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DOI
10.1016/S0006-3223(97)89928-3

Publication date
1997

Published in
Biological Psychiatry

Indirect Bright Light Improves Circadian Rest–Activity Rhythm Disturbances in Demented Patients

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Light is known to be an important modulator of circadian rhythms. We tested the hypothesis that an enduring increase in the daytime environmental illumination level improves rest–activity rhythm disturbances in demented patients. Actigraphy was performed before, during, and after 4 weeks of increased illumination in the living rooms of 22 patients with dementia clinically diagnosed as probable Alzheimer's disease, multi-infarct dementia, dementia associated with alcoholism, or normal pressure hydrocephalus. The results indicated that during increased illumination, the stability of the rest–activity rhythm increased in patients with intact vision, but not in visually impaired patients. © *1997 Society of Biological Psychiatry*

Key Words: Alzheimer's disease, dementia, circadian rhythm disturbance, bright light, sleep, actigraphy

BIOL PSYCHIATRY 1997;41:955–963

Introduction

In demented patients periods of wakefulness and sleep often lose their circadian organization and occur fragmented throughout the day (Aharon-Peretz et al 1991; Satlin et al 1991; Van Someren et al 1996; Witting et al 1990). This phenomenon appears to be closely linked with behavioral disturbances, as both usually occur simultaneously, and both improve with phototherapy (Hozumi et al 1990; Okawa et al 1991; Satlin et al 1992). The importance of the disturbance is evident from the fact that behavioral restlessness during the night is a major factor in the decision of a caregiver to have a demented relative institutionalized (Pollak and Perlick 1991; Rabins et al 1982; Sanford 1975). As the disturbance in sleep–wake rhythm is paralleled by attenuation of circadian rhythm amplitudes in, e.g., motor activity, hormone secretion, and body temperature, although phototherapy improves it, a central role for the "biological clock" (suprachiasmatic nucleus, SCN) is likely (Mirmiran et al 1992; Van Gool and Mirmiran 1986; Van Someren et al 1993).

Selective degeneration and cytoskeletal alterations in this hypothalamic nucleus have indeed been found in patients with Alzheimer's disease (AD) (Swaab et al 1985, 1992). Moreover, the retinohypothalamic input, transmitting information about environmental light to the SCN, is attenuated because: 1) AD patients are generally exposed to less bright light (Ancoli-Israel and Kripke 1989; Campbell et al 1988); and 2) they may suffer from degeneration

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Received January 29, 1996; revised June 7, 1996.

0006-3223/96/$17.00
PII S0006-3223(96)00304-6

of the optic nerve and retinal ganglion cells (Blanks et al 1989; Hinton et al 1986), although this could not be confirmed in more recent studies (Curcio and Drucker 1993; Davies et al 1995). As the intensity of environmental light modulates the amplitude of circadian rhythms (Czeisler et al 1987; Witting et al 1993), and increased light intensity prevented the age-related loss of vasopressin-expressing neurons in the suprachiasmatic nucleus in rats (Lucassen et al 1995), increasing the bright light exposure of demented patients appears to be a rational therapy for rhythm disturbances. Previous studies indicate that a daily 2-hour exposure to artificial bright light reduces behavioral disorders such as agitation or wandering in the night and improves the sleep–wake and rest–activity rhythm in patients with Alzheimer's disease or multi-infarct dementia (MID) (Hozumi et al 1990; Lovell et al 1995; Okawa et al 1989; Satlin et al 1992). The protocols that have been used in those studies were based on light therapy protocols as used in the treatment of seasonal affective disorder (SAD): patients were placed in front of an artificial bright light source (1500–3000 lux) for 2 hours a day. As the compliance of demented patients is minimal, continuous attendance by the nursing staff is necessary to keep the patients in front of the light source. Such a protocol has therefore two major shortcomings. First, in studies evaluating the effectiveness, a likely placebo effect is introduced by the simultaneous increase in attention for the patient by the nursing staff, a problem that has been addressed in only one study in demented patients (Okawa et al 1991). Second, few psychogeriatric wards have the nursing staff capacity to exclusively attend particular patients for 2 hours daily, so that the protocol, no matter how effective, is unlikely to be feasible. It is therefore important to find out whether a "pure" light effect exists that can be implemented without overtaxing clinical resources. The present study investigated the effect of enduring, unattended exposure to increased levels of indirect (ceiling-mounted) bright light during the daytime on rest–activity rhythms in demented patients.

