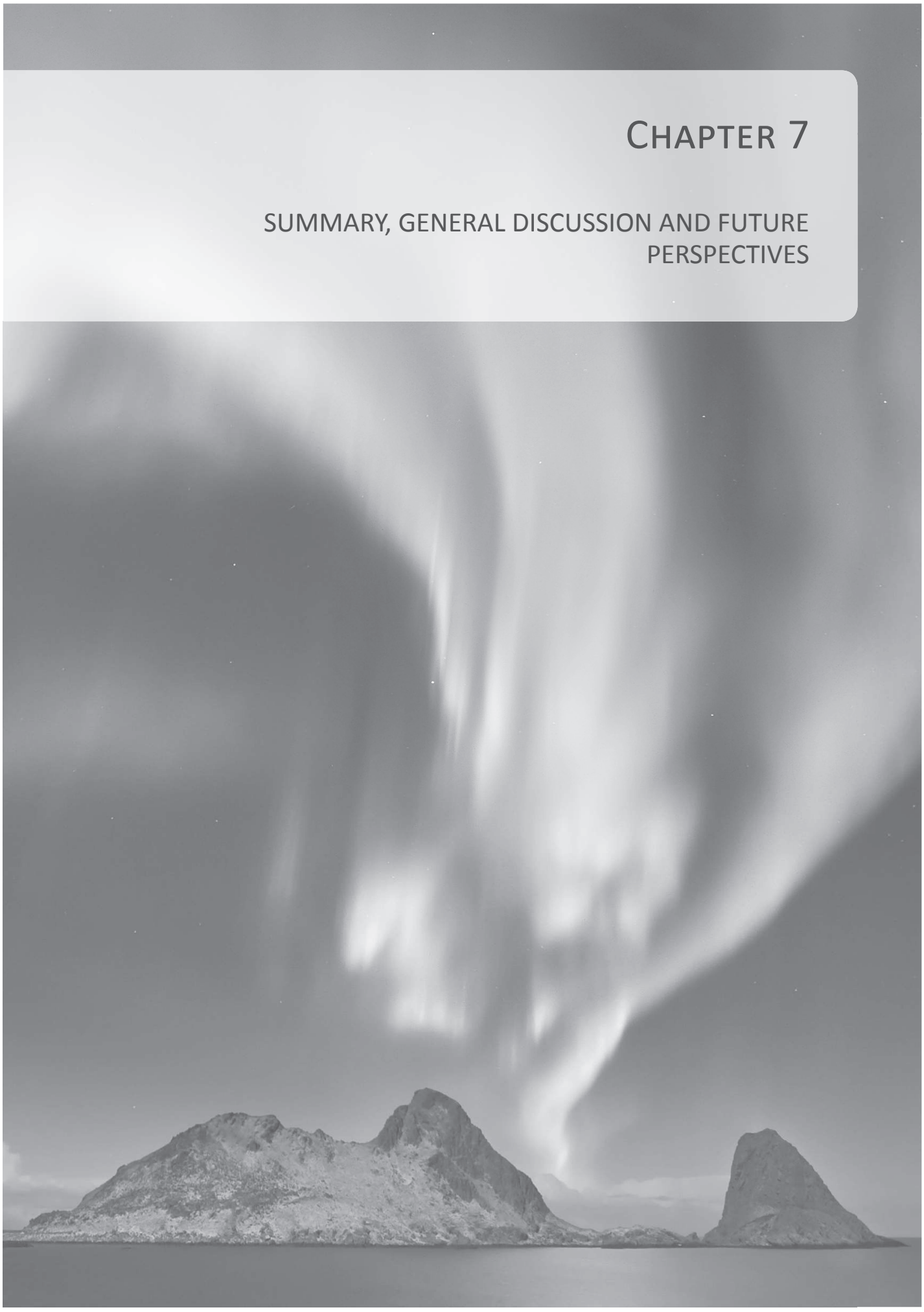
Chapter 7

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES



Alzheimer 's disease (AD), though first and foremost associated with memory complaints, has multiple behavioral symptoms. Many of these behavioral symptoms are linked to the circadian system, such as rest-activity disturbances and mood disturbances, which become more severe as the disease progresses. However, as is shown in the previous chapters and will be discussed further in this chapter, even though signs of a diminished functioning of the suprachiasmatic nucleus (SCN) are emerging early on in the AD process, not all aspects of the circadian system are yet disturbed in these stages.

