Non-pharmacological treatment of sleep and wake disturbances in aging and Alzheimer's disease: chronobiological perspectives

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Numerous studies indicate a deterioration of nighttime sleep and daytime cognitive performance in elderly people and Alzheimer patients. As a result of the increasing number of elderly people and Alzheimer patients in the western society, attention for these problems has grown. However, so far, the major research effort has been concentrating on the development of pharmacological therapies for an isolated age-related problem. In the present review it is argued that several age-related problems with sleep and wakefulness may reflect a dampening of circadian rhythm amplitudes. Non-pharmacological manipulation of circadian rhythms by means of various external stimuli appears to be effective in improving sleep and cognitive functioning in elderly people and Alzheimer patients.

INTRODUCTION

Circadian rhythms, i.e. rhythms of approximately 24 h, are present in many physiological and behavioral phenomena, including rest–activity, sleep–wakefulness, body temperature and hormone levels. Circadian rhythms are involved in the adaptation of the organism to the environment, e.g. to effectuate alert behavior during the day and sleep during the night in a diurnal animal. This requires a circadian timing system that properly synchronizes the various circadian rhythms with each other and with the environmental light–dark cycle. A brief review of the present knowledge on the circadian timing system is given in the first paragraph.

In several conditions that harm human well-being, e.g. affective disorders, night shift work and jet lag, a desynchronization of circadian rhythms has been demonstrated^{41,142}. Therapies aimed at resynchronizing the rhythms are able to alleviate such conditions effectively. However, the undermining of the well-being of elderly people and Alzheimer patients by sleep disturbances during the night and impaired cognitive functioning during the day, are not generally studied within a circadian perspective. Rather, most research addressed either daytime functioning or nighttime sleep. In the second paragraph, age- and Alzheimer-related changes,

e.g. in sleep–wakefulness, rest–activity, body temperature and hormone levels, are briefly reviewed, and it is argued that these changes, but also cognitive and EEG phenomena which are generally not considered from a circadian point of view, all indicate a dampening of circadian rhythm amplitudes.

The third paragraph addresses possible environmental and internal factors that may be involved in the dampening of circadian rhythm amplitudes, and in the fourth paragraph, non-pharmacological treatments that have been proposed to influence daytime functioning or nighttime sleep are discussed from a circadian rhythm perspective. Finally, the discussion addresses additional non-pharmacological treatments that are not based on chronobiological principles, and possible mechanisms underlying effects of treatments.

Two additional points remain to be dealt with in this introduction. Firstly, in the present paper, the sleep and wake problems of “healthy elderly people” and those of Alzheimer patients are viewed as differing quantitatively rather than qualitatively. It is estimated that half the population over 85 years of age is affected by Alzheimer's disease (cf. ref. 114). The exponential increase of Alzheimer's disease opens up the possibility that it is an accelerated, aggravated form of aging, differing only in quantitative and not in qualitative terms from normal aging.

Secondly, the present paper discusses tentative non-pharmacological treatments for improving daytime and

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nighttime functioning. We will not address pharmacological treatment in order to limit the subject of the present paper, but we do not want to discard the importance of drug treatment in a circadian rhythm perspective. Firstly, the findings that the toxicity, effectiveness and clearance of many pharmacological agents depend on the timing of administration may be of help in optimizing pharmacotherapy, and secondly, several pharmacological agents induce alterations in circadian rhythms (cf. ref. 142). Recently, melatonin was proposed as a pharmacological tool in the treatment of circadian rhythm disorders, and positive results have been reported in retarded blind children^{92,130} and jet lag⁴. Finally, special attention is required when combining drug treatment with non-pharmacological treatment from a circadian perspective. For example, patients taking neuroleptics are sometimes unusually sensitive to sunlight, and may develop rashes (cf. ref. 84), which would conflict with increased exposure to bright light as would be prescribed from a circadian perspective. Moreover, neuroleptics may upset hypothalamic thermoregulatory mechanisms (cf. ref. 84), which, as will be argued in the present paper, may be involved in the effects of treatments from a circadian perspective.

I. MECHANISMS UNDERLYING CIRCADIAN RHYTHMS

The hypothalamic suprachiasmatic nucleus (SCN) is of crucial importance in the generation and synchronization of circadian rhythms¹²². The SCN is capable of generating near-24-h rhythms in the absence of environmental clues, and is therefore called a "circadian pacemaker". The rhythm that emerges in the absence of environmental clues is referred to as a "free-running rhythm", and may have a period differing from 24 h. The SCN uses regular environmental clues to synchronize the rhythms exactly with the 24-h day, a mechanism referred to as "entrainment"¹²². Several environmental clues have shown to be effective in entrainment. Environmental light and physical activity are of major influence on the circadian timing system, but, in human, the daily routine of social contacts and meals are also thought to contribute to the entrainment (cf. ref. 185). These stimuli may all affect one or more of the three parameters that describe the circadian rhythms: phase, period and amplitude.

Of the inputs the SCN receives, only the pathway of environmental light is well described. The SCN receives information about the environmental light-dark cycle by a direct retinohypothalamic projection, of which the transmitter is unknown¹²². A second, indirect retina-intergeniculate leaflet-hypothalamus projection con-

taining neuropeptide Y was found in rat and monkey, but it is not certain whether it also exists in human. In addition to these projections the SCN is thought to receive inputs from other hypothalamic nuclei, from the limbic forebrain, the reticular formation and the hormonal milieu¹²², but the pathways of these projections are not well described, with the exception of a prominent serotonergic projection originating in the raphe nuclei, the exact function of which is unknown¹⁰⁹.

Within the SCN several types of neurons are found. As is the case in rat and monkey, the human SCN contains, among others, vasopressin (VP) and vasoactive intestinal polypeptide (VIP) producing neurons. The largest cell population of the human SCN consists of neurotensin (NT) neurons, while only few of these cells are found in rat and monkey. Another difference is that the human SCN contains neuropeptide Y (NPY) producing neurons¹²².

Although data on the efferents of the human SCN are lacking¹²¹, animal studies suggest projections predominantly to other nuclei within the hypothalamus, but also to the thalamus, basal forebrain and periaqueductal gray^{122,186}. Moreover, projections to the intergeniculate leaflet and raphe, which both have afferents to the SCN¹⁰⁹, could allow for neuronal feedback loops. Projections to the anterior hypothalamus could affect sleep-generating and thermoregulatory mechanisms localized there, and projections to the posterior hypothalamus may affect arousal-generating mechanisms (cf. ref. 113). A projection to sympathetic neurons in the upper thoracic intermediolateral cell columns of the spinal cord, which project via the superior cervical ganglia to the pineal gland, results in the secretion of melatonin with an endogenous circadian rhythm.

The relation between input and output in the circadian timing system is well illustrated in the melatonin rhythm. Melatonin output and rhythm are influenced by environmental light. Environmental light reduces *N*-acetyltransferase (NAT), which is the rate-limiting enzyme converting serotonin to *N*-acetylserotonin, the precursor of melatonin. Light can thus suppress melatonin secretion. The amount of melatonin suppressed by light depends on the intensity of the light, the time of day and the season¹²⁹. Entrainment of the circadian melatonin rhythm by light has been shown repeatedly, e.g. by Shahanan and Czeisler¹⁶², who have, furthermore, shown that the temperature rhythm consistently follows the melatonin rhythm with an inverse amplitude and a delay of approximately 1.8 h. A causal relationship, i.e. melatonin suppressing temperature, however, is not likely, since some individuals show a temperature rhythm in the absence of a melatonin rhythm. Although the minimum light intensity needed for plasma melato-

nin suppression in humans was originally reported to be approximately 2500 lux⁹⁸, later studies found melatonin suppression with as little as 5 to 250 lux^{17,24,65}. McIntyre et al.^{107,108} conclude that an intensity-, but not a duration-dependent relationship exists. This means that a faster and greater melatonin suppression can be achieved with more intense light, but that the level of suppression stabilizes after approximately 1 h.

