 this restlessness was not accompanied by turning on the lights, whereas in S#8 light exposure was often parallel to irregular and recurrent nocturnal restlessness (in S#5 and S#10 to a lesser extent).

2.7.2.3. Circadian phase. To investigate putative phase shifts, a detailed intraindividual analysis focused on the 3 h before and after lights off mornings and evenings.

An indirect method of estimating internal circadian phase without measuring melatonin rhythms has been developed in subjects with regular sleep–wake cycles (Terman et al., 2001). The average sleep midpoint during baseline, which is strongly correlated with the dim light melatonin onset, is calculated from sleep onset and wake-up times. Calculating sleep midpoint + 2.5 h yields an estimate of optimum circadian time to elicit phase advances with light therapy.

2.7.2.4. 'Sleep' analysis program. Sleep logs were kept by the nurses, and this ensured that patients were in bed in their rooms during the dawn and dusk periods. With the help of these logs, two independent raters estimated daily times of going to bed and getting up in the activity files (often difficult in such disturbed actograms). The sleep analysis program (Software: Actiwatch Sleep Analysis 98,

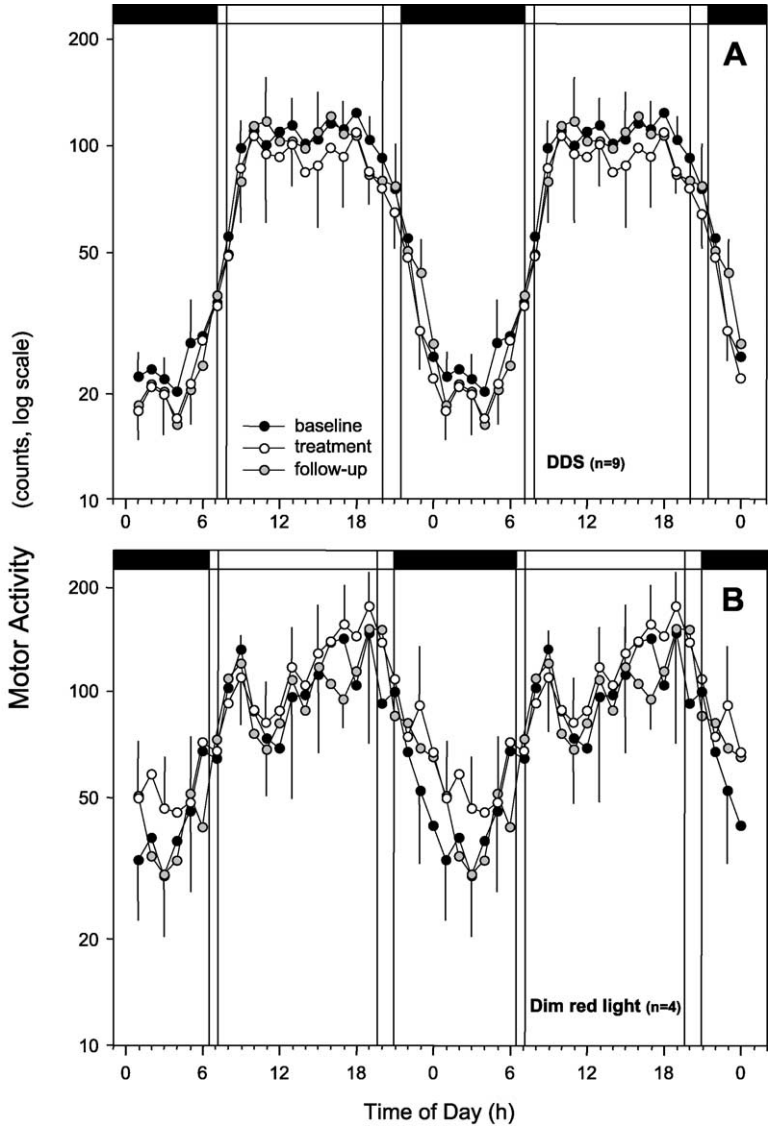

Fig. 3. Motor activity for each subject was averaged in 1 h bins and then over 7 consecutive days of baseline, treatment, and follow-up. The group averages are double plotted (24 h data repeated to see transitions more clearly) as a function of average timing of DDS or dim red light application before and after sleep (horizontal black bars). For clarity, only one SEM is given for every second value. The log scale increases resolution of low values. Although nocturnal activity under DDS and follow-up appeared somewhat less, this was not significant; only the timing of the L5 quiescent episode was advanced. The amount of light exposure in this same period of time decreased (see text for details). In contrast, dim red light appeared to worsen nocturnal activity (n.s.); these patients had (by chance) much higher nighttime activity than the DDS group.