First, a short summary of the data presented in this thesis, after which the results presented in chapters 3 to 6 will be discussed in relation to earlier findings of circadian functioning in the early and prodromal stages of AD: why light therapy yielded positive results in some, but not all, parameters studied and the effectiveness of light therapy as preventive therapy in AD. The chapter will conclude with recommendations for implementation of light therapy as well as for future research to improve its efficacy.

Summary

In **chapter 2** the background and methods of a double-blind, placebo-controlled, Randomized Clinical Trial (RCT) are presented. The aim was to evaluate the effects of bright light on community-dwelling elderly people with memory complaints related to the earliest stage of probable AD or at an increased risk of developing it. Participants were diagnosed to have either Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI) or Subjective Memory Complaints (SMC). After a baseline measurement (T_0), all participants received either a placebo (±200 lux) or an active (±10 000 lux) light box. They were then followed up for a maximum of four half yearly visits (T_1,T_2,T_3 and T_4). For comparison, one assessment was obtained in a reference group consisting of healthy elderly people. The purpose of this study was to investigate the following hypotheses:

1. Long-term daily bright light exposure attenuates the occurrence of depressive symptoms.
2. Long-term daily bright light exposure attenuates the occurrence of sleep-wake rhythm disturbances.
3. Long-term daily bright light exposure ameliorates cognitive deficits.
4. Long-term daily bright light exposure ameliorates caregiver burden.
5. The effects of light on mood and cognition are in part mediated by its effect on the circadian pacemaker, as read out from the 24-hour rhythms in activity, body temperature, heart rate and cortisol.

In **chapter 3**, we aimed to determine the effect of long-term daily bright light exposure on mood and hypothalamic pituitary adrenal (HPA) axis function in AD, MCI and SMC patients, using the protocol described in chapter 2. The primary outcome measure was the Geriatric Depression Scale

(GDS) rating. Secondary outcome measure was the diurnal profile of saliva cortisol. At T_0, the RCT participants showed more depressive symptoms than the reference group, but the average cortisol levels across the day did not differ significantly between the reference group and the RCT participants. Over time, daily bright light exposure improved mood in the active group as compared to the placebo condition. While evening cortisol increased over the years in the placebo condition, its levels did not change in the bright light condition, yielding a significant time-by-treatment interaction effect. It was concluded that long-term bright light treatment positively affects depressive symptoms and evening cortisol levels in community-dwelling elderly people with early or moderate probable AD or with an elevated risk of developing it.

Chapter 4 deals with our systematic evaluation of the appreciation of bright light therapy by elderly people with memory complaints and their caregivers. At the end of the light therapy treatment, both patients and primary caregivers completed a questionnaire aimed at quantifying the acceptance of the session schedule, consequences for daily life, favorable and adverse effects, preferences regarding light box design, and a willingness to continue to use the light box. To date, the literature has primarily concentrated on the behavioral, cognitive, physiological and psychiatric impact of bright light. However, there are also practical implementation issues to be considered, which are probably crucial for compliance and acceptance. Participants dropping out of the study prematurely rated the fixed exposure times, the brightness and the atmosphere of the light as significantly more burdensome as compared to participants who completed the study. In addition, completers attributed significantly more benefits than drawbacks to the therapy. Though the completers preferred pendant lighting, none of the dropouts did. Participants in the active condition rated the fixed times as more burdensome than those in the placebo condition, deemed the light to be brighter and used the lamp more often outside of the fixed session times. Overall, scores by participants as well as caregivers indicate that the application of light therapy represents only a marginal burden in daily life and has only few adverse effects.
For future light therapy studies we recommend that participants complete an evaluation questionnaire. Light therapy should be introduced as an everyday lighting option that addresses not only biological effectiveness but also takes into account the appearance of the luminaire and the visual ambience. The option to choose between a stand-alone box and a ceiling-mounted one may suit individual preferences better. Also, managing participant expectations may prevent disappointments: both patient and caregiver should be informed that any improvements are likely to be small and gradual.

In **chapter 5,** we studied the reliability of subjective sleep reports in early and moderate stage AD by investigating whether they differ from a healthy non-demented reference group with respect to the discrepancy of subjective and objective sleep estimates. Subjective sleep was estimated using the Pittsburgh Sleep Quality Index, the Sleep Disorders Questionnaire and the Athens Insomnia

Scale. Objective sleep was assessed using actigraphy. As compared to the reference group, AD patients complained less of insomnia, while in fact their objective sleep estimates indicated more disturbed sleep, with a longer sleep onset latency and a lower sleep efficiency. Using regression analyses, only very few subjective sleep questionnaire parameters could significantly predict their objective counterpart. Subjective reports of both the patients and the reference group could significantly predict actigraphic measures of total sleep time and bed time, while only subjective reports of the reference group, but not of the patients, significantly predicted actigraphic estimates of sleep onset latency and sleep efficiency. The results show that the overall predictive value of sleep questionnaires is limited, especially in early and moderate stage AD. Actigraphy may therefore be essential to prevent sleep problems from going undetected and hence untreated.

