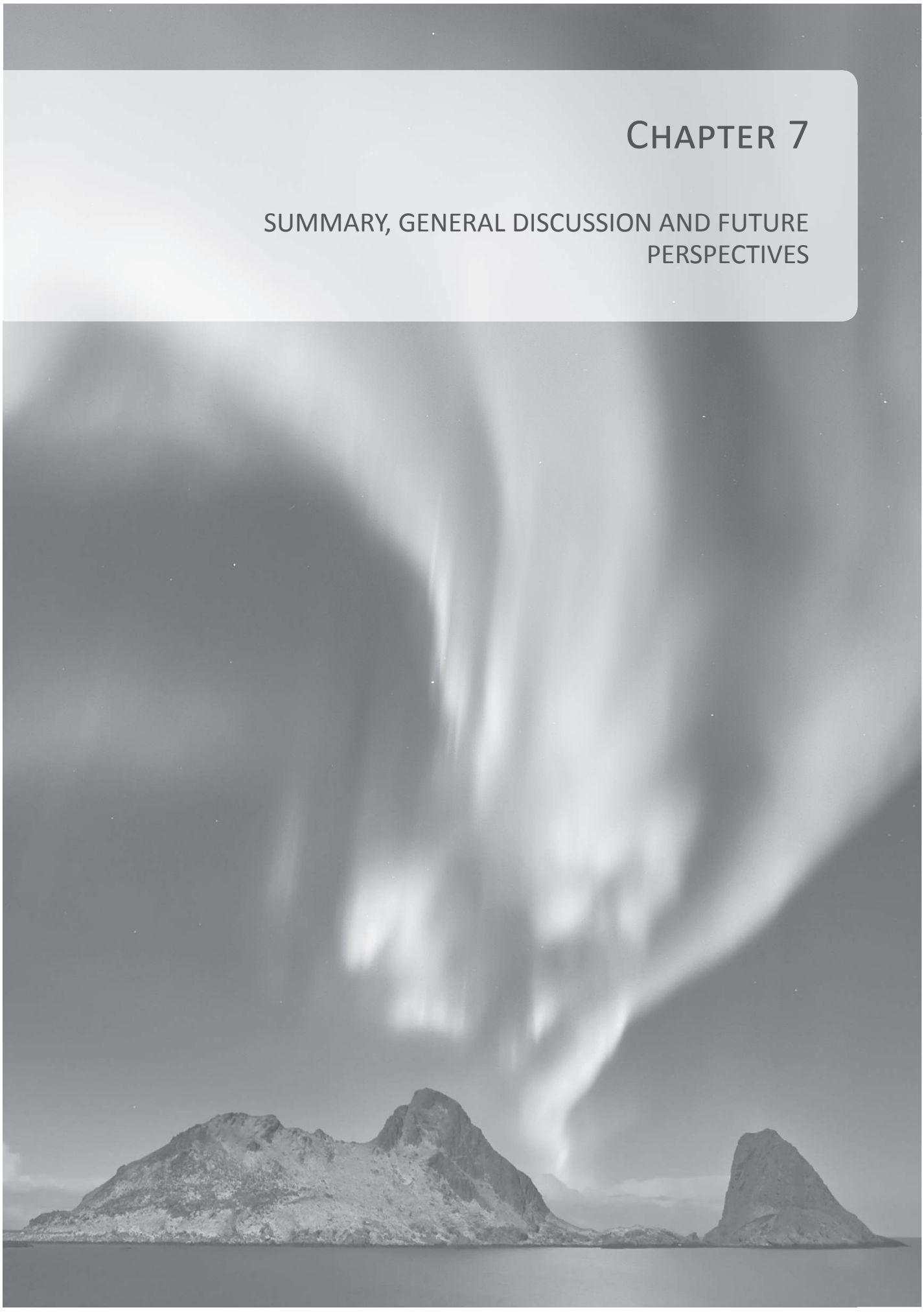
Chapter 7

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