Cambridge Neurotechnology Ltd. Version 4.07) was then applied to the data to determine 32 actimetry-derived 'sleep' variables (in quotation marks to emphasize that these are not the sleep-EEG equivalents).

Effect size (d) was calculated for the data sets showing a tendency ($p < 0.1$) to significance (Cohen, 1988). This parameter also defines the size of significant effects ($d = 0.3$, small; 0.5, medium; 0.8, large).

3. Results

DDS and dim red light groups did not significantly differ in age ($p = 0.2$) and MMS-E scores ($p > 0.8$). In addition, there were no significant effects of either treatment in the neuropsychological evaluations (CERAD, MMS-E, NPI and GDS; $p > 0.2$).

3.1. Actimetry and light exposure

The actograms revealed each patient's specific pattern of nocturnal disturbance and daytime napping. Individual examples of 1 min activity data over the entire study are shown in Fig. 2.

Visual inspection of the actograms revealed that

- the rest period was disturbed (as expected from the nurses' selection criterion);

- the daytime activity period often contained naps (sometimes more than once a day);
- the rest–activity cycle pattern was strongly influenced by the daily zeitgebers in each nursing home or on the ward;
- patients were usually put to bed rather early, resulting in 10–14 h spent in bed.

The day by day light exposure is presented in the same format beside the representative actograms, at a higher resolution (Fig. 2). Visual inspection of the individual light exposure patterns revealed that:

- overall light exposure was quite low (<300 lux during the day);
- the time of lights out and lights on in each nursing home or on the ward generally helped to estimate when patients went or were put to bed;
- lights on during the rest period indicated sporadic awakenings or longer episodes of wakefulness or restlessness or care-giver presence.

DDS did not modify mean activity over the 24 h, nor did dim red light (Fig. 3). Even adjusting each person's activity to the individual timing of DDS in the evening did not yield any significant differences.

Analyses of the light exposure data did not reveal any significant differences with either DDS or dim red light treatment. Since visual inspection of the mean curves suggested lower values during the night with DDS treatment, the data between 0 and 6 h were separately analyzed by rANOVA. Average nighttime light exposure tended to decline with DDS ($p = 0.07$), i.e. patients (or caregivers) turned the lights on less often or for a shorter time.

3.1.1. Circadian rhythm organization

None of the circadian stability or amplitude characteristics (IS, IV, RA) were modified by DDS or dim red light. However, the onset of L5, the period of the 5 consecutive least active hours, showed an advance in the DDS but not in the dim red light condition. A post-hoc *t*-test on the onset of the L5-phase during DDS treatment versus the pooled baseline and follow-up assessments confirmed this phase advance (23:48 ± 2:21 h [mean ± standard deviation] versus 1:02 ± 1:48 h, $t = 2.55$, df = 8, $p = 0.03$). No such advance occurred in the dim red light group (1:03 ± 2:20 h versus 0:34 ± 1:51 h, $t = -0.51$, df = 3, $p = 0.65$) (Fig. 4).

Detailed rANOVA of a putative phase shift during the 3 h before dawn and dusk, or the same period during dim red light, also did not yield statistical significance. However, 3/9 patients showed a phase advance of both rise and fall of activity after DDS compared with baseline (intraindividual comparison 3-way ANOVA), whereas none in the dim red group did so. In addition, motor activity in the evening