In **chapter 6,** we aimed to investigate the skin temperature rhythm in AD and its association with daytime sleepiness and nocturnal sleep. Changes in the diurnal skin temperature profile in AD as compared to the profile in normal aging have remained unexplored while recent work has suggested that even small changes within the thermo-neutral zone may contribute to daytime sleepiness and nocturnal sleep depth. Ambulatory recorders were used to measure sleep and 24-hour skin temperature rhythms in AD patients and in a healthy non-demented reference group. Subjective sleep and daytime sleepiness were obtained using questionnaires. The results show that AD patients had a significantly higher daytime proximal skin temperature as compared to the reference group. Both in AD patients and in the reference group, an elevated daytime proximal skin temperature was associated with more daytime sleepiness. The findings suggest a deficient down-regulation of daytime proximal skin blood flow, which might contribute to daytime sleepiness. Because daytime sleepiness contributes to cognitive dysfunction in AD, further research into the underlying mechanisms and possible reversibility is warranted.

Circadian functioning at baseline and the effects of light therapy

It has been suggested that patients with a more intact SCN, which is more likely to be the case in mild or moderate AD than in severe AD, might benefit the most from light treatment [1]. It was hypothesized that this would be an opportunity to implement light therapy as a preventive measure, as previous studies have shown that long-term light therapy in moderate to severely demented Alzheimer patients can improve mood [2], rest-activity rhythms [1, 3, 4] and cognition [2, 5, 6]. Below hypotheses presented in chapter 2 are discussed in the light of the results and related to the functioning of the circadian system at T_0.

Long-term bright light treatment positively affects subclinical depressive symptoms in the participants in the active condition of the RCT (chapter 3), thereby confirming the first hypothesis presented in chapter 2, that long-term daily bright light exposure attenuates the occurrence of

depressive symptoms. At T_0, the RCT participants showed more symptoms of depression than the reference group.

Initial analyses did not support the second hypothesis, that long-term daily bright light exposure would attenuate the occurrence of sleep-wake rhythm disturbances. During the two years of follow-up, there was no significant treatment effect in any of the actigraphic sleep parameters, nor for the circadian rest-activity parameters, with the exception of the onset time of the ten least active hours (M10). In the active group, the M10 onset time was significantly delayed from 9:58 to 10:33 - by 34±15 min, or 2% ($z = 2.18$, $p = 0.03$). It is likely that the morning and evening sessions were not balanced properly relative to the internal biological clock of the participants. Visual inspection of the actigrams, however, suggested that a considerable part of the residual variance resulted from different sensitivities to movement of the different units of the actiwatches used. Ancillary mixed effect regression analyses, including actiwatch unit as random factor to account for this part of the residual error variance, were therefore run. One-sided Wald tests, their use justified by previous reports of favorable effects of light on sleep [2, 7-10], revealed favorable effects of light, indicated by a light*time interaction effect on sleep efficiency (2.00 ± 0.90 %/year, $p = 0.01$), sleep onset latency (-2.24 ± 1.34 min/year, $p = 0.05$) and the sleep fragmentation index (-2.24 ± 1.22 a.u./year, $p=0.03$). Concertedly, these observations suggest a small, but favorable effect of light on sleep. Moreover, they suggest that the generation of actiwatches used may not be optimally suited for the detection of small treatment effects. The new generation of actiwatches that record the raw 3D accelerometry signal may solve the issue of sensitivity differences between different exemplars of the same actiwatch type.

Some previous studies showed that light therapy ameliorated rest-activity disturbances in AD [2, 3, 7, 8, 11]. However, other studies have failed to show these effects [12-14]. Actigraphic studies have shown that, as compared to healthy non-demented elderly people, severe AD patients have a more fragmented and less stable rest-activity rhythm, as well as lower daytime, but higher nighttime, activity [4, 15-17]. In contrast, a study with a limited number of AD patients suggested that the rest-activity rhythms of home-dwelling, moderately demented patients did not differ significantly from those of non-demented elderly people and were affected only in institutionalized demented elderly people [18]. Although actigraphic sleep estimates suggested that AD patients slept significantly shorter and more fragmented than the reference group, our current results show no significant differences in the circadian rest-activity parameters between the AD patients and the reference group (chapter 5), replicating the results of Van Someren (1996) [18]. With the rest-activity rhythm still intact and no difference between the active and placebo groups in this respect, it is possible that support by additional bright light was not yet required for these patients. On the other hand, sleep was disrupted in these patients as compared to controls, and small effects of light on sleep were indeed found. However, light alone might not be sufficient

