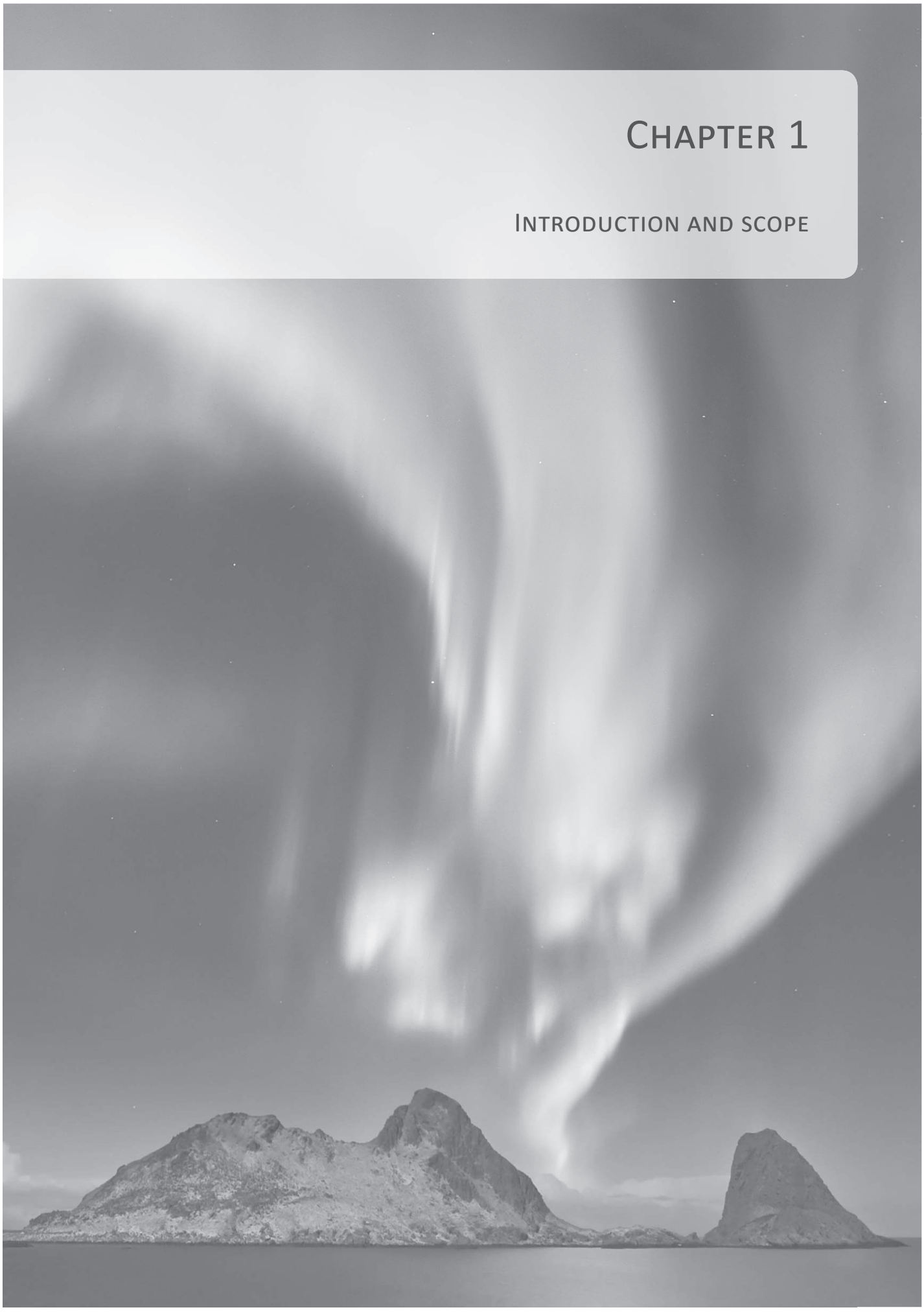
Chapter 1

Introduction and scope



People in the western society are living increasingly longer, but our physiology is not always able to keep up with this increased life expectancy. Unfortunately, growing old not only entails an increasing frailty of our bones and muscles, but also the degeneration of our brains. Alzheimer's Disease (AD), estimated to pass the 15 million cases mark in Europe by the year 2050 [1], of which almost 2/3 will be in an early stage of the disease [2], is therefore a significant and growing burden on caretakers, healthcare systems and the economy. It is expected that in the future most AD patients will have to remain at home until a higher age than presently, as care homes will cease to be able to keep up with demand. The chances of finding a cure or efficient medications are still slim [3].