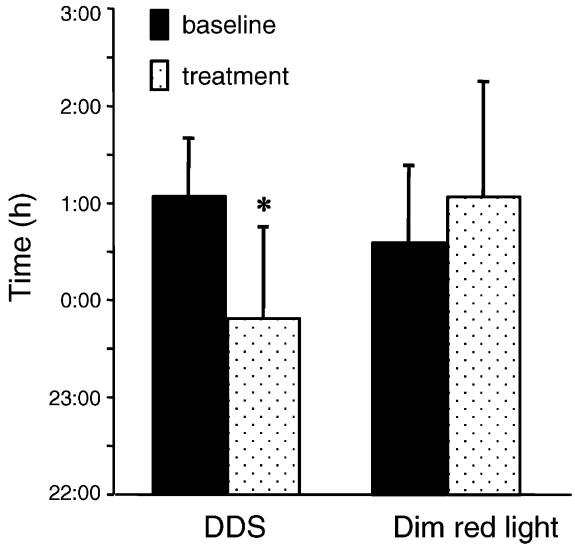

Fig. 4. The average timing of the L5 nocturnal quiescent period is shown for baseline (pooled with follow-up) versus treatment. L5 was significantly advanced by DDS (see text for statistics).

significantly decreased in 4/9 patients during and after DDS treatment, with no changes in the dim red group.

Possible factors that might explain the phase advance by (only) 3 patients were checked: first, whether they received different DDS scheduled light exposure or overall daytime light exposure (baseline versus treatment); second, ophthalmologic differences; third, the RA of the rest–activity cycle (lower RA is easier to phase shift). None of the *t*-tests was significant.

There were also no ophthalmological or light exposure differences in those patients who manifested decreased evening activity during and after DDS.

Post-hoc analysis showed that none of the patients had been given light at the calculated 'optimum' circadian time (Terman et al., 2001), because all slept beyond this time and were not awakened for the dawn exposure. However, this method was developed for healthy subjects, and may not be adequate for estimates of circadian phase from patients with disturbed sleep–wake cycles where the correlation often breaks down (Satlin et al., 1995).

3.1.2. 'Sleep' analysis

The 2-factor rANOVA with 3 repeated measures (baseline/treatment/follow-up) showed no significant main effects in any of the 32 'sleep' variables. However, in a variety of measures there was a tendency to amelioration with DDS treatment and worsening with dim red light, as shown by the interaction term. Sleep duration was estimated from sleep onset to sleep offset in two ways, by including or subtracting nocturnal wake episodes (defined as 'assumed sleep duration' or 'actual sleep duration', respectively). The DDS group tended to sleep longer during treatment (which did not last during follow-up) than the dim red light group

Table 2
Selected actimetry-derived 'sleep' variables (mean ± s.e.m. $N = 9$ DDS, 4 Dim red; h:min unless otherwise defined)

	Baseline		Treatment		Follow-up	
	DDS	Dim red	DDS	Dim red	DDS	Dim red
Time in bed	12:59 ± 0:33	12:25 ± 0:34	12:40 ± 0:34	13:58 ± 0:30	13:29 ± 0:32	12:51 ± 0:30
Sleep start	19:02 ± 0:27	18:49 ± 0:59	20:17 ± 7:17	17:42 ± 0:60	18:29 ± 0:38	19:05 ± 0:28
Sleep end	08:01 ± 0:26	07:14 ± 0:12	07:57 ± 5:36	07:40 ± 0:26	07:58 ± 0:23	07:56 ± 0:47
Assumed sleep duration	11:07 ± 0:43	10:34 ± 0:55	11:26 ± 7:35	09:28 ± 1:20	10:57 ± 0:43	09:50 ± 1:13
Actual sleep duration	09:13 ± 0:40	08:17 ± 1:16	09:36 ± 6:28	07:13 ± 1:30	09:00 ± 0:32	07:10 ± 1:30
Sleep efficiency (%)	77.2 ± 4.4	71.9 ± 7.2	80.4 ± 2.1	62.6 ± 10.6	76.5 ± 1.0	59.9 ± 10.3
Sleep latency	0:43 ± 0:23	0:37 ± 0:37	0:22 ± 1:32	1:41 ± 1:27	0:39 ± 0:17	1:41 ± 1:17
# Wake bouts	27.4 ± 0.4	26.5 ± 5.4	27.9 ± 3.5	25.2 ± 2.0	28.2 ± 4.5	26.1 ± 1.3
# Immobile phases	58.7 ± 6.5	62.4 ± 5.0	62.6 ± 6.6	56.0 ± 9.0	58.0 ± 7.2	49.7 ± 4.9
# 1-min Immobility epochs	15.9 ± 2.2	23.0 ± 4.4	18.3 ± 3.1	18.8 ± 0.6	18.1 ± 3.7	17.1 ± 1.1
Mean activity counts during sleep	24.2 ± 3.7	35.2 ± 9.9	22.7 ± 5.1	43.3 ± 12.2	22.3 ± 2.3	47.0 ± 14.1