to improve sleep. Treatment of insomnia often consists of a multimodal approach including sleep hygiene adjustments, stimulus control, relaxation techniques, and cognitive strategies. It remains to be evaluated whether a combination of light therapy with other sleep promoting therapies will better address the sleep problems in this population.
During the two years of follow-up, none of the sleep questionnaire scores diverged significantly between the active and the placebo group. As stated in chapter 5, there was a discrepancy between the subjective and objective sleep parameters in AD. The subjective evaluation of sleep was barely associated with objective actigraphic sleep estimates in the reference group, and this was even less the case in the AD group. Hence, the predictive value of the subjective reports was limited. Although the observed discrepancies between the subjective sleep questionnaires and actigraphic measured sleep were not related to cognitive functioning as measured using the MMSE, it cannot be excluded that the cognitive state of the patient has an impact on how sleep is experienced, or how the patient reports on it retrospectively. Furthermore, it might be that actigraphy is not sensitive enough to detect subtle changes in sleep, which could contribute to the subjective-objective discrepancies discussed in chapter 5. In fact, if improved, it could even increase the discrepancy. However, even if the objective way of measuring sleep improves, it is unlikely for light therapy to yield a positive outcome on sleep questionnaires if the patients' cognitive state alters their perception - and thus their subjective sleep reports.

In our study, none of the neuropsychological outcomes diverged significantly between the active and the placebo group over time, despite earlier findings of positive effects of light therapy on cognition [2, 5, 6]. The third hypothesis, that long-term daily bright light exposure would ameliorate cognitive deficits, could not be confirmed. Several explanations may be put forward to elucidate this discrepancy with the current literature. Memory disturbances, the key cognitive symptoms of AD, are strongly associated with hippocampal atrophy [19, 20]. Enhanced cortisol levels can induce hippocampal atrophy [21, 22] while hippocampal function is furthermore negatively influenced by impaired sleep [19, 23, 24] and rest-activity rhythms [25]. In fact, rest-activity rhythm stability predicts cognitive functioning in dementia [26]**.** However, in our study, rest-activity rhythms were not disturbed at T_0 and neither sleep nor the rest-activity parameters were positively affected by light therapy. Though evening cortisol levels remained stable in the active group (see below), which could have led to an improvement in cognition, it may be so that the absence of an improvement in sleep or rest-activity parameters counteracted these cognitive amendments.

Caregiver burden has not been studied in connection with light therapy effectiveness. However, it has been shown that caregiver burden is relieved once a patient's depression [27] and sleep disturbances are being treated [28]. As a fourth hypothesis it was therefore proposed that long-term daily bright light exposure would ameliorate caregiver burden. Although mood improved over time in the active group, this was not reflected in changes in caregiver burden. Information

on whether the studied parameters actually influence the caregivers' perceived burden should be identified at study start. This will make it possible to study the relationship between changes in the RCT participants and potential changes in caregiver burden more precisely.

Lastly, it was hypothesized that the effects of light on mood and cognition would in part be mediated by its effect on the circadian pacemaker, as read out from the 24-hour rhythms in temperature and cortisol. Daytime proximal skin temperature was significantly higher in AD patients than in the reference group (chapter 6). This same trend was observed in patients with MCI and SMC [29], even though the number of these patients included in our study was limited. The temperature parameters did not diverge significantly between the active and the placebo condition. As the mechanisms behind the daytime proximal skin temperature changes in AD and MCI are still unclear, the best therapeutic approach cannot yet be determined. It is possible that direct skin temperature manipulations would be more effective in normalizing the elevated daytime skin temperature than the applied light therapy.
Our findings furthermore indicate that night time skin temperature is associated with several indices of sleep quality (chapter 6). AD patients with a higher night time distal skin temperature had a lower nocturnal activity level, less wake time, a higher sleep percentage and shorter night time awakenings. In the reference group, individuals with a higher proximal skin temperature spent less time in bed and had shorter night time awakenings. It has been established that skin temperature affects the onset and maintenance of sleep [30] and that skin temperature manipulations can improve sleep, even in patients with disturbed temperature regulation [31, 32]. It is reasonable to hypothesize that temperature manipulations might be more effective in treating the sleep problems of AD patients than light therapy.