Although most studies apply light of at least 2000 lux, the actual intensity of light required to induce circadian rhythm alterations in human is equivocal. It is at present controversial whether light intensities that suppress melatonin correspond with light intensities necessary for the entrainment of circadian rhythms (cf. ref. 54). Czeisler et al.⁴² reported phase-shifting with ordinary room light of approximately 150 lux. Rosenthal et al.¹⁴⁸ reported that a 400 lux treatment was equally antidepressant as a 6000 lux treatment, although a more serious relapse into depression occurred after cessation of the 400 lux treatment. As this and other studies have shown antidepressive effects of light treatment in the range of 30 lux to 6000 lux, a placebo-effect has been suggested¹⁴⁸. On the other hand, the light intensity threshold for melatonin suppression, phase shifts and antidepressant effects may just be lower than originally reported.

II. CIRCADIAN RHYTHM ALTERATIONS IN AGING AND ALZHEIMER'S DISEASE

Several studies and reviews addressed the occurrence of circadian rhythm changes in elderly people and Alzheimer patients^{15,178}. These papers usually dealt with the circadian rhythms in hormones, body temperature, sleep-wake behavior or rest-activity behavior. In the present paragraph, age- and Alzheimer-related EEG and cognitive performance changes during the day and night will also be reviewed from a circadian perspective.

Hormones

Reviews indicate an age-related decrease in the circadian rhythm amplitudes of aldosterone, renin, testosterone, growth hormone, thyroid-stimulating hormone, estradiol, melatonin and cortisol^{15,178}, mostly caused by a decrease in the peak rate of secretion (cf. ref. 115). Epinephrine amplitudes do not appear to change with age, while the decreased amplitude or even inverted rhythm of norepinephrine levels result in relatively high levels of norepinephrine during the night, which may be associated with poor sleep. The norepinephrine amplitude decrease results from a reduced drop in secretion level at night. Increased amplitudes of luteinizing

hormone and prolactin have been found, although the latter could not be replicated. The phase of cortisol and thyroid-stimulating hormone rhythms appears to be advanced in the elderly (cf. refs. 15, 163, 178), while a delay was reported in the melatonin acrophase¹⁶³. This latter finding, however, remains to be replicated as it might be an artefact of an altered 24-h waveform, since the fit of the cosinor to the data of the elderly was significantly worse than the fit to the data of young subjects. Compared to healthy elderly people, similar as well as exaggerated decreases in hormone amplitudes have been reported in Alzheimer patients (cf. ref. 15). In a heterogeneous group of demented patients, a lower level and decreased amplitude of melatonin was reported^{124,126}. However, as only two samples per 24 h were taken, a change in waveform rather than a decrease in amplitude might also underlie this finding.

Body temperature

Core body temperature shows a circadian rhythm with a peak in the afternoon and a trough in the early morning. In an entrained environment young adults were reported to have peak-trough amplitudes of approx. 1.25 °C, decreasing to approx. 0.95 °C in the elderly^{184,189}. The decrease in amplitude may be caused by a reduced temperature drop during the night (cf. ref. 115) and a reduced temperature peak during the day¹⁴⁵. Under free-running conditions, the amplitude decreased in both young and elderly subjects, and the period increased more in young than in elderly subjects¹⁸⁹. A phase-advance has been found in some but not all studies and appears to be associated with differences in bedtimes and wake up times (cf. refs. 15, 184). The temperature rhythm amplitude in Alzheimer patients does not appear to differ from age-matched controls, but this conclusion may be based on the difficulties encountered when trying to measure rectal temperature continuously in uncooperative patients, and a greater day-to-day variability^{124,126,137}. Touitou et al.¹⁷² even reported that the age-related decrease in amplitude was not found in Alzheimer patients. The phase was found to be equally advanced in Alzheimer patients as in healthy elderly people, although an increased phase-advance in male Alzheimer patients has also been reported (cf. ref. 15). The free-running period of the rhythm has, as far as we know, not been investigated.

Sleep-wake rhythm

The sleep of elderly people and Alzheimer patients was recently reviewed extensively by Bliwise¹⁵. From the bulk of reviewed studies it can be concluded that elderly people nap more during the day and wake up frequently during the night. A loss of slow wave sleep

and, in Alzheimer patients, REM sleep (cf. ref. 181), is indicated by changes in the sleep EEG, which will be discussed later. Although sleep problems may be the result of other medical conditions, which is undoubtedly the case with sleep apnea and periodic leg movements in sleep, Jones et al.⁸⁷ recently found that only dementia and snoring affected sleep in nursing home patients, while several other medical conditions did not. In accordance with findings from animal research, sleep problems are more and more attributed to underlying disturbances of circadian function¹²¹. In rat, short sleep and wake periods alternate throughout the 24-h day. Thus, one can study the amount of sleep and wake during both the light and dark periods. Van Gool and Mirmiran^{177,178} found a reduction of the amplitudes of wakefulness, quiet sleep and paradoxical sleep in aged rats. Witting¹⁹³ confirmed the reduced amplitude in the distribution of wakefulness and quiet sleep over the light and dark period. As human sleep is usually monophasically distributed over a 24-h period it is less obvious to speak of a sleep-wake amplitude, but the emergence with aging of naps during the day and frequent awakenings during the night suggests a similar sleep-wake amplitude reduction (cf. refs. 15, 178). Moreover, an earlier timing of the sleep period may indicate a circadian phase advance. Several studies indicate that sleep-wake disturbances are more severe in Alzheimer patients as compared to healthy elderly people (cf. ref. 15), however not to the extent that polysomnography could be diagnostically useful to distinguish mild stage Alzheimer's disease¹⁸². The effectiveness of hypnotics in sleep complaints is limited and short-lived. As they affect daytime alertness and induce daytime sleep, they may even cause or worsen the dampening in the sleep-wake rhythm amplitude⁶³.

Rest-activity rhythm

Actigraphy, the continuous measurement of body movements with a small solid state device, has recently gained popularity in circadian rhythm research because of its easy applicability. Although sub-stages of sleep cannot be identified, periods of rest and activity may give a reasonable estimation of the time spent asleep and awake in young adults^{40,112}. However, this approximation was shown to be less accurate in insomnia⁷¹, which is likely to occur in elderly people and demented patients. Moreover, De Koninck et al.⁴⁵ have recently shown that the number of position shifts during sleep, which are counted as a movement by an actigraph, decreases with aging. As it is known that the elderly wake up more often, this results in a dissociation between wakefulness as indicated by polysomnography and wakefulness as indicated by actigraphy.