AD is first and foremost associated with memory complaints, though the disease has multiple behavioral symptoms, many of them linked to the circadian regulation system, such as, e.g., rest-activity disturbances and mood disturbances, such as depression, which become more severe during the disease progress. Any intervention targeting these symptoms should be applied as early as possible, to deter further decline.

The main purpose of the present thesis was to evaluate the long-term implementation and effectiveness of a bright light intervention aimed at supporting circadian functioning and thereby mood, cortisol regulation, sleep and cognition. This first chapter briefly discusses the clinical and physiological background of AD and the changes the circadian system undergoes during this process. It furthermore highlights how we adapted light therapy to improve feasibility and compliance of long term treatment in a home-dwelling population in the very early stages of AD.

Alzheimer's Disease

Alzheimer's Disease is characterized by a slow, progressive cognitive decline. The most common initial complaint and symptom is memory impairment. This impairment predominantly concerns the short-term episodic memory, though long-term memory may also become affected with time. In addition to memory impairment, patients often suffer from executive dysfunction, aphasia, apraxia or visual agnosia [4]. The underlying disease process consists of Amyloid-β (Aβ) peptides aggregating, forming oligomers and eventually plaques. Aggregated Aβ is neurotoxic, initiating oxidative stress, inflammation and dysregulation of lipid metabolism, which eventually leads to synapse loss and cell death [5]. In addition, the tau protein is abnormally hyperphosphorylated and accumulates as intraneuronal tangles of paired helical filaments, twisted ribbons and/or straight filaments, and the affected neurons undergo a retrograde degeneration [6, 7]. The pathological changes start in the transentorhinal and entorhinal cortex, subsequently spread to the hippocampus and adjacent allocortical areas and eventually affect the neocortical areas [8]. Most elderly AD patients also display vascular changes or comorbid degenerative changes such as Lewy body pathology [9].

The neurodegenerative process starts years, probably decades, before the symptoms become so evident as to justify a diagnosis of AD. In the early stages it can be difficult to establish objectively whether the cognitive decline has crossed the boundary between normal aging and a neurodegenerative process. In the spectrum of cognitive decline, intermediate diagnoses characterize the progress from cognitively intact to dementia:

In Mild Cognitive Impairment (MCI), patients exhibit impaired cognitive function in only one domain, most commonly memory, but without any other cognitive disorders or repercussions on daily life [10-12]. Furthermore, in contrast to AD, MCI does not necessarily feature a steady progression of cognitive decline [13]. The amnestic form of MCI likely represents a prodromal form of AD [14]. The annual conversion rate from MCI to AD is approximately 5–10%, although most people with MCI do not progress to dementia even after 10 years of follow-up [15].

Preceding MCI is a stage characterized by Subjective Memory Complaints (SMC, sometimes called Subjective Cognitive Impairment, SCI). This stage is diagnosed when patients complain of memory dysfunction, but impairment of memory cannot objectively be established, and therefore formal diagnoses of MCI or AD cannot be made [16]. Both the Geriatric Deterioration Scale and the Functional Assessment Staging identify a cognitive impairment stage before MCI, when subjective deficits in memory and recall are present, but individuals perform within the cognitively intact range on psychometric and mental status tests [17]. The literature shows that elderly diagnosed with SMC have a higher risk of cognitive decline and/or dementia [18], indeed the risk of AD was found to be three times higher in individuals with SMC [19, 20].

Circadian rhythms in aging and Alzheimer

The suprachiasmatic nucleus (SCN) is the central pacemaker of all physiological and behaviorial rhythms. Located in the anterior hypothalamus, just above the optic chiasm, it is synchronized to the exogenous day-night rhythm by light acting on the retinal ganglion cells projecting to the SCN through the retinohypothalamic tract. In addition, the SCN receives input from several other hypothalamic nuclei, from the locus coeruleus, as well as from physiological feedback loops [21-23]. Though less effective in affecting the SCN than light, hormones such as melatonin and cortisol, as well as temperature and activity play an important role in entrainment [24]. The SCN has direct and indirect projections to the medial preoptic, paraventricular and dorsomedial nuclei, and to the sub-paraventricular zone of the hypothalamus, the basal forebrain, the midline thalamus, the neocortex, the limbic system, the hippocampus, the anterior pituitary, the hypothalamus, and the reticular activating system [25]. Through these connections the SCN synchronizes all physiological and behavioral rhythms, including wakefulness and sleepiness, thermoregulation, and endocrine secretion. The SCN synchronizes these rhythms with each other, as well as with the external day-night cycle, in addition to synchronizing the clocks of other organs and tissues [26, 27].