Cortisol levels, in particular during the evening, diverged significantly between the active and the placebo group (chapter 3). In the active condition, participants maintained a stable evening cortisol level, while those randomized to the placebo condition showed a gradual increase in evening cortisol level. It has been shown that in particular the increase in evening cortisol is the main contributor to the elevated cortisol levels and flattened curve in AD [33]. There were no significant differences between the reference group at T_0 and the RCT participants regarding saliva cortisol levels (chapter 3). Other studies have shown elevated morning and all-day average cortisol levels in mild AD and MCI [34-37], but an absence of any cortisol differences between early stage AD and controls has also been reported [38]. Elevated cortisol levels are apparently not a robust characteristic of the very first stages of AD, but develop during the early to moderate stages.
Although our primary hypothesis - that long-term daily bright light exposure decreases depressive symptoms - was confirmed, it could not be verified that long-term light exposure ameliorates cognitive deficits or caregiver burden. Our last hypothesis, that the effects of light would in part be mediated by its effect on the circadian pacemaker, could only partly be substantiated: only an

effect on evening cortisol level was observed. However, it could not be confirmed that the change in cortisol is indeed a mediating factor.

How circadian functioning is lost in aging and AD

The light-induced activation of the SCN, via the retinal ganglion cells, becomes suboptimal in elderly and demented people because of the degeneration of ocular media, the retina and the optic nerve [39, 40]. Longer and more intense light exposure may thus be required to activate the SCN [41]. In addition, the SCN shows reduced activity at advanced ages, especially in demented elderly patients [42, 43] and will therefore need an increasingly stronger input signal to maintain optimal pacemaker function. This is apparent from the compromised circadian regulation in severely demented AD patients, evidenced by a decrease in 24-hour amplitudes and a reduced number of active SCN neurons [44]. However, contradictory to the neurological state of the SCN, which has been shown to be affected by the neurodegenerative process at a very early stage [45], only few indications of rhythmicity loss in rest-activity, temperature and cortisol rhythms at T_0 were found in the current population. An explanation of this could be variability in the onset and pace of the worsening of the different circadian rhythms [46]. For example, Balschun and coworkers observed an aggravation of corticosterone rhythms before the onset of rest-activity rhythms in mice [47]. It would be logical, based on the results shown in this thesis, to hypothesize that the degeneration of rhythms in humans, too, may progress differently.

Several tissues and organs with intrinsic rhythmicity of gene transcription have been identified that have the molecular mechanisms necessary for the generation of circadian rhythms. These 'peripheral body clocks' are involved in almost all pathways of the circadian system [48]. A primary function of the SCN is to synchronize all these clocks, but individual rhythms might become misaligned when the circadian pacemaker has ceased to function optimally. However, it has been shown that peripheral clocks can be transiently synchronized by several intrinsic and environmental signals when SCN control is lost [49], such as strict feeding schedules [50] and amphetamine [27]□e˝s5T¨b. As such, otherwise entrained peripheral clocks might, by their feedback signals, actually keep the SCN entrained for some time. However, feedback entrainment is unlikely to be effective in the long term, as the various clocks and rhythms will progress at their own individual paces. It can be hypothesized that, as is seen in physiology and behavior, the output signals of the circadian system may degrade differently, depending on the peripheral clocks involved and how they entrain. Also, more than a dozen brain regions have been identified that show intrinsic rhythmicity, and some of these regions, such as the dorsal medial hypothalamus, are semi-autonomous [51]. In the intact brain, the SCN synchronizes these populations of weakly coupled or non-coupled cells [49], and many of these populations are in fact important efferent nuclei of the SCN, such as the paraventricular nucleus (PVN) and the pituitary. It is not known whether these brain areas could maintain some level of rhythmicity, even with a weakened SCN