Methods

Subjects

Informed consent was signed by the responsible relatives of 29 severely demented inpatients of a psychogeriatric ward; however, due to death (n = 3), noncompliance (n = 3) and harming nurses with the actigraph (n = 1), 7 patients left the protocol after or during the first measurement period. Twenty-two patients, 15 female and 7 male, finished the whole protocol, with an age of [mean ± standard error of the mean (SE)] 79 ± 2 years (range 64–97). Patients were clinically diagnosed according to DSM-III-R (American Psychiatric Association 1987), NINCDS/ADRDA (McKhann et al 1984), and Hachinski (Hachinski et al 1975) criteria, resulting in the diagnosis of probable Alzheimer's disease in 16 patients, multi-infarct dementia in 3 patients, dementia associated with alcoholism in 2 patients, and normal pressure hydrocephalus in 1 patient. We choose not to exclude patients with types of dementia other than Alzheimer's disease, because previous studies indicate that rhythm disturbances also occur in patients with other types of dementia, but that there may be differences in the type and severity of the disturbance as well as in the response of the disturbances to bright light therapy (Aharon-Peretz et al 1991; Mishima et al 1995). Regression analyses were used to investigate whether the type of dementia was associated with the effectiveness of the treatment. In 6 patients the dementia started presenile, i.e., before the age of 65 years. The severity of the dementia on the Global Deterioration Scale (GDS) (Reisberg et al 1982) ranged from 5 to 7 and averaged (mean ± SE) 6.3 ± 0.13. Patients had been institutionalized for (mean ± SE) 2.1 ± 0.33 years. Nine patients used neuroleptics. They were on a stable doses with the exception of 1 patient, where the daily dose was heightened just after the first actigraphic assessment. Medical histories indicated severe visual deficiencies (severe cataract, loss of an eye) in 5 patients. As all patients had been physically examined on a regular basis, visual deficits of this extent could be excluded in the other 17 patients. By including patients with severe visual deficits in the treatment protocol, it could be determined whether changes were likely to result from photic input or rather from a placebo effect, e.g., due to altered behavior of the nursing staff. The patients were housed in groups of 6–12 and spent most of the day in the living room. Patients were relatively free to choose their bedtimes and the time for rising and having breakfast. In general, none of the patients was up between midnight and 6:00 AM, and none of the patients was in bed between 9:00 AM and 9:00 PM. More stable "Zeitgebers" were formed by the fixed times of meals (12:30 PM and 5:00 PM), toilet-going (1:30 PM), and tea and coffee breaks (2:30 PM and 7:00 PM).

Study Design

The repeated measurement study design is shown in Figure 1. Environmental light and rest–activity rhythm were assessed 2 weeks before treatment (baseline 1). This allowed for a repeated assessment the week before treatment in case of noncompliance or apparatus failure. Hereafter, bright light equipment was installed in the living rooms late at night, when all patients had left the room. In the 3rd week after installation a second environmental light and rest–activity rhythm assessment was

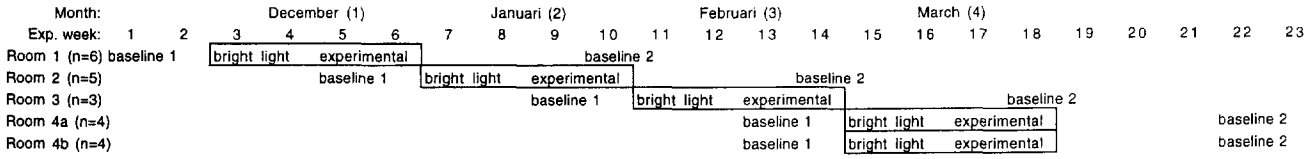

Figure 1. Protocol of the study. See text for further explanation.

performed (experimental). In case of noncompliance or apparatus failure the assessment was repeated during the 4th week after installation. Hereafter, the bright light equipment was removed, again at an hour when no patients were in the living room. In the 4th week after removal a third assessment of environmental light and rest–activity rhythm was done (baseline 2), again repeated in the 5th week if necessary. The protocol was repeated in time to include patients from several living rooms, and in order to evaluate a possible time of year effect, which is known to exist in seasonal affective disorder (Rosenthal et al 1984), rhythm disturbances in Alzheimer patients (Van Someren et al 1996), and neuronal activity in the SCN (Hofman et al 1993; Hofman and Swaab 1993). The study was performed between November and April in five living rooms. A repeated assessment was necessary in 11 out of 66 registrations.