In the aging SCN, neuronal activity and vasopressin expression are decreased, and this reduction is more pronounced in AD [28, 29]. However, in AD this is not markedly due to tangles, and plaques do not appear to be involved in the deteriorated function of the SCN either [30]. Rather, the decreased SCN activity appears to be a consequence of cells shrinking and becoming inactive. As an effect of the diminished functioning of the SCN, rhythm amplitudes are reduced [31], which has been demonstrated in cortisol [32], temperature and activity [33]. The severity of activity rhythm disturbances is strongly correlated with the loss of vasopressin neurons in the SCN in demented elderly individuals [34]. Reduced control of the central pacemaker also induces internal uncoupling of the rhythmic processes and the desynchronization of the other body clocks [35].

The decay of the SCN is relevant for many of the symptoms of AD: sleep-wake rhythm disturbances [36-41] and daytime sleepiness [42], behavioral disturbances, including agitation and psychosis [43-47] and mood disturbances, notably depression [48, 49]; all directly or indirectly worsened by the decreased functionality of the SCN [40, 50]. Insufficient SCN functioning is also thought to aggravate the cognitive consequences of the neurodegenerative process of AD.

Mood in aging and AD

As stated above, the deterioration of the circadian system could be an important factor for developing mood disturbances, both in the healthy aged populations as well as in AD. When SCN control is insufficient, its inhibitory control on the hypothalamic-pituitary-adrenal (HPA) axis is lessened and this can contribute to HPA axis hyperactivity to which depressive symptoms are strongly associated [51]. It has been shown that the risk of developing depressive symptoms, as well as minor and major depression increases with age [52-56], but even more so in elderly with cognitively impairment [57] and that SCN function is compromised in the elderly, in depression and in AD [58].

Depressive symptoms have a significant impact on the quality of life and activities of daily living of demented patients [48, 49, 59]. They can contribute to the development of depression in their caregivers [60-62], and increase the prescription of medications, the risk of institutionalization and mortality [63]. Although the prevalence of depression between mild and severe dementia do not differ much [64], this is difficult to assess in severe dementia, something which may indicate an underestimation of the actual occurrences.

There is some evidence that the neuropathological features of AD play a role in the etiology of depression; AD pathology in the locus coeruleus may be involved [65], as well as the dorsal raphe serotonergic nuclei [66]. Newer studies have, on the other hand, failed to replicate these data [67, 68], and the precise part of AD neuropathology in the risk of developing depression is still an ongoing discussion. However, a key predictor of depressive symptoms is the presence of sleep disturbances [69-72], again implicating the involvement of the biological clock. Elderly people experience more difficulties with sleeping than the young [73], thereby increasing the probability of developing mood problems. As sleep problems become very distinctive in AD [36], it can be assumed that the chances of developing mood disorders in this population are even greater.

Light therapy

It has been proposed that reactivation of the SCN by proper stimulation can improve its functioning, and thereby also partly restore the affected physiological and behavioral processes that are under control of the SCN [28, 74]. It has been hypothesized that inactive neurons run a higher risk of degenerating, and that reintroducing sufficient stimuli to the SCN can promote restoration of neuronal functionality. Elderly individuals, and especially AD patients, are exposed to less environmental light and are less physically active, both of which reduce the rest-activity rhythm amplitude [37, 43, 75, 76]. In addition, age-related changes to the eye inhibit light input [77]. This reduced light exposure can induce a cyclic cascade of processes; diminished light exposure reduces the SCN function, which in turn abates circadian rhythms, decreasing internal SCN feedback. However, in the case of the SCN, function can be improved by augmented exposure to its primary zeitgeber (time cues): light [78].

Light, or light therapy, can be administered by exposing individuals to natural light outdoors or to special lamps, visors, or other artificial light sources. The most common method is the administration of light via a light box, where an individual sits in front of a panel of fluorescent lights with a high illumination level (2000-10000 lux) [79-81]. Light can be administered at several different time points, even before sunrise, as in dawn simulation [82], or it may span an entire day [80].