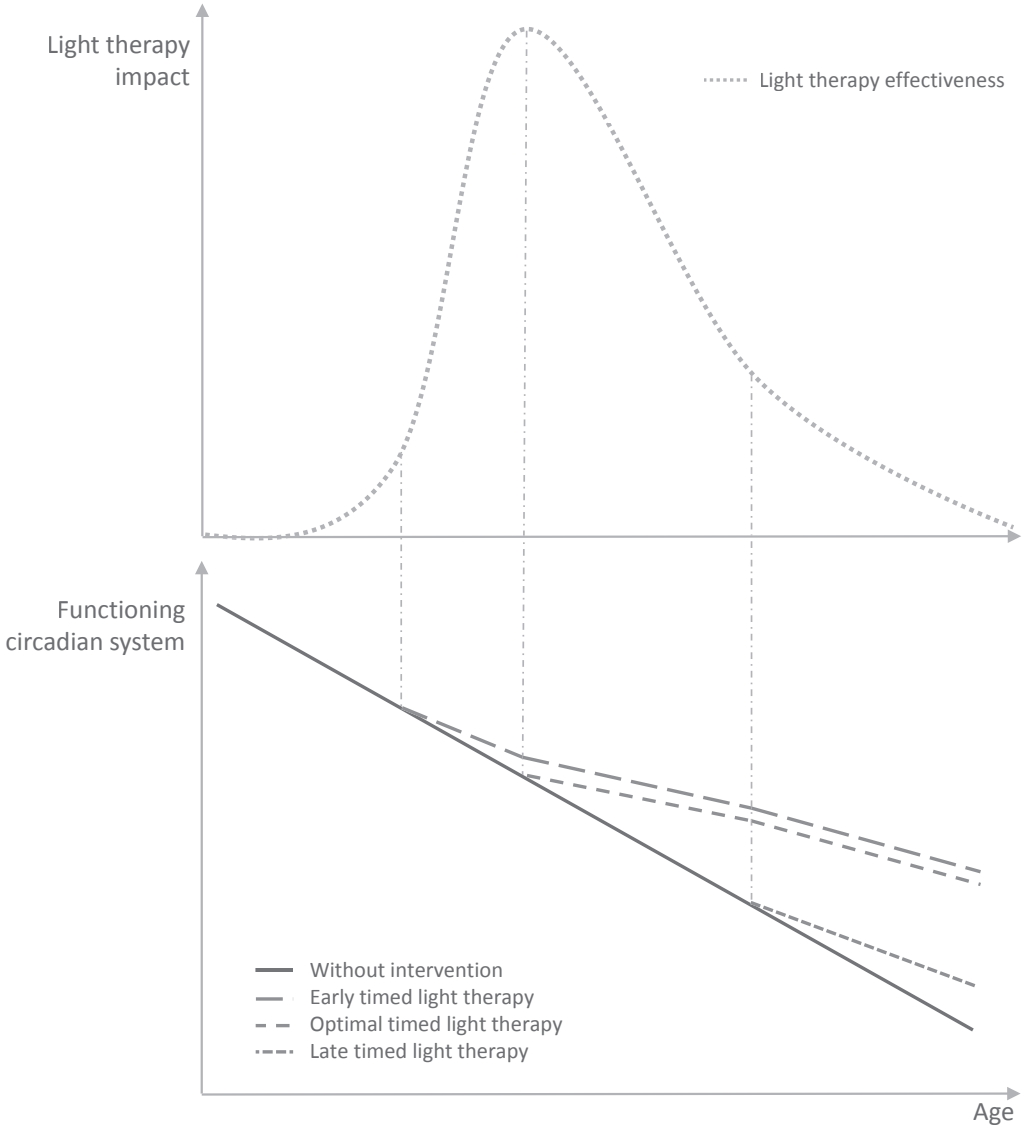


Figure 1. hypothesized optimal timing of light therapy during aging (upper panel). The yellow dotted line depicts the light therapy effectiveness, with its impact on the circadian system on the right hand axis. The decay of the circadian system is shown as a solid black line with the degeneration of the circadian system is depicted in the lower panel. Before the optimal timing of implementing light therapy, the effect of added light is small (long dotted line), while added light therapy when it's impact is optimal the reduction in degeneration of the circadian system is the largest (median dotted line). Implementing light therapy after the optimum peak will again result in small effects (small dotted line).

function. If they can, it is likely that the intrinsic rhythmicity of these cell populations will gain a more independent pacemaker function. Depending on the behavioral and physiological rhythms these nuclei are part of, these rhythms could obtain their own oscillation pace.
Furthermore, individual differences in the neurodegenerative disease progress could affect the circadian system differently. Although AD pathology tends to follow a common pattern [52], there are of course individual differences, especially between presenile and senile onset AD [53]. The latter group often has vascular damage or comorbid degenerative changes such as Lewy body pathology [54]. As such, behavioral and physiological rhythms can be individually affected by the neurodegenerative processes.

These mechanisms, either alone or in combination, could explain the variability of the different output signals of the circadian system of early to moderate AD. Moreover, it shows that, although the SCN might be functionally impaired [45], the circadian system is still sufficiently flexible to compensate for the shortcomings downstream.