Therefore, rest-activity data should be distinguished from sleep-wake data. An increased interdaily variability of the rest-activity rhythm may not only be the result of a deteriorating circadian timing system, but may also contribute to a decreased circadian amplitude in other processes, as Madokoro et al.¹⁰² recently found a decreased melatonin amplitude in nurses on an irregular shift schedule. Several studies report a decrease in daytime activity with normal aging (cf. refs. 46, 179). Although one actigraphy study reports an increase in daytime activity and rest-activity amplitude⁹⁹ in an apparently very healthy and active group of elderly people, most studies in institutionalized elderly people report a fragmented rest-activity rhythm, i.e. more periods of rest during the day and more periods of activity during the night. In heterogeneous samples of aged nursing home patients, actigraphy and behavioral observations indicated fragmentation of the rest-activity rhythm (cf. refs. 3, 15, 83). In multi infarct dementia (MID) and Alzheimer patients, fragmentation of the rest-activity rhythm has been reported². In a group of Alzheimer patients, Witting et al.¹⁹² found increased fragmentation and a looser coupling to Zeitgebers. Van Someren et al.¹⁸⁰ found fragmentation of the rest-activity rhythm in institutionalized but not in Alzheimer patients living at home. Satlin et al.¹⁵⁴, in his study of Alzheimer patients, found a decreased amplitude and interpreted the increased end of day activity as a phase-delay in the circadian rhythm, which contrasts with several findings that indicate a phase-advance in aging and AD patients (cf. ref. 15).

We suggest that the data of Satlin et al.¹⁵⁴ indicate "sundowning" rather than a phase-delay. Sundowning, i.e. a relative increase in agitation in the late afternoon or early evening, is frequently reported in demented patients¹⁸¹, especially in the winter months (cf. ref. 15), and requires treatment as it is a severe load to the caregivers. Restlessness and awakenings during the evening and night are serious problems and were even found to be a primary factor in the decision of a caregiver to have an elderly relative institutionalized^{134,135,139,152}. The effectiveness of neuroleptics and benzodiazepines in the treatment of sundowning is often short-lived and the majority of patients do not show significant improvement (cf. ref. 106). Moreover, the elderly run higher risks of developing severe tardive dyskinesia as a side effect of neuroleptic treatment (cf. ref. 84). Akathisia, another side effect, presents with the very symptoms neuroleptics try to suppress: motor restlessness and sleeplessness (cf. ref. 84). The invariable emergence of the agitation at the end of the day, and the fact that sundowning, like many circadian rhythms, shows seasonal variation (cf. ref. 15), makes the

involvement of the circadian timing system likely. Treatment of sundowning by stimuli affecting this system therefore deserves more serious attention in treatment strategies.

Electroencephalographic activity

Age-related changes in the sleep and wake electroencephalogram (EEG) have been reviewed by Prinz et al.¹³⁸. Compared to younger subjects, the background EEG of elderly people during relaxed wakefulness shows an increase in slow wave activity (delta: 0–4 Hz and theta: 4–8 Hz), a reduction in alpha activity (8–12 Hz) and often an increase in beta activity (> 12 Hz). In the resting EEG of Alzheimer patients slow wave activity is even more prominent, and appears to be related to the severity of the disease¹⁵⁹. The alpha activity of Alzheimer patients, furthermore, is more reduced than that of healthy elderly people. Whereas the delta, theta and alpha changes in Alzheimer patients are thus merely an expansion of the changes in healthy elderly people, a decrease in beta activity was found in Alzheimer patients, which contrasts with the increase in beta activity in healthy elderly people¹⁵⁹. Interestingly, the age-related EEG changes resemble the EEG during a transition from alertness to drowsiness, and suggest that the elderly may be less aroused during the day (cf. ref. 138). However, the slow wave activity during cognitive tasks shows a trend quite opposite to that observed in relaxed wakefulness: compared to younger subjects, the elderly show less slow wave activity, while the increase in beta activity reported in resting EEG persists in the EEG during task performance (cf. refs. 50, 138).

In contrast to the increase in slow wave activity during relaxed wakefulness, the sleep of elderly people and Alzheimer patients differs most prominently from the sleep of healthy adults in decreased slow wave activity (cf. ref. 138). Slow wave activity has been associated with depth of sleep or sleep intensity ever since the Blake and Gerard paper was published in 1937¹⁴. Consequently, the EEG slow wave activity shows a reduced circadian amplitude. It has been noted that it may even be difficult to discriminate sleep and wake EEG recordings of demented patients¹⁵. These findings have implications for existing hypotheses on the underlying cause of increased slow wave activity during the day in elderly people and Alzheimer patients. The increase has, for example, been attributed to a cholinergic deafferentation of the cortex (cf. ref. 114). This hypothesis, however, does not incorporate the findings of decreased slow wave activity during the night. We suggest that the circadian timing system is somehow involved in the alternating predominance of fast or desynchronized and

slow or synchronized EEG during wake and sleep respectively.

Cognitive performance, sleepiness and alertness

Several authors have suggested a circadian rhythm in cognitive performance and alertness. For example, Reinberg and Smolensky¹⁴² state that "Just as certain aspects of sleep are closely related temporally to the circadian trough of the body temperature rhythm, so are certain aspects of activity such as the maximum of alertness and best task performance closely related temporally to the acrophase of this rhythm". By now, cognitive performance, alertness and sleepiness have been shown—in real-life situations as well as in several laboratory tasks—to have a circadian rhythm that parallels the temperature rhythm^{85,145,178} and EEG activity.

In aging, the daytime performance in several cognitive tasks worsens but, interestingly, if subjects are awakened during the night, task performance is relatively better in the elderly and even more so in elderly insomniacs²¹. The lack of decrease in task performance after nighttime awakening as compared to daytime performance was paralleled by a lowered arousal threshold and a reduced temperature drop during the night, suggestive of a damped circadian rhythm amplitude²¹. Moreover, the elderly show a trend towards a reduced circadian sleepiness amplitude¹⁴⁵. In Alzheimer patients, as far as we know, only daytime studies have been performed, which obviously showed cognitive deterioration. Of interest in this respect is a study of Duffy et al.⁴⁹, who found that poor cognitive performance in Alzheimer patients correlated with increased delta and theta slow wave activity and decreased beta activity. We suggest that a damped circadian amplitude may contribute to the deterioration of cognitive performance with aging and in Alzheimer's disease.

III. POSSIBLE MECHANISMS UNDERLYING CIRCADIAN RHYTHM ALTERATIONS IN AGING AND ALZHEIMER'S DISEASE

Several findings indicate deterioration of the circadian circuitry with aging. The information processing and rhythm generating part of the circadian circuitry, the SCN, shows a decrease in its size and number of cells expressing vasopressin, one of its major neurotransmitters, in subjects over 80 years old and even more so in Alzheimer patients¹⁶⁹. The deterioration appears to be specific to the SCN part of the hypothalamus as adjacent nuclei appear to be unaffected⁶⁸. In the rat SCN the number of vasopressin and vasoactive

intestinal polypeptide (VIP) expressing neurons decrease with aging^{37,146}. In animal studies, lesioning of the SCN affected the rhythmicity in locomotor activity, feeding, drinking, sexual behavior, deep body temperature, sleep–wakefulness and hormones (cf. refs. 15, 109). It is important to note that the phenomena still occur but just lose their rhythmicity. For example, although an animal's ability to sleep is not compromised, the ability to temporally organize the level of arousal, and thus sleep, is suppressed¹⁸⁶. In addition to age-related deterioration of the SCN itself, other central nervous system (CNS) structures projecting to the SCN may deteriorate as well.