Light Equipment and Assessment of Brightness

In three larger living rooms the existing ceiling-mounted illumination (four fittings, each with four relatively low-intensity Philips TLD18W tubes) was replaced by 12 new fittings, each containing three high-intensity white fluorescent tubes (Philips TLD32W). The fittings were covered by Plexiglas diffusers that filtered ultraviolet light. In two smaller living rooms, the four existing fittings were replaced by six new fittings. The light intensity at the place where the patient was seated mostly during the day was measured every day between 9:00 and 11:00 AM during the assessment weeks by holding a BBC Goertz Metrawatt MX 4 lux-meter near the eyes in a horizontal direction. A weekly average was calculated for each patient. As the study was designed to avoid extra attendance by staff, it is likely that some patients had their eyes closed incidentally when dozing off. Also, patients did not receive extra light at times when they left the living room. Thus, exposure varied per individual, but was always more in the experimental than in the baseline conditions. The light intensity in the sleeping rooms was measured once during the night with a Gossen Mavolux digital lux-meter with memory, and never exceeded 0.0 lux, the minimum sensitivity of the device.

Assessment of Rest–Activity Variables

Before, during, and after the bright light treatment, the rest–activity level was measured continuously for 5 days and nights (from Monday until Saturday) using actigraphy. The small (57 × 46 × 22 mm) and light-weight (70 g) wrist-worn actigraph, a miniaturized version of the actigraph described by Mirmiran et al (1988), senses movement-induced accelerations. The sensitivity is set in such a way that even small movements are detected ($> \pm 0.1$ *g*). No patients with tremor or other involuntary movements as may result from the use of neuroleptics were included in the present study. When the actigraph detects a movement a counter is activated and the input is blocked for 16 sec. The number of counts per hour, a value between 0 and 225, is stored in an EEPROM memory, which is read out later for off-line analysis. From the series of hourly movement counts, three circadian variables were calculated.

1. The interdaily stability (IS) is the 24-hour value from the chi-square periodogram (Sokolove and Bushell 1978; Witting et al 1990), normalized for the number of data, and gives an indication of the strength of coupling between the rest–activity rhythm and Zeitgebers. IS is calculated as the ratio between the variance of the average 24-hour pattern around the mean and the overall variance

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

where n is the total number of data, p is the number of data per day (in this study 24) $\bar{x}_h$ are the hourly means, $\bar{x}$ is the mean of all data, and x_i represents the individual data points.

2. The intradaily variability (IV) gives an indication of the fragmentation of the rhythm, i.e., the frequency of and extent of transitions between rest and activity, and is calculated as the ratio of the mean squares of the difference between successive hours (first deriv-

ative) and the mean squares around the grand mean (overall variance) (Witting et al 1990).

$$IV = \frac{n\sum_{i=2}^{n}(x_i - x_{i-1})^2}{(n-1)\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

3. The amplitude (AMP) of the rest–activity rhythm was calculated as the difference between the means of the most active 10-hour period (M10) and the least active the 5-hour period (L5) in the average 24-hour pattern (Witting et al 1990).

Statistical Analyses

For each of the variables describing the rest–activity rhythm (IS, IV, and AMP), stepwise regression analyses were performed to determine how patient and environmental characteristics related to the responsiveness to the therapy. Twelve variables were introduced as predictor variables for the response size, i.e., the difference between bright light (experimental) and pooled baseline (average of baseline 1 and 2) level. The following variables were introduced: sex; age; Alzheimer diagnosis; presenile onset; use of neuroleptics; presence of a severe visual deficit; dementia severity (GDS); the individual increase in bright light exposure, i.e., the difference between the experimental and pooled baseline levels; the pooled baseline level of the dependent variable (i.e., IS, IV, or AMP); the pooled baseline activity level as indicated by M10; and two variables describing the "season" when treatment took place, being the day length and the rate of change in day length. The latter three variables were included as they were found to have predictive value in the presence of rhythm disturbances (Van Someren et al 1996). The critical F values were set at 4.32, corresponding to a significance level of .05 for any single test (Neter et al 1990).