The timing of light therapy

There is an optimal window within the day for the time when bright light has its maximal effect; when given at the appropriate time, light therapy strengthens rhythmicity [8]. Conversely, it has also been shown that untimely application of light pulses reduces the circadian output amplitude, which can weaken the rhythmicity [55, 56]. The timing of the intervention is also important for the antidepressive effects of light to become effective: careful timing according to one's personal rest-activity rhythm is required for maximum effect [57].
It can be discussed whether there is also an optimal time for light intervention within the neurodegenerative progression. Implementing therapy at an early stage of the neurodegenerative process means the circadian system will still be functioning normally, and a regularly functioning circadian system will profit only marginally from an added input signal. Implementing it too late means neurodegeneration has become too severe, and there is nothing left to activate (figure 1). In addition, understanding the state of, and the mechanisms behind, circadian system fragmentation might be a crucial factor for correct timing. Below the processes and conditions leading to an optimal intervention timing will be elaborated on.
It is hypothesized that additional light will only have a limited effect in the early stages of AD. Either the SCN is still able to maintain pacemaker function, even with a limited number of active neurons, or, as argued in the previous sections, at least some aspects of the circadian system are flexible enough to maintain rhythmicity with less top-down control. However, although the circadian system might function (sub)optimally for a period of time even without strong SCN pacemaker functioning, ultimately the loss of top-down control will lead to rhythmicity loss. This loss will become steadily more apparent in physiological and behavioral output signals. From then

on, the circadian system will have an increasing need for an additional synchronizing agent. This will last until either the SCN has too few cells to engender reactivation, or the efferent pathways are too degraded to relay a timing signal, leaving both the SCN and the circadian system unable to reactivate.
The timing of this process is likely to be different for each individual. Lifetime SCN 'maintenance', i.e. regular exposure to ambient light, high daytime activity levels and regular sleep-wake timing could probably enhance SCN functioning [43]. Individuals who adhere to these principles are thought to have less need of early light therapy interventions. In addition, if circadian rhythms deteriorate in a serial order, specific parts of the circadian system might benefit from light therapy earlier than others. Knowing which circadian physiological and/or behavioral parameter to select for treatment in an early stage of AD could be imperative to a positive outcome.

It might be that the timing of light therapy is only optimal for a certain period of time and that this period is different for different pathways. In this case, the preventive effect of light therapy would actually be most effective if it were started before dementia onset, even though the behavioral effects will not be noticeable. When started during or after dementia onset, the effect might be noticeable, but is possibly less effective in the longer run.
Although a functional circadian system would only benefit marginally from the added input, an early start would ensure capturing the optimal timepoint of implementing the therapy, reducing the risk of developing any circadian disturbances later on. This would indicate that patients could spend a considerable period of time receiving light therapy without any significant changes in their physiology and behavior. In addition, as it is unclear when the circadian sytem starts to unravel and at what speed, one would have to continue the therapy for the rest of one's life for maximal benefit. However, building a resilient SCN in old age would entail a much earlier implementation of strong entrainment signals, perhaps as early as adolescence [43].

The circadian system, when relatively intact (chapter 3) but also when severely degenerated [2], needs time to adapt to the increased synchronizing agent. As explained above, a functioning circadian system might only work due to compensating mechanisms, such as alternative pacemakers. Activating the SCN cells, reinstalling the SCN as main pacemaker or aligning desynchronized rhythms takes time. Even healthy and young individuals may need days, or even weeks, to adjust to circadian modifications such as jet lag and shift work. This renders the prospect of finding significant, clinically detectable effects in short term light therapy in (early) demented elderly patients to be less likely.

Concluding, the output signals of the circadian system in the very early stages of AD are in various stages of disintegration. This variabilitly can be explained by the degeneration of the SCN and its efferent pathways, or by different compensating mechanisms in the circadian system. Light

therapy implementation should take into account that there is a balance between a circadian system functioning well enough to render an additional sychronizing agent uneccesary and a system too degenerated to be reactivated. Preventive light therapy might not be noticable for a considerable time and may then only work on specific aspects of the circadian systems.

Clinical implications and future perspectives

Light therapy studies in early AD and its prodromal stages should focus on long-term effects, as argued above, as there is a substantial risk of implementing light therapy too early or have it last for too short a time to elicit an effect. There is great variation between individuals within a study population including patients with a neurodegenerative disease, but, as reflected in the cortisol as well as the GDS outcomes of our data and long term core body temperature recordings [58], there is also great variation over time within individuals. In addition, seasonal variations have an impact on most circadian and behavioral rhythms [59]. Therefore, measurements should be sampled more frequently than in the current protocol in order to better track intra-individual changes. The study research question, the burden of the measurements and the duration of the study should of course also be taken into account when deciding on the follow-up intervals. In the ideal situation, multiple studies would investigate a limited number of questions, thereby reducing the load of each measurement for the patient.
In general, large study populations are needed to reach a significant change on group levels. Careful considerations were given to estimate the group size before the start of inclusion (see chapter 2; section: Sample Size). However, as stated above, in a practical clinical trial, when studying a diverse group such as the early to moderate AD population over an extended period of time, the intra-individual variations become very large. When performing power calculations for practical clinical trials, especially involving a population with neurodegeneration, increased variation must be taken into account.