In addition to deterioration of the circadian circuitry, changes in the environmental stimuli and their appreciation may hamper entrainment to these stimuli. In the first place, age-related changes in environment and physiology contribute to a reduction in the input to the circadian clock from light sources. Elderly people, and, even more, Alzheimer patients, expose themselves to significantly less bright environmental light^{34,153}. Campbell et al.³⁴ and Savides et al.¹⁵⁶ investigated the time subjects were exposed to more than 2000 lux and reported average daily exposure times of 1.5 h in healthy young adults, 1 h in healthy elderly people and 0.5 h in ambulatory, early-stage Alzheimer patients. Maximum light exposure occurred between 12.00 and 13.00 h in elderly people and Alzheimer patients and around 15.00 h in young adults. Sanchez et al.¹⁵³ investigated the time subjects were exposed to more than 1000 lux and found daily averages of 1.7 h in young adults and 0.6 h in healthy elderly people. In addition, the sensitivity of the eye to light declines with age, most markedly after the age of 60¹², and a decreased ultra-violet transmission through the ocular media with aging has been reported¹⁸. In Alzheimer patients degeneration of the optic nerve and retinal ganglion cells was found^{13,73}.

In addition to a reduction in input from light sources, several studies report an age-related decrease in daytime activity (cf. refs. 46, 153, 179), which is known from animal studies to be another important modulator of circadian rhythms¹⁷⁶. Other age-related changes may also contribute to a reduction in input to the circadian timing system. Not only in the visual, but also in the auditory, kinaesthetic, somatosensory and vestibular sensory systems age-related decrements have been described¹⁶⁵. Such a general reduction in sensory input is likely to lower the "general level of excitement", which is thought to play an important role in the entrainment of circadian rhythms^{5,176}. A reduction of the general level of excitement may furthermore be caused

by the loss of social contacts, e.g. by placement in a residential home.

IV. TREATMENT OF CIRCADIAN RHYTHM DISTURBANCES IN AGING AND DEMENTIA

In the treatment of sleep–wake disturbances and agitation, sedatives and neuroleptics have to be used with extreme caution. Drug dependency is likely and adverse effects may exacerbate many of the AD symptoms¹⁸¹. Therefore the potentialities of non-pharmacological treatment deserve attention. Just as resynchronization of the circadian rhythm is used in the treatment of depression (e.g. ref. 97), amplification of the circadian rhythm may ameliorate sleep–wake complaints in elderly people and Alzheimer patients.

Light

A vast amount of literature demonstrates the effectiveness of bright light therapy in depression, jet lag and night shift problems. Bright light has recently been suggested as a therapy in aging and Alzheimer's disease, where the transmission and processing of light input by the circadian timing system is hampered.

Sleep is influenced by the timing and intensity of environmental light. The preferred phase of the day for sleeping is strongly dependent on the phase of the light period. The amplitude of the sleep–wake cycle in rats is modulated by the intensity of light, and the decreased sleep–wake cycle amplitude in aged rats can be restored to the level of young rats by increasing the environmental illumination¹⁹³. In human, Bunnell et al.²⁸ has shown that bright light given during the day enhances nighttime EEG slow wave activity and may also cause a shift towards a later sleep phase. Although these are precisely the effects that are suitable to reverse sleep alterations in the elderly only few studies have been performed. Campbell and Dawson³³ report a 1.5-h delay in the body temperature nadir, more slow wave sleep, less stage transitions and less wake time after sleep onset in elderly people with sleep maintenance problems after exposure to bright light of 4000 to 5000 lux, individually timed two h a day for 7 to 10 days. In another study by this group^{35,155}, ten male probable Alzheimer patients with *sundowning* and sleep maintenance problems were treated with bright light. Patients were exposed to 1500–2000 lux from 19.00 to 21.00 h for 1 week. Nurse ratings and actigraphic recordings indicated improved sleep quality, less *sundowning* and an increase in the circadian rest–activity amplitude. Patients with more severe behavioral and sleep disturbances showed the greatest improvement. A Japanese

research group reported a reduction in sleep disturbances and *agitated behavior* in 50% of a group of 24 demented patients after bright light treatment^{82,124,125,126,127}. Their patient sample consisted of 20 MID and 4 Alzheimer patients, all moderately to severely demented, who were selected on the presence of an irregular sleep-wake rhythm. In their reports, the intensity of the light varies between 2000 and 3000 lux, given from 9.00 to 11.00 h in the morning for 2 to 6 months. Morning light was found to be more effective than evening (17.00–19.00) light. The effectivity of the treatment in reducing agitation did not appear to be mediated by changes in temperature or melatonin rhythm, which were present in, respectively, only 4 and 0 of the 24 patients. However, the conclusion on melatonin is inconclusive as the sampling rate was only twice per 24 h.

Although a vast amount of reports indicate the effectiveness of light therapy in certain types of depression, we are aware of only one study evaluating the effect of bright light on the *mood* of elderly people. Hanger et al.⁷⁰ found that 2 h of morning (9.00–11.00) or evening (17.00–19.00) bright light (2500 lux) for 10 days were equally effective in reducing the depression scores of nursing home residents.

No studies on bright light effects on daytime *EEG*, *alertness* and *performance* in the elderly have been reported. Studies in young adults are equivocal. Light elicits subjective arousal, and heart rate and blood pressure indicate autonomic nervous system arousal (cf. ref. 90). As early as 1937, Blake and Gerard¹⁴ reported suppression of alpha-waves in the EEG by shining a light on the eyes, although more recently a lack of effectiveness on EEG and performance parameters during the day was reported^{7,29}. However, as bright light during the night is more effective⁷, a ceiling effect appears to exist, which prevents further improvements during the day in young subjects. Nighttime bright light of 1000 lux or more, but not of 100 lux, was found to raise body temperature, to increase EEG beta activity, which is associated with alertness, to reduce sleepiness and to improve task performance on cognitive rather than reaction time parameters^{7,31}. Similar results, and improved subjective alertness and subsequent sleep, have been reported in studies evaluating the effect of exposure to bright light in night shift workers^{22,41,69,95,171}. It remains to be investigated whether these findings extend to daytime functioning in the elderly, where a ceiling effect is less likely.

The *mechanisms* of improvement in daytime and nighttime functioning with increased environmental light are at present unclear. Bunnell et al.²⁸ suggested that bright light could exert its effect on subsequent

sleep by raising the deep body temperature, probably mediated by the light-induced suppression of melatonin, which has a temperature lowering effect in most species. However, an endogenous melatonin rhythm exists, as darkness during the day does not induce melatonin secretion. Consequently, bright light during the day will only suppress melatonin if this is released during daytime as a consequence of a chronobiological disorder. In demented patients, daytime melatonin secretion was even lower than in controls, and unaffected by light therapy, while sleep and restlessness improved^{82,124,126,127}. As the body temperature rhythm was also unaffected by light therapy, the results were attributed to an increased regularity of the rest-activity rhythm. Melatonin profiles have also limited value in the evaluation of the effectiveness of bright light treatment in depression. Rao et al.¹⁴⁰ showed that light treatment modifies the circadian melatonin profiles of depressed patients and healthy subjects only marginally, while a profound increase in serotonin was established by bright as well as dim light. Whether or not reflected in temperature and melatonin levels, it is likely that the circadian timing system is indirectly influenced by the effect that bright light might have e.g. on the general state of arousal, behavior, or the suppression of microsleeps (cf. refs. 55, 90).

