GENERAL INTRODUCTION

"Birds do it, bees do it, even educated flees do it…" – Cole Porter

Sleep is an integral part of life.[1] Everyone will agree that humans need sleep, judging from what happens when you do not get it for a night. Yet, sleep is poorly understood compared to other basic things you do every day, such as eating, drinking or breathing. We largely lack insight into what brings about sleep, what are its underlying biological mechanisms, and why we sleep. Even defining sleep can be difficult and may require long, sometimes sleep-inducing descriptions. One definition describes sleep as "*a recurring, reversible neuro-behavioral state of relative perceptual disengagement from and unresponsiveness to the environment, typically accompanied by postural recumbence, behavioral quiescence, and closed eyes*".[2] Essentially, sleep differs from 'chilling out' by sensory disconnection that cannot be achieved voluntarily.[3] Yet, this neuro-behavioral state, in which nothing much seems to be happening, involves unique patterns of brain activity, and seems preserved across all animal species.[1] Assuming that '*if sleep does not serve an absolutely vital function, it is the biggest mistake evolution ever made*' (Allan Rechtschaffen, University of Chicago Sleep Laboratory, Smithsonian Institute, 1978), sleep research is thus empowered. Answers to questions on the mechanisms and functions of sleep will surely provide essential biological insights into one of the key behavioral experiences of everyday life. These insights are especially relevant to learn about sleep's role in health and disease.

As sleep is primarily 'by the brain, for the brain',[4] its role in brain health and disorders is specifically interesting. Neurodegenerative diseases in the aged, such as Alzheimer's disease, other forms of dementia, and Parkinson's disease are common and highly burdensome diseases.[5-7] The societal impact of these diseases, in terms of healthy years lost and healthcare costs, is enormous.[8,9] Treatment aimed at modifying these diseases are currently thought ineffective as too much brain damage has already accumulated by the time recognizable symptoms emerge. This helped fuel the search for factors that identify the disease earlier, or that causally contribute to its development or progression. In the search for such factors, sleep has gained increasing attention.[10-13] Recent studies into the 'nightlife' of neurons and astrocytes have helped understand the potential functions of sleep, most of which are highly relevant to the study of neurodegenerative processes and diseases. Non-mutually exclusive hypotheses on sleep's function include the synaptic homeostasis hypothesis,[14,15] which states that sleep '*is the price the brain pays for synaptic plasticity*'.[3] During wakefulness, synapses – the connections that allow neurons to communicate – are on average strengthened while the brain is continuously processing information, or learning.[3] Information from experiences is continuously materialized in synaptic strength, and sleep allows going offline from the environment to reduce synaptic strength, sorting out the most salient information collected along the way. This reduction also decreases expenditure of cellular supplies and energy on costly

synapses.[3] Another hypothesis posits that sleep is necessary for 'housekeeping' in the brain, as it drives fluid exchange in the brain which circulates signaling molecules and clears metabolic waste.[16-18]

Both aforementioned hypotheses imply that disturbed sleep, if severe or chronic enough, may harm the brain by dysfunction of aforementioned homeostatic processes. Importantly, these processes overlap with the key pathological features found in neurodegenerative diseases in the aged, e.g. synaptic dysfunction[19] or a detrimental accumulation of proteins.[20] Against this background, observing associations of sleep disturbances, i.e. sleep disorders or otherwise abnormal sleep, with a higher risk of cognitive decline or neurodegenerative diseases in humans suggests an etiological, causal role of sleep disturbances.[13,21] As sleep disturbances are common in the aged,[22] and have been hypothesized to be modifiable,[11,23] this supposed causal relation may harbor a large preventive potential for these conditions. It is therefore important we try to further substantiate the etiological role of sleep disturbances in these diseases.

This thesis is rooted in epidemiology,[24] a scientific discipline concerned with quantifying (biomedical) relations through comparing groups of individuals, aimed at controlling health problems.[25] Its principles and methods are applied by many if not all researchers in the biomedical field seeking to answer causal questions. This thesis uses observational data from the population-based, prospective Rotterdam Study cohort of middle-aged and elderly individuals, designed to investigate risk factors of common chronic diseases. The Rotterdam Study focuses among others on neurodegenerative diseases such as dementia, including Alzheimer's disease, and Parkinson's disease. Study participants routinely undergo measurements relevant to these conditions such as cognitive tests, locomotor screening, blood sampling or a brain MRI. Also, virtually all participants consented to provide access to their medical records, allowing continuous ascertainment of any neurodegenerative diseases for which any care was given. The study incorporated sleep measurements since 2002 and leverages over a decade of follow-up for neurodegenerative disease.

The aim of this thesis is to investigate the etiological role of sleep in neurodegenerative diseases, specifically dementia and Parkinson's disease, and related neurobiological correlates measures in middle-aged and elderly persons. First, in chapter 2, we describe sleep in the general population, using individual-level data from 36 national sleep cohorts, as well as objective and subjective sleep data from different countries. We also review recent studies investigating the 24-hour activity rhythm in relation to common age-related diseases in older adults. The 24-hour activity rhythm is a behavioral reflection of functioning of the circadian timing system, a key determinant of the sleep-wake cycle. In chapter 3, we investigate the relation of sleep characteristics with incident dementia including Alzheimer's disease, and Parkinson's disease. In chapter 4, we investigate associations of sleep characteristics with related aspects of brain aging: Neuronal

damage indicated by neurofilament light chain in plasma, brain waste clearance indicated by the structural appearance of perivascular spaces on brain magnetic resonance imaging, and brain functional connectivity measured with resting state functional MRI. Lastly, the main discussion in chapter 5 synthesizes results of chapters 2-4, discusses key methodological considerations in appraising these findings, and discusses implications for current clinical and public health practices, and future research.

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