Researchers should be aware that subjective sleep quality might not be a good outcome measure, as AD patients are not able to rate their sleep adequately. The current study population showed that AD patients are not able to reliably report on the quality of their own sleep. When using questionnaires, these should be developed and validated specifically for demented patients and their caregivers.

Our study set-up included several measuring equipments, such as an actiwatch, temperature sensors, a heart rate monitor and saliva samples. Although the devices used were already small and easily wearable, the application of the devices and wearing them for +24 hours was often a considerable burden for the patient. However, recent developments in home monitoring

move towards less obtrusive assessment of physiological parameters, with wireless and remote uploading of data and decreasing device size, but with increasing storage capacity. These developments open up the possibility of long-term assessments without burdening the patient with wearing the device. This is especially convenient in circadian research, which often depends on measurements lasting for several days.

Unobtrusive measurement devices could furthermore offer an objective understanding of the participants' environmental situations, which could help identify who would benefit from light therapy. Active patients, for instance those engaging in outdoor activities, might experience less additional effect of light therapy than inactive patients, who spend most of their time indoors. For example, based on conversations with our participants and their caregivers, the study population appeared to be active and regularly spending time outdoors. This active and outdoor behavior of the study population may already have saturated the input to the circadian system and adding light in the light treatment condition did thus not result in extra effective input to the biological clock. However, to evaluate such covariates, these activities need to be more closely and systematically tracked.

Recently, van Hoof et al (2012) urged for better standards when describing the lighting equipment, the light measurements and the interaction with daylight. Differences in protocol and bright light implementation may be a source for the inconsistencies in the effectiveness of light therapy [60]. Especially in studies conducted at participants' homes, where conditions might vary considerably, documentation and/or recording of the surroundings could provide additional information on the effectiveness of light therapy.

Not only the severity of the disease, but also the varying underlying neuropathology of AD, may, in part, affect the effectiveness of the applied light intervention. The underlying disease process in AD, consisting of aggregated Abeta peptides and hyperphosphorylated tau, generally follows the same path from the transentorhinal and entorhinal cortex to the neocortical areas [52], but there are individual differences in the distribution and severity of the neuropathological process. Though Abeta and tau apparently are not involved in the neurodegeneration of the SCN [61], it is not yet known how the distribution of these proteins throughout the brain might influence the circadian system. New techniques, such as Amyloid PET-scans, could perhaps provide new insights regarding AD pathology-dependent changes in circadian rhythms - and thereby yield a better prognosis regarding therapy effectiveness.
Furthermore, an examination of the patients' eyes before the start of light therapy could give valuable information on how much light is needed [62], as age-related degeneration of ocular media and the retina [63, 64] can severely limit the amount of light reaching the retina.

Light therapy is an intervention likely to have beneficial effects that exceed mere stimulation of the SCN. Proper lighting can improve vision and could increase the atmosphere and usability of a room, if the light and luminaires are designed to meet these objectives. As such, the physical properties and user scenarios of the light and the light casing deserve proper attention. For instance, although fixed light boxes are convenient for the scientist as it ensures that the therapy is always given in the same manner and the light input remains constant, patients might prefer different placements of the luminaire over time. In addition, blue light sources have effective physiological and behavioral effects [6]. It remains questionable, however, whether patients would appreciate such lighting for long-term treatment, since blue light is perceived as cold and considered clinical rather than cozy. Studies never report on the selection and implementation of the features of the light and the light casing itself, do not address the possible effects of this choice and hardly involve the participant in these choices. However, when we asked the participants for their opinion, we found that appearance and ambience should be taken into account and that the ability to choose between a stand-alone box and a ceiling-mounted one may suit individual preferences better, which could prevent treatment dropouts (chapter 4).

In addition, providing information on progress and outcome of the study in a way that is comprehensible to the patient is important. Informing patients that the expected improvements are small and gradual would improve acceptance and managing expectations could thus improve the outcome of light therapy and compliance. Based on these results it would be interesting to systematically explore, in all light therapy studies, which non-biological features could be important for successful long-term implementation.

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