Furthermore, for IS, IV, and AMP, two-tailed paired t tests at a .05 significance level were performed on two orthogonal contrasts (Kirk 1968); baseline 1 versus baseline 2 and experimental versus pooled baseline. Baseline levels were pooled to reduce the repeated measurement within-subject variability that appeared to be significant in previous pilot studies. The use of this procedure results in a gain of discriminative power as compared to an overall F statistic of an analysis of variance (ANOVA), and is appropriate when a lack of difference between two levels (baseline 1 and 2) can be demonstrated. The latter was tested using t tests, and was a priori likely as all studies on demented patients (Hozumi et al 1990; Lovell et al 1993; Okawa et al 1989; Satlin et al 1992) and the majority of studies on depressed patients (Rosenthal et al 1984) reported relapse after discontinuation of bright light treatment.

Results

Light Exposure

Depending on the orientation and distance from the window of the chair where the patient was seated mostly, the amount of light reaching the eyes of the patients differed. The baseline 1 weekly average light intensity was (mean ± SE) 436 ± 90 lux, and ranged from 93 to 1417 lux for individual patients, depending on their position relative to the windows. During the assessment week in the increased illumination condition, the average intensity was 1136 ± 89 lux and ranged from 790 to 2190 lux. During the 2nd baseline assessment week, the average intensity was 372 ± 65 lux, and ranged from 110 to 1106 lux.

Rest–Activity Variables

The baseline 1 recording of 1 patient was not used because the daily dose of neuroleptics was heightened just after this recording. In this patient the pooled baseline levels were accordingly derived from only the second baseline assessment. Thus, t tests on differences between baseline 1 and 2 levels are based on 21 patients.

An example of the activity data of an Alzheimer patient is given in Figure 2. A high level of intradaily variability and a low level of interdaily stability is seen in the pre and post measurements, whereas both variables improved during the light treatment.

Table 1 shows the results of the regression analyses. For the effect of bright light on interdaily stability (IS), two predictor variables reached significance; the presence of a severe visual deficit prohibited an increase in stability, whereas patients using neuroleptics showed a stronger increase. For the effect of bright light on intradaily variability (IV), one single predictor variable almost reached significance ($p = .05$); the presence of a severe visual deficit prohibited a decrease in the variability. For the effect of bright light on the circadian amplitude (AMP), three predictors reached significance; an increase in the circadian amplitude was associated with a diagnosis of Alzheimer's disease, the absence of a severe visual deficit, and a low rate of change in day length.

Because the regression analyses revealed, as expected, that the visual deficiency resulted in a lack of effectiveness of bright light on all three variables, t tests were performed after excluding the 5 patients with severe visual deficiency from the sample. t and F tests indicated no differences