As was indicated above (sub I), there is no consensus on the light *intensity* required in light therapy. It may be speculated that higher values are necessary in elderly people and Alzheimer patients with deterioration of the visual system or the circadian timing system.

The optimal *time* of day for light exposure is also equivocal. Hozumi et al.⁸² found that morning (9.00–11.00 h) exposure but not evening (17.00–19.00 h) exposure to 2500 lux reduced behavioral agitation in a sample of, mainly, multi infarct dementia (MID) patients. Satlin et al.¹⁵⁵ found evening (19.00–21.00) exposure to 1500–2000 lux to be effective in Alzheimer patients. Results obtained in young healthy adults indicate that early morning or late night light exposure may induce adverse effects. Cajochen et al.²⁹ reported that morning light reduced sleep duration without affecting EEG power density. Campbell and Dawson³² found shorter sleep latency, followed, however, by more arousal and a worse sleep efficiency. The effect of light just prior to sleep is equivocal. Cajochen et al.²⁹ found increased sleep latency and decreased temperature amplitude while Bunnell et al.²⁸ found slow wave sleep potentiation.

In depressed patients light therapy is mostly applied by putting the patient in front of a light box for a few hours a day, scheduled either during the morning or during the evening, depending on the presumed circa-

dian phase distortion in the individual patient. However, sitting in front of a light box for a few h a day was found to be most inconvenient by 69% of seasonal affective disorder patients using light therapy at home¹²⁸. In addition one should note that a patient that does not comply with the request to look into the light receives much less light⁴³. Thus, when using light boxes in Alzheimer patients, continuous attendance is needed. Such a demanding procedure is likely to compromise the practical feasibility of light therapy for the great number of Alzheimer patients in nursing homes. For this reason and supported by the relationship between duration and efficacy of light treatment (cf. ref. 147), we are currently investigating the effect of a whole day increase in the illumination of the living room in a nursing home. This may also better suit our main objective as far as elderly people and Alzheimer patients are concerned, i.e. to amplify rather than phase shift the circadian rhythms. However, in comparison to the numerous reports on the effect of light pulses, literature on the effects of whole-day constant increased illumination is scarce.

The *spectrum* of light sources used in light therapy may also be of importance. Brainard et al.²³ found that monochromatic light with a wavelength of 509 nm achieved the largest suppression of nocturnal plasma melatonin. On the other hand, broad spectrum light gives a higher apparent brightness and perceptual satisfaction and may reduce glare, to which the elderly appear to be more sensitive (cf. refs. 90, 91).

In addition to daytime light, *darkness* during the night is also important, as is reflected in the traditional belief held by Shetlanders living near the arctic cycle, i.e. that moonlight should never fall on the face of a sleeping person¹⁶⁶. During the night, the melatonin suppressing mechanism has maximum sensitivity¹²⁹ and consequently even little light may disturb its secretion. Eastman⁵⁶ recently reported the effectiveness of darkness during the sleep period in addition to bright light during wakefulness in the adaptation to shift work. Although we are not aware of other studies on human, the importance of a circadian rhythm in environmental light is supported by several findings in rat. Firstly, light during sleep suppresses the amplitude of slow waves in the EEG¹⁷³. Secondly, Eastman and Rechtschaffen⁵⁷ found dampening of the sleep-wake rhythm amplitudes in rats exposed to constant light. And, finally, prolonged exposure to constant bright light in nocturnal rodents, or constant darkness in diurnal rodents, induced a so-called "splitting" of the drinking, eating, activity and temperature rhythms, i.e. a rhythm of approximately 12 h emerges^{109,110}. In conclusion, it is suggested that elderly people and Alzheimer patients

may not only profit from brighter days, but also from darker nights. The latter is of practical importance in nursing homes, where bedrooms are often lighted by adjacent corridors when the doors are not closed.

Increasing daytime physical activity

Changes in activity level can be equally effective as light pulses in phase shifting free-running rhythms, at least in animals¹⁷⁶. In rat, exercise was found to enhance slow wave sleep¹¹⁷. In human, Winget et al.¹⁹¹ and Campbell³⁰ found that hypokinesia induced by forced bed rest disturbed sleep and depressed the mean and amplitude of body temperature. Although the period of the temperature rhythm did not change, it tended to become desynchronized with the environment. These findings suggest that an increase in daytime physical activity might improve circadian rhythms in the elderly, possibly reflected in performance and sleep.

In young adults, Matsumoto¹⁰⁵ found that a whole day of exercise lowered cortisol secretion during subsequent sleep, which could indicate an increased circadian amplitude. Theron et al.¹⁷⁰ found a short-lived increase in plasma melatonin, cortisol and prolactin levels during and shortly after vigorous exercise. The findings of Paxton et al.¹³² indicate that fit adults have nonsignificantly larger circadian amplitudes in cortisol and growth hormone levels than unfit adults. Trinder et al.¹⁷⁴ suggested that all effects of exercise on sleep are mediated by alterations in the circadian body temperature rhythm. To our knowledge, no studies on the *circadian rhythms of hormone levels* in exercising elderly people have so far been reported.

However, several reports indicate that exercise of sufficient vigour and duration may improve task *performance* in suboptimal fit adults. Regular exercise in elderly people was found to improve response speed, cognitive performance and visuospatial processing^{8,9,51,53,164}. Moreover, it tended to reverse age-related changes in EEG and ERP's⁵². Powell¹³⁶ investigated the effect of exercise in institutionalized geriatric mental patients and did not find increases in cognitive performance until after 12 weeks of exercise. In a similar patient group, Diesfeldt and Diesfeldt-Groenendijk⁴⁸ also found a short-term effect of exercise on cognitive performance.

Exercise was also found to affect *sleep*. In young adults, increases in slow wave sleep and shorter sleep latencies have been reported^{105,120,131}. In elderly people, 6 months of fitness training improved subjective sleep quality¹⁸³. Edinger et al.⁵⁹ found no acute effect of exercise on sleep, although the aerobically fit elderly had more slow wave sleep than the sedentary elderly. In

healthy elderly subjects without sleeping problems, a single exercise session during the afternoon did improve subjective sleep quality, but did not improve objectively scored sleep or temperature¹¹.

Reviewing positive and negative findings in literature, fitness acquired by long-term regular exercise appears to be more effective than acute exercise. Powell¹³⁶ suggested, therefore, that the effect of long-term exercise on cognitive performance might be mediated by afferent stimulation of the brain through proprioceptive feedback. Moreover, acute exercise appears to be effective only when it is so vigorous that an increase in deep body temperature is achieved⁷⁶, which is hard to accomplish by less fit humans. Horne and Staff⁸¹ suggested, therefore, that the effect of exercise on sleep was mediated by an increase in body temperature, and the same group later showed that the effect of exercise on subsequent sleep could be prevented if the body was cooled during exercise⁷⁷. Horne and Porter⁷⁸ furthermore showed that exercise coinciding with the temperature peak during the afternoon subsequently elicited more delta sleep, whereas exercise during the morning did not affect sleep. These findings initiated research into the effect of passive body heating on subsequent sleep, which appears to be a more practical tool than exercise in sedentary elderly people and Alzheimer patients.