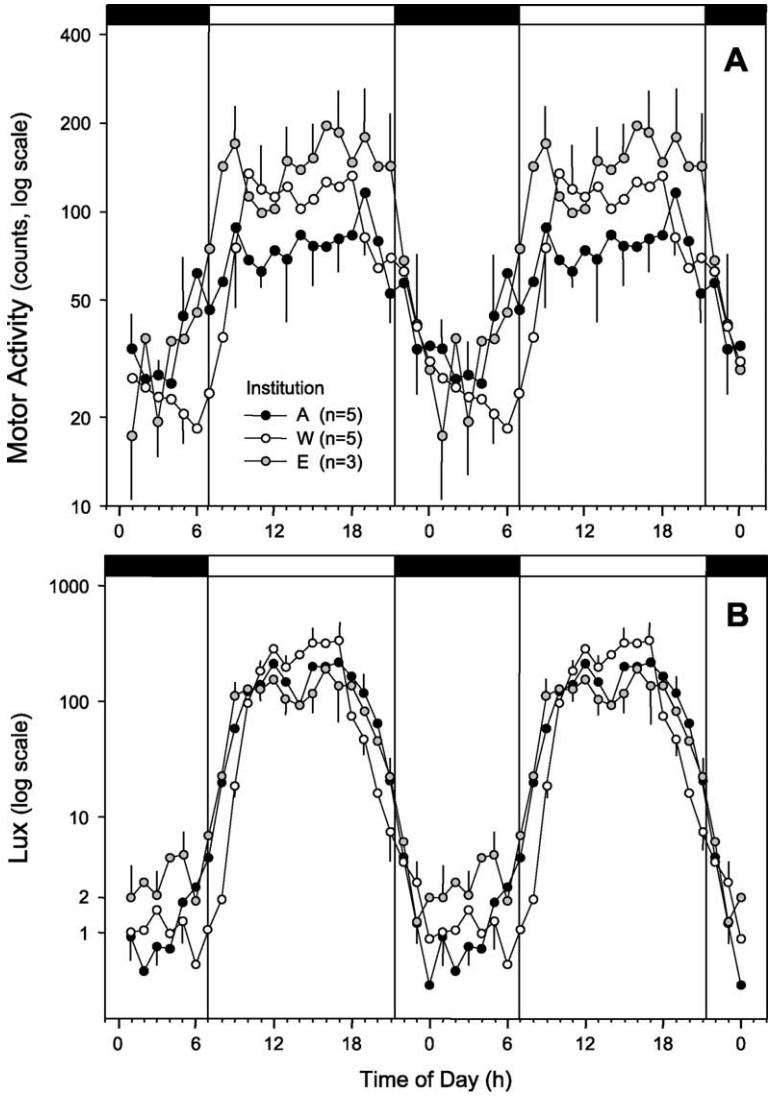

Fig. 5. Motor activity for each subject was averaged in 1 h bins and then over 7 consecutive days during baseline. Group averages were created for the two nursing homes (A, W) and the ward (E), and double plotted with respect to average sleep timing of the entire group (horizontal black bars). For clarity, only one SEM is given for every second value. The log scale increases resolution of low values. Similar calculations were carried out for the lux values. The timing of lights on and off differed in the different environments, as did motor activity (see text).

(assumed sleep duration $F = 3.06$, df $= 2$, $p = 0.07$, $d = 0.86$; actual sleep duration $F = 3.07$, df $= 2$, $p = 0.07$, $d = 0.99$, both large effects). DDS treatment tended to shorten 'sleep latency', and this was reversed in follow-up; in contrast, 'sleep latency' lengthened in the dim red light group ($F = 2.8$, df $= 2$, $p = 0.09$, $d = 1.0$, also a large effect). Sleep quality was also improved with DDS: less nocturnal activity ($F = 2.61$, df $= 2$, $p = 0.1$, $d = 0.86$, a large effect) and more 'immobile phases' ($F = 2.6$, df $= 2$, $p = 0.1$, $d = 0.27$, a small effect), which did not last during follow-up; these items worsened in the dim red light group. The raw data averages for a selection of these actimetry-determined 'sleep' variables are shown in Table 2 (without statistics). The patients spent more than 50% of their 24 h in bed.