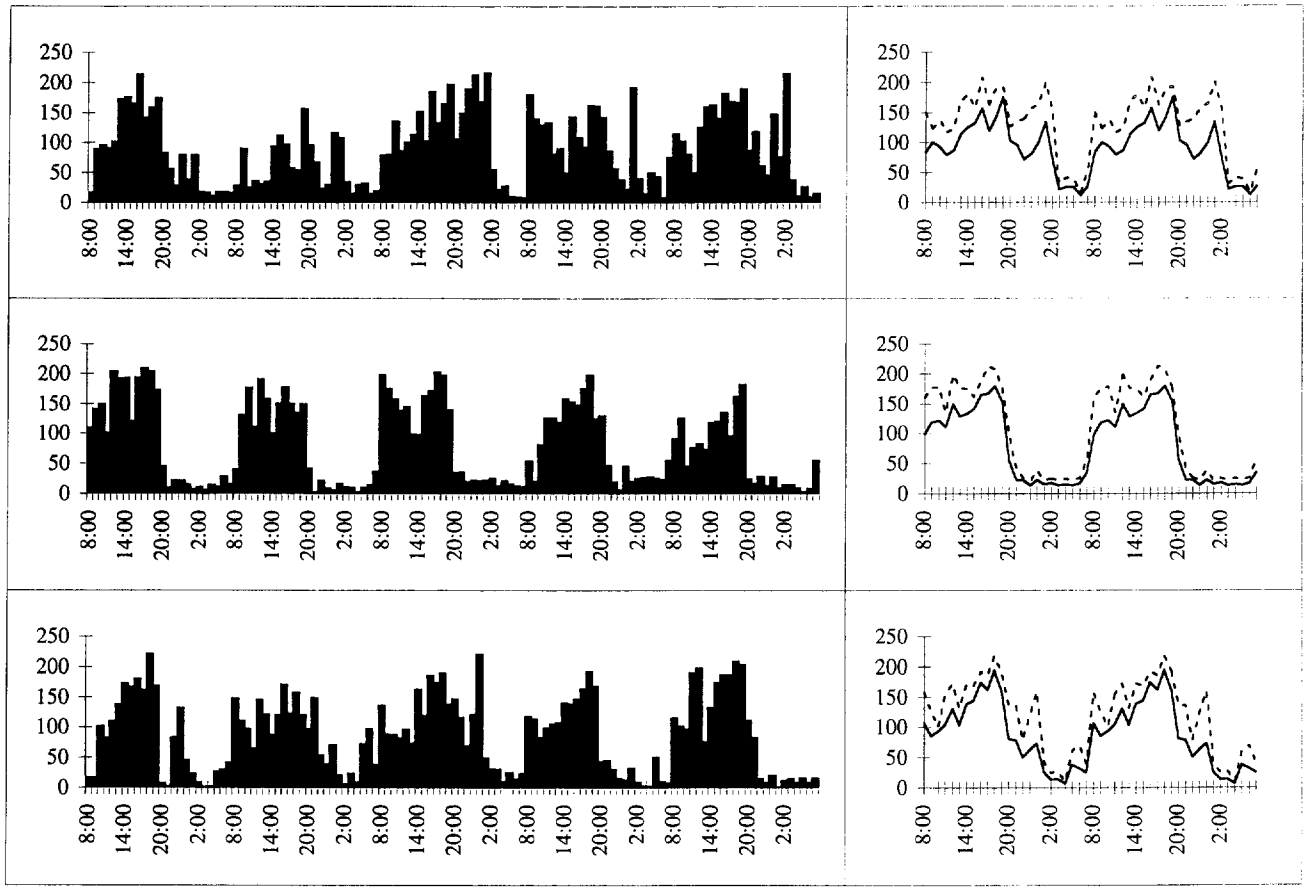

Figure 2. Raw activity data (left panels) of a patient with Alzheimer's disease assessed three times for 5 days: before (upper left panel), during (middle left panel), and after (lower left panel) light treatment. The right panels show double plots of the average 24-hour activity level (solid line) and one standard deviation above this level (dashed line). Note the decreased variability and the smoother average during light treatment. Furthermore, note that the average daytime and nighttime activity levels do not change markedly, indicating that bright light induces a reduction in "noise" rather than an increase in amplitude.

Table 1. Results of the Stepwise Regression Analyses for Variables Involved in the Effect of Light the change in (experimental–baseline) on Interdaily Stability, Intradaily Variability and Activity Amplitude

Predictor	beta	F	p
Interdaily stability[a]			
Visual deficit	−.54	10.67	.004
Neuroleptics	.42	6.23	.02
Intradaily variability[b]			
Visual deficit	.42	4.21	.054
Activity amplitude[c]			
Alzheimer's diagnosis	.67	24.90	<.0001
Δ-day length	−.65	23.85	.0001
Visual deficit	−.36	7.08	.02

[a] R^2 = .47, F = 8.53, df = 2, 19, p = .002.
[b] R^2 = .17, F = 4.21, df = 1, 20, p = .054.
[c] R^2 = .72, F = 15.62, df = 3, 18, p < .0001.
R^2, coefficient of multiple determination; beta, standardized partial regression coefficient.

between the baseline 1 and 2 mean levels (all p values > .30), and no differences in variance of the experimental and pooled baseline contrasts on any of the variables, justifying t tests on the contrasts of the experimental versus pooled baseline levels. Table 2 shows averages and standard errors of the experimental and both baseline conditions. The stability (IS) during light treatment (mean ± SE 0.65 ± 0.04) was significantly (p < .002) higher than the pooled baseline level (0.54 ± 0.04). The fragmentation (IV) during light treatment (0.80 ± 0.07) was significantly (p < .01) lower than the pooled baseline level (0.97 ± 0.09). The circadian amplitude (AMP) during light treatment (84 ± 11) did not differ significantly (p = .18) from the pooled baseline level (77 ± 10).