Heating

Although exercise may be beneficial in several ways, the physical ability of many elderly people will not allow them to train vigorously. While even modest training will induce some general excitation, and might in the long run affect circadian rhythms, a body heating effect with vigorous exercise may be impossible to achieve. Extremely sedentary persons may need even higher levels of exercise to reach a certain body temperature threshold, as Winget et al.¹⁹¹ found that hypokinesia induced a long-term depression of the mean body temperature. However, it has been reported that a passive heating of the body may have a similar effect on sleep as exercise. In fit as well as in unfit young adults, body heating in a warm bath was shown to induce a subsequent increase in slow wave sleep^{79,81}.

A warm bath of $\pm 41^{\circ}\text{C}$ raises the body temperature 2°C in approximately 15 min and 20 to 30 min of heating at the right time increases plasma melatonin and affects sleep^{27,64,80}. Considering the timing of a warm bath, several findings favour the late afternoon or early evening. First, during and some time after the daytime bathing, subjective sleepiness increases, which would not be a desirable effect during the day⁷⁹. Interestingly, subjective sleepiness does not increase after

early evening bathing²⁶. Second, despite the lack of increased sleepiness, sleep onset latency is reduced most after early evening bathing²⁶. Third, late and early evening heating produce the largest increase in slow wave sleep, while heating 5–6 h or more before sleep was found to be less or ineffective^{26,47} and heating just before going to bed may disrupt sleep⁸⁰. In conclusion, passive daytime body heating appears to offer a promising alternative to increasing body temperature by means of exercise. However, further research is needed, as in all studies the subjects were young adults without any sleeping problems, and not in elderly people or insomniacs. Moreover, we are not aware of any study on daytime effects of passive body heating.

Comparable to the findings of environmental light, the amplitude of the environmental temperature, i.e. difference between daytime and nighttime temperature, might also be of importance. In a constant and thermoneutral environment, the circadian temperature amplitude is reduced^{104,141}, and Lee and Tokura⁹⁴ recently reported that insulating clothes hamper the heat loss variation and thus reduce the circadian rhythm in core temperature. The effects of heating or cooling during the night are equivocal. Nighttime heating was reported to disturb sleep⁴⁷ and diminish the nightly fall in temperature¹⁹, but also to induce slow wave sleep (cf. ref. 10). Cooling during the night was reported to increase the amount of stage 4 sleep, lengthen the first sleep cycle and increase the amplitude of the circadian temperature rhythm in adult women¹⁶¹. However, the whole night polysomnographic data and a subjective report indicated a worsening of sleep quality under this condition. Moreover, Szymusiak and Satinoff (cited in ref. 143) have suggested that the impaired sleep of Alzheimer patients resembles sleep disturbances during cold exposure. Thus, a thermoneutral environment and clothing and sheets that allow heat loss, may be preferable during the night.

Deprivation of naps and restriction of time in bed

Sleep deprivation induces a "rebound" of sleep during the following night. This response is characterised by an augmentation of sleep continuity and slow wave sleep and is preserved in elderly people although it may be compromised in Alzheimer patients¹⁴³. These characteristics as well as the finding that forced inactivity and bed rest disrupted sleep in young subjects³⁰, and, in addition, the observation that elderly people who habitually sleep-restrict themselves have a better sleep continuity (cf. ref. 144), indicate possible therapeutic effects of curtailment of the time in bed on sleep quality. Two strategies were applied: deprivation of daytime naps and reduction of the time in bed during the night.

Several studies revealed that the elderly take more frequent and longer naps²⁵ (cf. ref. 111). Whereas total sleep duration decreases with age, an increase due to napping has been noted after 50 years of age¹⁷⁵, but sleep quality during naps is as poor as during the night⁹⁶. It has been suggested that curtailment or deprivation of naps might alleviate sleep problems in the elderly. At present, correlative research does not suggest a convincing relation between napping and sleep problems in the elderly, although it may exist in younger subjects^{25,111}. Positive as well as negative nonsignificant trends in the elderly have been reported. First, naps of long duration may be related with increased nighttime sleep latency. Second, frequent napping may be related with shorter nighttime sleep latency^{25,111}. Moreover, as napping has been suggested to shorten the free running rhythm period⁴⁴, while lengthening of the period would be preferable in the elderly, correlative studies do not indicate that nap reduction would effectuate better sleep. Experimental studies on napping in the elderly are scarce. Aber and Webb¹ studied the effect of induction of a nap rather than elimination, on the sleep of healthy elderly women, and did not find any effect. However, in a behavioral approach consisting of elimination of daytime naps and standardising wake up times in adult and elderly psychiatric patients, positive effects were found⁶⁰. Sleep onset latencies, wake time after sleep onset and total sleep time improved most prominently in patients that were institutionalized for a long time.

Most nighttime sleep restriction studies include elderly people, although no studies with Alzheimer patients have been reported. In nighttime sleep restriction, the actual amount of sleep while in bed is assessed in a pre-treatment phase. This duration is consequently used as a limit to the time in bed. Step by step, the allowed time in bed is altered following some rule, e.g. keeping the time in bed spent sleeping between 80% and 85%. In studies using self reports and/or actigraphy, nighttime sleep restriction in insomniacs was found to reduce sleep latency and wake after sleep onset. Whether the total sleep time was found to decrease^{149,158}, to be unchanged⁷⁵ or to increase^{63,150,167} by the treatment, the patients were in general more satisfied with their sleep, indicating the importance of sleep quality over sleep quantity. In a polysomnographic study similar changes occurred, but did not reach significance¹⁵⁰.

Reports on the effect of sleep restriction on daytime functioning are scarce. Rubenstein et al.¹⁴⁹ found that nighttime sleep restriction shortens daytime sleep latencies on the Multiple Sleep Latency Test (MSLT), which was interpreted as an increase in daytime sleepi-

ness. However, it has been argued that the MSLT measures the ease with which a state transition from wake to sleep occurs, rather than sleepiness⁹³, and it has been shown that MSLT does not correlate with performance on a vigilance task⁷⁴. In another study, Rubenstein et al.¹⁵⁰ report investigation of alertness, performance and mood without mentioning results.

The mechanism underlying the effect of nighttime sleep restriction is subject to speculation. As sleep deprivation very likely results in more activity and exposure to light, these factors might mediate this effect. However, although sleep is restricted at the onset of the therapy, sleep quality improves regardless whether the therapy finally decreases or increases sleep duration. The same problem holds for the hypothesis of a homeostatic build-up of "sleep propensity" mediating the sleep enhancement. The involvement of a homeostatic mechanism, in addition to a circadian mechanism, in sleep-wake regulation has been addressed extensively by the group of Borbély²⁰. In their 'two-process model' sleep propensity' builds up during wakefulness and degrades during sleep, while a second process varies the upper and lower threshold that should be reached by the sleep propensity in order to induce transitions between the sleep and wake states. Similar to light and activity, sleep propensity may mediate effects at the onset of the therapy, but the improved sleep quality after the therapy does not require an increase in any of them. Temperature regulating mechanisms may be involved, as it has been shown that the usually very intense recovery sleep after total sleep deprivation is accompanied by a steeper temperature drop, and that the anti-depressive effect of sleep deprivation in depressives is marked by an increased temperature drop (cf. ref. 160).