3.2. Environmental factors

The baseline activity and light exposure data for each patient were averaged according to the environment they lived in (Fig. 5). The number of patients in each group is small and no significant differences emerged. However by looking at the raw motor activity data one can see for example that patients in home W (that had less strict social zeitgebers) were quiet in the early morning and began to be active ca. 3 h later than the other two groups. Mealtimes were identified by small peaks of activity, e.g. breakfast at 9 h. The W-group had an earlier evening meal at 18 h than the other two groups at 19 h, and an earlier decline of activity (longer time in bed). This behavior is reflected in the luxmeter values, light exposure in the W-group beginning later in the morning and decreasing earlier in the evening. Although not significantly different, average daytime light exposures (from 11 to 17 h) were higher in the W group (283 lux), compared with 163 lux in the other two groups, who also had an afternoon dip (probably reflecting napping time). Patients on ward E received more nighttime light (average 3.5 lux from 1 to 7 h) that might reflect worse sleep in hospitalized patients compared with nursing homes (A: 1.7 lux, W: 1.1 lux), or that the ward situation implicated lights on more often.

4. Conclusions

In summary, these actimetry data indicate that DDS induced a small advance in the circadian rest–activity cycle by inducing an earlier onset of the most restful period of the night. This suggests preservation of functional 'plasticity' of the circadian timing system even in aged patients with dementia. Additionally, there was a tendency in many actimetry-derived 'sleep' measures towards amelioration with DDS (and worsening with dim red light): shortened sleep latency, longer sleep duration, more nocturnal immobility and less activity. A tendency to diminution of nocturnal light exposure also suggested that with improved sleep the patients and/or caregivers turned on the lights less often during the night.

With respect to circadian variables measured intraindividually, some patients did phase advance or diminish nocturnal activity after DDS, which needs further study, since neither light exposure, ophthalmologic status or RA of the rest–activity cycle could explain this selective response.

While promising, these results from a pilot study with a small number of subjects took 4 years to complete. Limitations are also a perhaps negative selection of patients (advanced stage of dementia and age), and that DDS light treatment was used for only 3 weeks—newer studies in nursing homes are using daytime light therapy from 6 months to years as a more realistic application (Riemersma et al., 2001).

Actimetry-derived measures are not necessarily equivalent to time asleep. Thus, when the sensitive phase for morning light therapy according to Terman et al. (2001) is calculated, the rest midpoint may not necessarily be the same as the sleep midpoint. Since it appears that many patients with AD have delayed circadian rhythms (Harper et al., 2001), a phase advance is indicated to improve entrainment (as indeed occurred here with DDS). It may be advantageous to first determine from actimetry records the individual's bedtime and duration, and on this basis time light treatment according to the above algorithm. Clinically, restriction of time in bed, and self-choice of bedtime where possible, may itself be beneficial to circadian organization and sleep in dementia. From our records, it could be seen that patients were usually put to bed rather early, resulting in an average of nearly 13 h spent in bed at night, a duration which is obviously too long and may indeed contribute to the sleep disturbance.

The finding of large effect sizes of DDS on sleep latency, sleep duration, and nocturnal activity—exactly what one would hope for as improving—mandate further investigation, given the relative ease of application of DDS without care-giver attendance. To achieve sufficient power (0.8), a follow-up study would require $N = 22$ patients in each group. Additionally, the effect may be greater in younger, milder demented patients. It should be noted that the average intensity of daytime light these patients received was rather low (<300 lux, and usually much lower) to provide adequate zeitgeber strength for appropriate entrainment.

