OXFORD

Sleep Research Society

SLEEP, 2022, 1–3

https://doi.org/10.1093/sleep/zsac112
Advance Access Publication Date: 11 May 2022
Editorial

EDITORIAL

Moving towards core sleep outcomes in neurodegenerative disease—the time is now

Rani A. Sarkis[1,*] and Brendan P. Lucey[2,*]

[1]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA and [2]Department of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA

*Corresponding authors. Rani A. Sarkis, Assistant Professor of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. Email: rsarkis@bwh.harvard.edu; Brendan P. Lucey, MD, MSCI, Associate Professor of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA. Email: luceyb@wustl.edu.

Alzheimer's disease (AD) is a current and growing public health crisis with the worldwide prevalence of AD expected to rise from 46.8 million individuals affected in 2015 to 131.5 million in 2050 [1]. Differentiating AD from other neurodegenerative diseases is frequently difficult on clinical grounds, especially in the earliest stages of disease, and neuroimaging and biochemical markers of AD pathology are often used to supplement the clinical diagnosis. However, the development of these markers was initially impeded by the heterogeneous methods used by investigators. To address this heterogeneity of data collection, the AD field undertook multiple steps to ensure that uniform and standardized data were collected by investigators. A Minimum Data Set for Alzheimer Disease Centers (ADC) was developed by the Executive Committee of the ADC Directors to characterize individuals with mild AD and mild cognitive impairment (MCI) in comparison with the cognitively unimpaired elderly [2]. A multicenter Alzheimer's disease research project called the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched with the goal of optimizing methods and uniform standards for the acquisition of neuroimaging data [3]. Both of these initiatives and others were driven by the need to improve the accuracy of clinical diagnosis of AD and differentiate AD from other neurodegenerative diseases.

Increasing evidence supports a bi-directional relationship between sleep and AD [4]. Sleep may potentially serve as a marker for AD progression and/or as an intervention to prevent/delay AD onset. A major focus of current research is determining how sleep changes at different stages of AD and a similar problem of heterogeneous methods now faces the sleep research community. Studies investigating the relationship between sleep and AD (and other neurodegenerative diseases) have used self-reported sleep measures [5], actigraphy [6], electroencephalography (EEG) [7], and polysomnography (PSG) [8]. Blackman et al. [9] address this issue by determining how sleep has been measured in studies of individuals with early AD and non-AD dementia, what parameters were reported, the extent of heterogeneity that prevents pooling and comparison across studies, and finally suggests guidelines to standardize collection of sleep measures.

A majority of studies in patients with MCI and early dementia relied on validated questionnaires for self-reported sleep measures with fewer studies using more objective methods such as actigraphy or PSG. Each of these methods have strengths and weakness, and the authors recommend the collection of both objective and subjective sleep measures. Multiple methods of measuring sleep in the same participants will provide more comprehensive sleep phenotyping as well as increase the ability to compare sleep outcomes to previous studies that used only one method, such as self-reported sleep logs or validated questionnaires. Further work standardizing the collection of objective data, such as actigraph characteristics, also needs further discussion.

The field of wearable and non-wearable technologies to measure sleep is rapidly advancing. Home-based EEG monitoring may be administered over multiple nights and future studies are likely to increasingly rely less on in-lab polysomnography. Monitoring sleep in the home environment is more naturalistic and will facilitate more cost-effective longitudinal measurements. Also, patients and caregivers are asking for comfortable and convenient monitoring devices [10]. The array of devices potentially available for research includes limited scalp electrodes, electrocardiography patches on the chest, wrist-worn sensors

(e.g., temperature, accelerometry, photoplethysmography, and electrodermal activity), oximeters, mattress sensors, and motion detection sensors placed in rooms [11]. Any future guidelines will first have to keep these in mind as they establish minimum reporting criteria for limited scalp electrode devices vs. accelerometry-based devices which have variable levels of accuracy [12]. Wearable technologies will allow us a better understanding of sleep over months to years and can also be used in patients with more advanced disease who have been excluded so far from most studies. We are still in need of other devices that can help us better understand sleep-disordered breathing in neurodegenerative disease, and what endotypes and phenotypes exist in the various populations [13].

The review also highlights a dearth of sleep micro-architecture data in patients with MCI and dementia. Several relevant EEG features have already been shown to correlate with cognitive performance in healthy cohorts [14, 15] including measures of executive function and memory consolidation. Unfortunately, unlike sleep scoring parameters which are well established and agreed on, sleep micro-architecture analysis is performed on different signal processing software of unclear reproducibility. For instance, different investigators use customized spindle detector and spindle-slow oscillation coupling analysis methods. Efforts to establish publicly available gold standard datasets to allow the comparison of these algorithms are strongly encouraged [16].

In their review, the authors also highlight the heterogeneity of participants with MCI and early dementia where the underlying cause of early dementia is often specified but that of MCI is unclear. Investigations of sleep and neurodegeneration need to determine the underlying pathology in each cohort and their cognitive phenotype to allow meaningful comparisons. For instance, individuals who develop symptomatic AD progress through an asymptomatic cognitively normal "preclinical" stage when amyloid-β (Aβ) is deposited as insoluble extracellular plaque and neurofibrillary tangles of hyperphosphorylated tau accumulate intracellularly eventually leading to neuronal loss, cognitive dysfunction, dementia, and death [17, 18]. Lumping participants into the mild dementia or MCI categories is problematic in the absence of good phenotyping due to the potential of including multiple neurodegenerative disease in the same cohort. PET ligands and CSF biomarkers are the gold standard for measuring AD pathology in vivo, although they are expensive and invasive respectively. Blood-based biomarkers [19] are now available and will soon be well-established as an alternative, allowing researchers to recruit larger well-characterized populations who can be compared across studies. Finally, Blackman et al. focused on MCI and early dementia but the issues raised in their review apply to cognitively normal individuals with amyloid deposition (i.e., preclinical AD), a group found to have changes in sleep despite the absence of cognitive symptoms [20, 21].

Another under-reported aspect of sleep that is highlighted in the review is that of circadian rhythm disruptions. In patients with neurodegenerative disease, alterations in the sleep-wake cycle are common, and disruption in circadian circuitry has relevant clinical implications with immediate effects on cognition, the autonomic system, and clearance of pathological proteins [22]. Actigraphy-based studies have already been explored, whereas the study of home-based salivary cortisol and melatonin measurements as well as serum assessment of circadian genes is still in its infancy. Multi-modal based approaches will allow us a better understanding of how these biological rhythms change with disease and will help usher in several circadian-based interventions. Guidelines will be needed to better define circadian rhythms beyond solely relying on actigraphy. Light therapy and non-photic circadian synchronizers such as physical activity are already being explored [22], and future clinical trials will need robust reproducible outcomes. We can also foresee machine learning algorithms that analyze this multi-modal data and help us predict risk of falls, changes in blood pressure, nocturia, or sun-downing.

Now is an exciting time to study sleep and neurodegeneration. We will have to keep up with the advances in wearables, biomarkers, home-based testing, and quantitative EEG analysis. We agree that expert-based core outcomes are needed to guide us as we explore these relationships further and expand sleep-based clinical trials.

Disclosure Statement

Rani A. Sarkis has nothing to disclose. Brendan P. Lucey has consulting relationships with Merck and Eli Lilly.

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