Social interaction

Social cues have long been seen as the main Zeitgebers in man, but they received little attention since the finding that light suppresses melatonin in man⁹⁸. Enforced social interaction with nurses on fixed hours was reported to reduce behavioral agitation and sleep-wake rhythm disorders in 33% of a heterogeneous group of demented patients^{125,126}. However, as walking outdoors was part of this treatment, increased exposure to bright light and increased activity may have contributed to this outcome. This suggestion is supported by the finding of the same research group that bright light treatment was more effective than social interaction. Monk et al.¹¹⁹ could not find a decreased social interaction in healthy elderly people as compared with young adults. The study on day schedules, napping and nocturnal awakenings in home living elderly of Minors

et al.¹¹⁵ also indicates little contribution of social environment to the entrainment of circadian rhythms, as similar results were found in subjects living alone and subjects living in company. A 12-week social interaction program in institutionalized geriatric mental patients was found to result in negligible changes on cognitive performance¹³⁶.

V. DISCUSSION

Age- and Alzheimer-related circadian rhythm disturbances are expressed in body temperature, hormone levels, sleep-wake rhythms and rest-activity rhythms and, as discussed in the present paper, may also contribute to alterations in EEG and decreased performance and alertness. Whereas circadian rhythm disturbances in depression, jet-lag and shift work are related to phase-shifts, the most prominent disturbance in elderly people and Alzheimer patients appears to be a decrease in the amplitude. Therefore, chronobiological treatment should be directed primarily at increasing the amplitude. From reviewing the literature one might expect chronobiologically based treatment with bright light, physical activity, body warming or sleep restriction to affect one or more of the circadian parameters in a way that would be beneficial for the sleep and wake disturbances in elderly people and Alzheimer patients. The effectiveness of regularly scheduled social interaction on circadian parameters is equivocal: when effects were reported they could also result from increased activity and exposure to bright light. Although far from all treatment effects have been evaluated, and even less so in elderly people and Alzheimer patients, the present state of knowledge certainly warrants further research. The common feature of the discussed effective chronobiological treatments, amplification of circadian rhythms, distinguishes them from presently available pharmacological treatments. For example, unlike sleeping pills, enhancement of sleep does not result in subsequent daytime sleepiness. Another example is that bright light increases EEG beta activity and tonic skin conductance levels during the day^{6,7}, indicating increased alertness, but has also been found to induce increased slow wave activity during the subsequent night, which indicates deeper sleep. Such a bifurcation of effects has not been described in pharmacology. Whereas, e.g., DuP-966 resembles bright light in enhancing alpha and beta and attenuating delta and theta (cf. ref. 114) this effect would be suitable only for the daytime and certainly not during the night. The dual, opposed day and night effects of the discussed non-pharmacological treatments support the idea that the effects are actually

mediated by the circadian timing system rather than by some other CNS mechanism.

At present one can only speculate on the mechanism by which chronobiological treatments influence the circadian timing system. A first possibility is that an amplification of the circadian input (light-dark, rest-activity) facilitates the entrainment with a relatively weak circadian timing system, without improving the functionality of this system per se. On the other hand, increased exposure to circadian input may actually improve the functionality of one or more stages in the circadian timing system. This distinction has practical implications. In the first case, circadian amplitude improvements would *immediately* follow increased circadian input, and removal of this input would lead to an immediate relapse. In the second case, improvements by increased input might show a slower development, reflecting a *gradual* rehabilitation of one or more of the circadian timing system components, and removal of the input would not lead to an immediate relapse. The developmental course of the treatment effects as summarised in the present paper suggest the involvement of both mechanisms.

Immediate effects on circadian parameters have been reported after (1) bright light treatment and appropriately timed (2) vigorous exercise or (3) body heating. Melatonin, which was reported to induce evening fatigue and enhance sleep when ingested in the late afternoon¹⁹⁴, has been suggested as a mediating factor in all three treatments. However, as bright light suppresses melatonin²⁸, whereas active¹⁷⁰ or passive⁶⁴ body heating raises melatonin secretion, the melatonin level appears not to be the final common pathway of the treatments. A more likely candidate is the body temperature, which increases with all three treatments. Whereas a temperature increase was found to be a prerequisite for an immediate effect of exercise, and is evident in passive body heating, several studies also indicate that bright light treatment raises body temperature^{7,28,58,69}. Moreover, since exercise and body heating are most effective in the afternoon and adverse effects were reported with very early or late bright light treatment, it appears to be crucial that the heating occurs in the afternoon, coinciding with the circadian temperature peak. These considerations point to the possible importance of increasing the temperature peak as a final common pathway in immediate effects of circadian treatments.

The involvement of temperature is a priori likely from an evolutionary perspective, as the environmental light-dark cycle, mostly mentioned as the important factor in the evolution of circadian rhythms, is of course

paralleled by an environmental temperature rhythm. Although we are not aware of models on the relation between body temperature and performance, the relation between body temperature and sleep has led several authors to speculate on underlying mechanisms. Horne and Shackell⁸⁰ suggested that an increased brain metabolism due to heating might accelerate the production and accumulation of a sleep factor with a delayed action, possibly prostaglandin D₂, a sleep inducing substance sensitive to tissue heating. Interestingly, a prostaglandin mediated temperature change has also been suggested as a mechanism underlying pharmacologically induced changes in circadian rhythms (cf. ref. 142). Bunnell and Horvath²⁷ suggested that heat, by increasing serotonergic raphe neuron firing¹⁸⁷, would lead to an increase of a delta sleep inducing substance. Obviously, also this model would be in need of some delay factor. A light therapy induced increase in plasma serotonin has been reported in depressed patients⁷². However, these homeostatic hypotheses do not account for the fact that heating in the morning and early afternoon does not affect subsequent sleep, while the build up of a sleep inducing factor would be similar²⁶.

Sewitch¹⁶⁰ and Bunnell et al.²⁶ suggested that the degree of decline in body temperature is related to the amount slow wave sleep. Berger and Philips¹⁰, on the other hand, suggested that slow wave sleep is related to the absolute temperature, rather than the derivative. Jordan et al.⁸⁸ tried to do a critical experiment for both hypotheses and found that an increase in slow wave sleep after body heating was accompanied by a higher temperature but not by a fall in temperature, in favour of the idea of Berger and Philips¹⁰. However, this decline did in fact occur just before sleep onset, and may have caused a delayed increase in slow wave sleep. The rate of temperature decline before sleep may be as important as the rate of decline during sleep in determining slow wave sleep propensity. Such a rapid decline might form a sequence of optimal temperatures for several biochemical processes in a relatively short time, so that, before one or more of the biochemical products will be degraded again, they have the opportunity to concertedly induce a sleep promoting factor. As, on the other hand, this factor may also be degraded, its formation should not be too distant from bedtime. This hypothesis accounts for some of the conflicting results of nighttime heating and cooling, as a short term increase or decrease in temperature is predicted to have a different effect than a whole night of constant hot or cool environment. A similar mechanism, also stressing the importance of change in addition to level, is found in the effect of environmental light on circadian rhythms. In animals, a short light pulse at dusk and

dawn may entrain as effectively as continuous light from dusk to dawn, and dusk and dawn simulation is more potent than simply turning lights on and off (cf. ref. 123), indicating that the change in environmental light is at least as important as the level of environmental light.