Acknowledgements

This study was funded by the Velux Foundation. We thank the nursing staff of the different institutions for their collaboration, support, and interest, and Drs Sonia Ancoli-Israel, Konstantin Danilenko, David Harper, Jennifer Martin, and Michael Terman for very helpful comments on the manuscript. Information about the DDS apparatus can be obtained from www.cet.org

References

Ancoli-Israel, S., Clopton, P., Klauber, M.L., Fell, R., Mason, W., 1997a. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. Sleep 20, 24–27.

Ancoli-Israel, S., Klauber, M.R., Williams Jones, D., Kripke, D.F., Martin, J., Mason, W., Pat-Horenczyk, R., Fell, R., 1997b. Variation in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients. Sleep 20, 18–23.

Ancoli-Israel, S., Martin, J.L., Kripke, D.F., Marler, M., Klauber, M.R., 2002. Effect of light treatment on sleep and circadian rhythms. JAGS 50, 282–289.

Avery, D.H., Eder, D.N., Bolte, M.A., Hellekson, K.J., Dunner, D.L., Vitiello, M.V., Prinz, P.N., 2001. Dawn simulation and bright light in the treatment of SAD: a controlled study. Biol. Psychiatry 50, 205–216.

Bliwise, D.L., 1993. Sleep in normal aging and dementia. Sleep 16, 40–81.

Campbell, S.S., Terman, M., Lewy, A.J., Dijk, D.J., Eastman, C.I., Boulos, Z., 1995. Light treatment for sleep disorders: consensus report. V. Age-related disturbances. J. Biol. Rhythms 10, 151–154.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, Lawrence Erlbaum, Hillsdale, NJ.

Colenda, C.C., Cohen, W., Mc Call, W.V., Rosenquist, P.B., 1997. Phototherapy for patients with Alzheimer disease with disturbed sleep patterns: results of a community-based pilot study. Alzheimer Dis. Assoc. Disord. 11, 175–178.

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314.

Danilenko, K.V., Wirz-Justice, A., Kräuchi, K., Cajochen, C., Weber, J.M., Fairhurst, S., Terman, M., 2000a. Phase advance after one or three simulated dawns in humans. Chronobiol. Int. 17, 659–668.

Danilenko, K.V., Wirz-Justice, A., Kräuchi, K., Weber, J.M., Terman, M., 2000b. The human circadian pacemaker can see by the dawn's early light. J. Biol. Rhythms 15, 437–446.

Dijk, D.J., Duffy, J.F., Czeisler, C.A., 2001. Age-related increase in awakenings: impaired consolidation of non-REM sleep at all circadian phases. Sleep 24, 565–577.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiat. Res. 12, 189–198.

Haffmans, P.M.J., Sival, R.C., Lucius, S.A.P., Cats, Q., Van Gelder, L., 2001. Bright light therapy and melatonin in motor restless behaviour in dementia: a placebo-controlled study. Int. J. Geriatr. Psychiatry 16, 106–110.

Harper, D.G., Stopa, E.G., Mc Kee, A.C., Satlin, A., Harlan, P.C., Goldstein, R., Volicer, L., 2001. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. Arch. Gen. Psychiatry 58, 353–360.

Martin, J., Marler, M., Shochat, T., Ancoli-Israel, S., 2000. Circadian rhythms of agitation in institutionalized patients with Alzheimer's disease. Chronobiol. Int. 17, 405–418.

Mishima, K., Hishikawa, Y., Okawa, M., 1998. Randomized, dim light controlled, crossover test of morning bright light therapy for rest–activity rhythm disorders in patients with vascular dementia and dementia of Alzheimer's type. Chronobiol. Int. 15, 647–654.

Mishima, K., Okawa, M., Shimitzu, T., Hishikawa, Y., 2001. Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. J. Clin. Endocrinol. Metab. 86, 129–134.

Morris, J.C., Heyman, A., Mohs, R.C., Hughes, J.P., van Belle, G., Fillenbaum, G., Mellits, E.D., Clark, C., 1989. The consortium to establish a registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 39, 1159–1165.

Okumoto, Y., Koyama, E., Matsubara, H., Nakano, T., Nakamura, R., 1998. Sleep improvement by light in a demented aged individual. Psychiatry Clin. Neurosci. 52, 194–196.

Partonen, T., Magnusson, A. (Eds.), 2001. Seasonal Affective Disorder. Practice and Research, Oxford University Press, Oxford.