Discussion

The present study indicates that indirect whole-day unattended bright light affects objectively recorded rest–activ-

Table 2. Actigraphy Variables for the 17 Patients with Intact Vision

	Baseline 1	Experimental	Baseline 2	t	p
IS	0.50 ± 0.05	0.65 ± 0.04	0.57 ± 0.04	3.79	.002
IV	1.01 ± 0.10	0.80 ± 0.07	0.93 ± 0.11	2.92	.01
AMP	72 ± 12	84 ± 11	81 ± 11	1.39	.18

The first three columns show the means and standard error of the mean of the repeated measurements before, during, and after bright light treatment. The fourth and fifth columns show the p values of the t tests with 16 degrees of freedom on the contrast between the levels during bright light treatment versus the levels before and after treatment. Baseline 1 and 2 levels never differed significantly. Rows show the actigraphic variables interdaily stability (IS), intradaily variability (IV), and activity amplitude of the average 24-hour pattern (AMP).

ity rhythm in demented patients with relatively unimpaired vision, whereas it does not in patients with severe visual deficits. Bright light treatment increased interdaily stability, indicating an increase in the strength of the coupling of the rhythm to environmental Zeitgebers, and decreased intradaily variability, indicating a decreased fragmentation. These improvements indicate a more stable organization of the circadian rest–activity rhythm; however, no significant changes were found in the amplitude of the rhythm, indicating that the improvements in signal to noise ratio (IS and IV) result from a decrease in noise (variability) rather than from an increase in the amplitude (see also Figure 2).

The finding that patients with a severe visual deficit did not improve suggests that a placebo effect is not very likely in the present study, certainly if compared to previous studies assessing either behavioral or actigraphic improvements, because patients with a severe visual deficit were not treated any differently from well-sighted patients. Indirect effects of the expectation of nurses—aware both of the condition of the patients' eyes and of the environmental change—cannot be excluded, but are very unlikely, as we had the impression that only half of the nurses expected bright light to be effective, whereas the other half did not. Furthermore, activation of the central nervous system through increased visual input, and changes in perception of the environment, are possible effects of bright light treatment that may be difficult to differentiate from a direct effect of light on the biological clock in humans. It should be noted here, however, that the SCN is directly innervated by the optic nerve (Moore 1992).

The results of the stepwise regression analyses have to be interpreted with caution because of the relatively small sample size and the chance of introducing type I errors by repeated testing of correlations; however, with the exception of the regression for IV, the predictors included were highly significant, and are in accordance with previous findings and circadian rhythm theory. Overall, the most pronounced predictor of the response was the presence of a visual deficit, which inhibited improvements in the stability, fragmentation, and amplitude of the rhythm. This finding is in agreement with the knowledge that visual input is the primary input to the circadian timing system (Moore 1992). Furthermore, patients on neuroleptics showed more improvement in interdaily stability. Since patients with the most severe rest–activity disturbances are the most likely to receive neuroleptics (Witting et al 1990), this suggests that bright light is most effective in patients with a tendency toward unstable rhythms. A further result from the regression analysis was that patients diagnosed with probable Alzheimer's disease responded with a stronger increase in amplitude than patients with other diagnoses, which contrasts with a recent study of Mishima et al (1995), who found stronger improvements in MID patients. Finally, an increase in amplitude was more likely when day length changed at a low rate. Seasonal effects have previously been reported for rhythm disturbances in Alzheimer patients (Van Someren et al in press), and for neuronal activity in the SCN (Hofman et al 1993; Hofman and Swaab 1993). In conclusion, although type I errors cannot be excluded in stepwise regression analyses, the predictors that emerged generally agree with previous findings.