In addition to the—possibly temperature mediated—immediate effects of treatments, a second, *gradual* mechanism with a longer time course appears to be involved. The present review indicates that long-term exercise, or the resulting better fitness, results in better sleep and performance. We propose that a repeated *increase in the overall input* to the central nervous system (CNS) by means of bright light, activity, passive heating or restriction of time in bed may be involved in this second, gradual enhancement of circadian rhythms. Bright light will not only affect neurons projecting to the SCN, but obviously also induce an increased visual input. Motor activity and, indirectly, restriction of time in bed, increase the amount of various sensory and proprioceptive stimuli¹⁹⁰, while passive heating results in CNS stimulation mainly by thermosensitive organs. The involvement of “excitation” has been suggested previously by Aschoff⁵, and Turek¹⁷⁶ recently argued that the effects of various hormones and neuroactive compounds on the circadian rhythm might all be mediated by the way they affect the “general level of excitement” or “overall activity”. A consequence of the proposed ‘excitation hypothesis’ is that improvement of circadian rhythms should also result from several non-pharmacological treatments for (daytime) problems in dementia that did not originate from a chronobiological perspective, and have therefore not been discussed above, as they have this increase in CNS input in common with the treatments discussed above. An animal model for an increased CNS input and some of the non-chronobiological treatments will therefore now be addressed shortly to evaluate if they appear to induce improvements in circadian rhythms.

The “*enriched environment*” paradigm is an animal model in which the standard laboratory housing is replaced by a housing with more room, objects and animals, allowing more exploratory and social behavior (for a review, see ref. 116). This environmental stimulation was found to be associated with various changes in the anatomy and biochemistry of the brain, e.g. an increase in the thickness and weight of the visual cortex, increased dendritic branching and synaptic contacts, enhanced protein synthesis and cholinergic activity and nerve growth factor (cf. refs. 116, 118). Functional effects of an enriched environment have been evaluated mostly on performance during wakeful-

ness and include improvements in learning and memory. The minority of studies that included sleep-wake parameters reported that an enriched environment increased the amount of slow wave sleep in young as well as in old rats (cf. ref. 116). Another circadian parameter was measured by Zucconi et al.¹⁹⁵, who reported that the circadian amplitude of rat brain DNA content increased in an enriched environment and decreased in an impoverished environment. Although the enriched environment paradigm has been studied experimentally almost exclusively in animals, one correlative study indicates a similar effect in human. Marchini et al.¹⁰³ have shown that good sleepers as compared to insomniacs spend their day in what can be summarised as an enriched environment: more activity, involvement in their work and social contacts. Moreover, the treatments mentioned in the present paper as well as non-chronobiological treatments might also be considered as "enriching". For example, "psychomotor therapy" usually combines sensory, motor and social activation. Another example is "music therapy", a form of auditory stimulation with some anecdotal evidence of improving the quality of life in Alzheimer patients^{66,67,100,101}. Scherder et al.¹⁵⁷ recently reported that transcutaneous electrical nerve stimulation (TENS), a more direct form of CNS stimulation that is usually applied in pain suppression, improves the verbal long-term memory and fluency in Alzheimer patients, and recent unpublished findings of this researcher indicate similar effects after peripheral tactile stimulation. The most direct non-intrusive form of CNS stimulation, transcranial electrostimulation treatment (TCET) has been used to improve subsequent sleep. Whereas TCET just before sleep did not affect sleep in healthy young adults⁶¹, insomniacs responded with shorter sleep latencies, less time awake after sleep onset and an increase in delta and theta waves in the EEG^{36,62,151,188}. Interestingly, in addition to improved sleep, Philip et al.¹³³ recently reported also improved daytime alertness after TCET in depressed inpatients during drug withdrawal. It can be concluded that circadian rhythm improvements are evident in the "enriched environment" animal model, that sleep has not been evaluated in most therapies that were not placed in a chronobiological perspective, but that circadian rhythm improvement was found in at least one treatment (TCET) in which both daytime and nighttime parameters have been assessed.

At present the underlying mechanism of the improvement of circadian amplitude is far from clear. Several authors have suggested that brain stimulation in various forms might prevent or even partially reverse brain atrophy. Jolles⁸⁶ made the analogy of brain atrophy to muscular dystrophy by disuse. This model, paraphrased

as "Use it or lose it" by Swaab¹⁶⁸, states that activation of nerve cells within the physiological range by internal stimuli like hormones, growth factors and transmitters or by environmental stimuli, prevents their degeneration and may even restore their function in aging and neurodegenerative diseases. Applying this model to the circadian timing system, a gradual restoration of function in neuronal systems providing information to the SCN will result in the facilitation of entrainment. Moreover, such an increased input could induce a restoration of function in the SCN itself. Studies on the functionality or anatomy of the SCN after prolonged environmental stimulation are in progress. The possible restoration of systems that provide input to the SCN has some experimental support. For example, exercise, which is accompanied by increased amounts of sensory and proprioceptive stimuli¹⁹⁰, has been shown to increase stimulus sensitivity (cf. ref. 8) and may thus counteract the decrements in the visual, auditory, kinaesthetic, somatosensory and vestibular sensory systems that have been described in the elderly¹⁶⁵.

Despite the lack of knowledge on the mechanisms of the treatments mentioned in the present paper, the mere findings of circadian rhythm enhancement are of clinical importance. Many of the amplitude-enhancing conditions appear to be absent in nursing homes. A few studies do indicate that institutionalized elderly people may have more circadian rhythm disturbances than the home living elderly. Clapin-French³⁸ investigated alterations in sleep behavior in the elderly before and after admission to a nursing home. She reports more napping, more sleep interruption and slightly more difficulties in falling asleep. In addition, once in a nursing home, bedtimes were earlier without changes in wake up time or sleep duration and thus indicating a prolonged time in bed. Kerkhof and Wauquier⁸⁹ compared ambulatory 24-h polysomnographic recordings of healthy institutionalized and home-dwelling elderly people, and found that the latter showed more napping and an earlier phase position of the main sleep. On the other hand, EEG-analysis of sleep structure and depth did not show any differences. Kerkhof and Wauquier⁸⁹ suggested that differences in exposure to daylight might have played a major role in the development of fragmentation and phase-advance. Interestingly, sleep logs of Alzheimer patients residing at home indicate longer sleep, as compared to healthy elderly people¹⁶. Actigraphic recordings also indicated that rest-activity rhythms are disturbed predominantly in institutionalized Alzheimer patients, which could not be attributed to the severity of the disease¹⁸⁰.

Apparently, institutionalization may contribute to sleep-wake problems in several ways. Proximity of others, and meals, medication or other activities of the nursing staff contribute to frequent awakenings³⁸. Sun-downing, pacing and aggressive behavior may be positively related to nocturnal awakenings by the staff (cf. refs. 15, 39). Two studies^{115,119} investigated age-related changes in self imposed Zeitgebers as eating times, bed-time and wake up time, and found that the home living elderly have a more rigid schedule, i.e. less variation over the days, which might be interpreted as a stronger adherence to Zeitgebers. Moreover, the variability in day schedules between subjects was much larger in the elderly¹¹⁵, which implicates that for many elderly admittance to a nursing home requires the resetting to an imposed schedule that differs from their own optimal schedule.

Also lighting may be far from optimal. The opportunities to go outdoors – and receive very bright light – are usually very limited, and the indoor light is rarely over 500 lux (cf. ref. 54). Moreover, lights left on in corridors during the night, resulting in a lack of darkness during the night, might also contribute to rhythm disturbances, as was argued above.

In conclusion, despite the gaps in the present knowledge on the effectiveness of treatments on various sleep and wake parameters in elderly people and Alzheimer patients, the chronobiological approach appears to be a promising road towards improvement of the quality of life.

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