The study described in this thesis applied a photoperiod skeleton: a brief exposure time both during the morning and during the evening. Whereas whole-day exposure is not easily accomplished in home-dwelling AD patients, a photoperiod skeleton still informs the circadian system on the onset and the offset of the daytime period [83]. Light intensity was aimed to reach 10000 lux, to ensure sufficient light to modulate SCN activity.

Scope of the present thesis

The main purpose of the present thesis was to evaluate the long-term implementation and effectiveness of a bright light intervention aimed at supporting circadian functioning and thereby mood, cortisol regulation, sleep and cognition in elderly people with memory problems. Also, we sought to investigate potential differences in (circadian) physiology between elderly people with and without memory complaints, such as temperature regulation and sleep. Lastly, we aimed to show what impact practical implementation issues can have. The discussion mainly focuses on the question why light therapy had an effect on some, but not all parameters studied.

During a randomized clinical trial (RCT) several circadian output signals were monitored, focusing on signals known to be directly associated with depressive symptoms, such as cortisol and the rest-activity rhythm. We also assessed skin temperature given its recently demonstrated association with sleep and sleepiness [84].

We focused on a population showing the entire spectrum of cognitive decline, including SMC, MCI and AD. The study was designed to evaluate the efficacy of light treatment in the earliest stage of AD, or the prodromal stages of AD. A number of participants initially diagnosed with MCI or SMC converted to AD.

The data collected repeatedly in elderly with memory complaints during the RCT, were collected in a single assessment in a group of elderly people without memory complaints, in order to provide reference values. The inclusion of this reference group allowed us to draw conclusions regarding potential differences in physiology between elderly people with and without memory complaints, including their clock function. Little is known about the circadian changes in the initial stages of AD.

Finally, the study also included an evaluation of the light therapy by the individual participants, on conclusion of their participation. Studies often focus exclusively on the efficacy of light therapy and the biological foundation of the effects, and often neglect the patients' subjective evaluation and acceptance of the treatment. However, the efficacy of the treatment is most likely also dependent on compliance with and acceptance of the light therapy, which is likely to be affected by aspects that are not reflected in biological parameters.

Based on existing literature it was hypothesized that long-term, rather than short-term, light treatment at home would improve or prevent depressive symptoms [80]. These effects could be a direct result of the light therapy, but it is more likely that the treatment effect was mediated through either improving or preventing a disruption of sleep or through improving or stabilizing the circadian rhythms in general. Futhermore, it was hypothesized that changes in circadian rhythm, sleep or mood would be reflected in an improvement in the cognitive performance of the participants.

In **chapter 2** the background and methods of the double-blind, placebo-controlled RCT are presented. Bright light therapy has beneficial effects on rhythms and mood in institutionalized moderate to advanced demented elderly people and it is a potentially safe and inexpensive treatment option. However, will the use of long-term daily light therapy prevent worsening of circadian rhythms and mood in early to moderately demented home-dwelling elderly individuals? The primary outcome measure is depressive symptoms, secondary outcome measures are cortisol and rest-activity rhythms.

Chapter 3 presents the results of the RCT on long-term effects of bright light therapy. Does daily bright light exposure ameliorate depressive symptoms and attenuate elevated cortisol in community-dwelling elderly people with memory problems?

Chapter 4 discusses implementation of long-term bright light therapy. Practical implementation issues may be crucial for compliance and acceptance. Are there specific characteristics of participants and implementation that favor or obstruct successful long-term application of light therapy at home?

Chapter 5 discusses the subjective-objective sleep discrepancy in early AD patients. Do early stage AD patients differ from non-demented elderly people with respect to the level of discrepancy (or congruence) between subjective sleep obtained from questionnaires and objective sleep parameter estimates obtained from actigraphy?

Chapter 6 focuses on the possible association of skin temperature with daytime sleepiness and nocturnal sleep. How are proximal and distal skin temperature regulated throughout the 24-hour day in AD versus non-demented elderly individuals? And is the association of skin temperature with daytime sleepiness and nocturnal sleep different in AD patients as compared to non-demented elderly individuals?

The general discussion in **chapter 7** integrates the results of chapters 5 and 6 with the outcomes of the RTC. It furthermore discusses the outcomes of the RCT in regard to the hypotheses presented in chapter 2. Also, the chapter relates the findings to the recommendations given in chapter 4, evolving into suggestions for future research and possible implementations.

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