Riemersma, R.F., Van Hutten, R.S., Kalis, A., Hoekstra, R.A., Hoogendijk, W.J.G., Scherder, E.J.A., Swaab, D.F., Van Someren, E.J.W., 2001. Indirect bright light therapy decreases sleep fragmentation in institutionalized demented elderly. Sleep–Wake Res. Netherlands 12, 96–98.

Satlin, A., Volicer, L., Ross, V., Herz, L., Campbell, S., 1992. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am. J. Psychiatry 149, 1028–1032.

Satlin, A., Volicer, L., Stopa, E.G., Harper, D., 1995. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiol. Aging 16, 765–771.

Savaskan, E., Olivieri, G., Meier, F., Brydon, L., Jockers, R., Kräuchi, K., Wirz-Justice, A., Müller-Spahn, F., 2001. Cerebrovascular melatonin 1a-receptor alterations in Alzheimer's disease. Neurosci. Lett. 308, 9–12.

Savaskan, E., Olivieri, G., Meier, F., Brydon, L., Jockers, R., Wirz-Justice, A., Müller-Spahn, F., 2002a. Increased melatonin 1a-receptor immunoreactivity in the hippocampus of Alzheimer's disease patients. J. Pineal Res. 32, 59–62.

Savaskan, E., Wirz-Justice, A., Olivieri, G., Pache, M., Kräuchi, K., Brydon, L., Jockers, R., Muller-Spahn, F., Meyer, P., 2002b. Distribution of melatonin MT1 receptor immunoreactivity in human retina. J. Histochem. Cytochem. 50, 519–526.

Sheikh, J.A., Yesvage, J.A., 1986. Geriatric depression scale (GDS): recent findings and development of a shorter version. In: Brink, T.L., (Ed.), Clinical Gerontology: A Guide to Assessment and Intervention, Harworth, New York, pp. 165–173.

Stopa, E.G., Volicer, L., Kuo-Leblanc, V., Harper, D., Lathi, D., Tate, B., Satlin, A., 1999. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. J. Neuropathol. Exp. Neurol. 58, 29–39.

Swaab, D.F., Fliers, E., Partiman, T.S., 1985. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain. Res. 342, 37–44.

Terman, M., Terman, J.S., 2000. Light therapy. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), Principles and Practice of Sleep Medecine, 3rd Ed. W.B. Saunders Company, Philadelphia, pp. 1258–1274.

Terman, M., Schlager, D., Fairhurst, S., Perlman, B., 1989. Dawn and dusk simulation as a therapeutic intervention. Biol. Psychiatry 25, 966–970.

Terman, J.S., Terman, M., Lo, E.S., Cooper, T.B., 2001. Circadian time of morning light administration and therapeutic response in winter depression. Arch. Gen. Psychiatry 58, 69–75.

Van Someren, E.J.W., Hagebeuk, E.E.O., Lijzenga, C., Scheltens, P., De Rooij, S.E.J.A., Jonker, C., Pot, A.M., Mirmiran, M., Swaab, D.F., 1996. Circadian rest–activity rhythm disturbances in Alzheimer's disease. Biol. Psychiatry 40, 259–270.

Van Someren, E.J.W., Kessler, A., Mirmiran, M., Swaab, D.F., 1997. Indirect bright light improves circadian rest–activity rhythm disturbances in demented patients. Biol. Psychiatry 41, 955–963.

Van Someren, E.J.W., Swaab, D.F., Colenda, C.C., Cohen, W., Mc Call, W.V., Rosenquist, P.B., 1999. Bright light therapy: improved sensitivity to its effects on rest–activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol. Int. 16, 505–518.

Werth, E., Savaskan, E., Knoblauch, V., Fontana Gasio, P., Van Someren, E.J.W., Hock, C., Wirz-Justice, A., 2002. Decline in long-term circadian rest–activity cycle organization in a patient with dementia. J. Geriatr. Psychiatry Neurol. 15, 55–59.

Witting, W., Kwa, I.H., Eikelenboom, P., Mirmiran, M., Swaab, D.F., 1990. Alterations in the circadian rest–activity rhythm in aging and Alzheimer's disease. Biol. Psychiatry 27, 563–572.