Rest–activity recordings were reported in two earlier bright light studies in demented elderly. In Alzheimer patients, Satlin et al (1992) found an increase of the circadian amplitude and improvement in intradaily variability but not in interdaily stability, (double typed), which partly contrasts with our findings of a strong improvement in interdaily stability, some improvement in intradaily variability, and no increase in amplitude. Mishima et al (1995) reported that unspecified improvements in the rest–activity rhythm were found more in MID patients than in Alzheimer patients. Several factors may be involved in the difference. First, in the previous studies, alterations other than the intensity of bright light could have contributed to the treatment effect. As patients were placed in front of a light box and attended by a nurse for 2 hours daily, which necessarily entails an enormous increase in individual attention, a placebo effect may well have been introduced. In the present study a placebo effect was very unlikely because: 1) the daily care-giving activities remained unchanged; 2) none of the patients gave the impression of having noticed the change in illumination; and 3) the presence a severe visual deficiency prohibited

improvements in the circadian rhythm. A second factor that may be involved in the difference is the severity of dementia, which was rated as moderate to severe in the previous studies and severe to very severe in the present study. Other factors of importance in actigraphic assessment of the effect of bright light therapy are the type of actigraph used, the variables derived, and the characteristics of the treatment protocol, i.e., the intensity, duration, and timing of bright light exposure.

It may be argued that the average light intensity was low (± 1136 lux) in the present study. Using indirect light, it is very difficult to reach levels of 2500 lux, the accepted intensity for "2-hour" bright light therapy in seasonal affective disorder. This standard, however, appears to be merely a matter of convention, as the effect of variation of intensities between 500 and 2500 lux has not been studied systematically, and several studies have shown that bright light within this range is effective in the treatment of seasonal affective disorder (cf. Lingjaerde et al 1993). Moreover, as several authors have suggested an interaction of light intensity and exposure duration (Kronauer and Czeizler 1993; Terman 1993; Wirz-Justice et al 1986), the cumulative dose of the whole-day bright light exposure in the present study may actually have been quite high. However, given the general deterioration of the visual system in the elderly, and the fact that Satlin et al (1992) found no improvement for agitation in demented patients treated with bright light of an intensity lower than 2000 lux, whereas agitation did improve in those studies where more than 2000 lux was applied (Hozumi et al 1990; Lovell et al 1995; Okawa et al 1989), an intensity of more than 2000 lux is recommended in future studies, even if this may be hard to accomplish with indirect lighting. Although an increase in brightness may thus be expected to be even more effective, it seems unlikely that effects would increase with a longer treatment duration, as the effect of bright light treatment is reported to be immediate in the majority of bright light studies; we measured the effectiveness only in the 3rd, and occasionally even in the 4th week of treatment.

Concerning the timing of bright light administration, behavioral improvements have been obtained in demented patients with morning as well as evening exposure, and a recent study showed equal effectiveness of morning and evening exposure in seasonal affective disorder as well (Wirz-Justice et al 1993). As far as we know, the present study is the first to apply a whole-day increase in light intensity in patients with disturbed circadian rhythms. As compared to the application of a 2-hour daily pulse of bright light, the effect of a whole-day increase in illumination with the aim of amplifying the circadian rhythm has hardly been studied. Most studies on bright light have focused on shifting the phase rather than increasing the amplitude of circadian rhythms. Although in theoretical models on the effect of bright light on circadian rhythms an appropriately timed increase in bright light is predicted to result in an increase in the circadian amplitude, surprisingly little research has been done to support this notion (Kronauer and Czeizler 1993). To our knowledge, only one such experiment has been performed in animals, and none in humans. Witting et al (1993) found a linear increase of the sleep–wake rhythm amplitude with whole-day increases of the environmental light in young and old rats, which are nocturnal animals. In the present study, no increase in the absolute amplitude but a significant improvement of the circadian organization, i.e., signal (amplitude) to noise ratio, was found.

In conclusion, the present study is the first to show that a whole-day increase in bright light improves the circadian rest–activity rhythm disturbances in severely demented patients. The lack of effect in patients with a severe visual deficiency makes it less likely that the findings should be attributed to placebo effects.

Financial support was provided by Senter, The Hague, The Netherlands (Project MTR 89026).

This study would not have been possible without the help of nurses, physicians, and technicians of Nursing Home "Groenelaan," Amstelveen, The Netherlands. Actigraphs were supplied, maintained, and repaired by J. Overdijk (Netherlands Institute for Brain Research). Bright light equipment was supported by Philips Nederland B.V., Eindhoven, The Netherlands.

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