1-1-2024

Predicting neurodegeneration from sleep related biofluid changes

Yue Yang

Woojin S. Kim

Johannes C. Michaelian

Simon J. G. Lewis

Craig L. Phillips

See next page for additional authors

10.1016/j.nbd.2023.106369

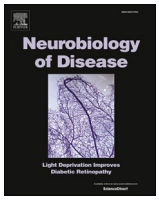
Yang, Y., Kim, W. S., Michaelian, J, C., Lewis, S. J. G., Phillips, C. L., D'Rozario, A. L., . . . Naismith, S. L. (2024). Predicting neurodegeneration from sleep related biofluid changes. Neurobiology of Diseases, 190, article 106369. https://doi.org/10.1016/j.nbd.2023.106369

Neurobiology of Disease 190 (2024) 106369

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Review

Predicting neurodegeneration from sleep related biofluid changes

Yue Yang [a,1], Woojin Scott Kim [a,b,1], Johannes C. Michaelian [c], Simon J.G. Lewis [a,b,d], Craig L. Phillips [e,f], Angela L. D'Rozario [c,e], Pratishtha Chatterjee [f,g], Ralph N. Martins [f,g,h], Ron Grunstein [e,i], Glenda M. Halliday [a,b,*], Sharon L. Naismith [c,**]

[a] Brain and Mind Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2050, Australia
[b] School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia
[c] Healthy Brain Ageing Program, School of Psychology, Brain and Mind Centre & The Charles Perkins Centre, The University of Sydney, Sydney, NSW 2050, Australia
[d] Parkinson's Disease Research Clinic, Brain and Mind Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2050, Australia
[e] CIRUS, Centre for Sleep and Chronobiology, Woolcock Institute of Medical Research, Macquarie University, Sydney, NSW 2109, Australia
[f] Macquarie Medical School, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia
[g] School of Medical and Health Sciences, Edith Cowan University, Perth, WA 6027, Australia
[h] School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA 6009, Australia
[i] Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2006, Australia

ARTICLE INFO

Keywords:
Sleep-wake disturbances
Neurodegenerative diseases
Dementia
Biomarkers

ABSTRACT

Sleep-wake disturbances are common in neurodegenerative diseases and may occur years before the clinical diagnosis, potentially either representing an early stage of the disease itself or acting as a pathophysiological driver. Therefore, discovering biomarkers that identify individuals with sleep-wake disturbances who are at risk of developing neurodegenerative diseases will allow early diagnosis and intervention. Given the association between sleep and neurodegeneration, the most frequently analyzed fluid biomarkers in people with sleep-wake disturbances to date include those directly associated with neurodegeneration itself, such as neurofilament light chain, phosphorylated tau, amyloid-beta and alpha-synuclein. Abnormalities in these biomarkers in patients with sleep-wake disturbances are considered as evidence of an underlying neurodegenerative process. Levels of hormonal sleep-related biomarkers such as melatonin, cortisol and orexin are often abnormal in patients with clinical neurodegenerative diseases, but their relationships with the more standard neurodegenerative biomarkers remain unclear. Similarly, it is unclear whether other chronobiological/circadian biomarkers, such as disrupted clock gene expression, are causal factors or a consequence of neurodegeneration. Current data would suggest that a combination of fluid biomarkers may identify sleep-wake disturbances that are most predictive for the risk of developing neurodegenerative disease with more optimal sensitivity and specificity.

1. Introduction

Sleep is an essential daily physiological process that plays crucial roles in the maintenance and repair of body functions. Within the central nervous system, sleep contributes to the promotion of synaptic plasticity and memory consolidation, as well as the removal of toxic brain metabolites (Tononi and Cirelli, 2014; Xie et al., 2013). Sleep-wake is a term describing both sleep and circadian cycles. Sleep-wake disturbances are common in the elderly, with about half of older adults aged ≥55 years reporting sleep complaints (Crowley, 2011). Sleep-wake disturbances commonly do not present in isolation and may also represent prodromal features or risk factors for certain neurodegenerative diseases. These symptoms highlight the need for early and broad screening of individuals with sleep-wake disturbances to identify those at risk for neurodegeneration who could

* Corresponding author at: Brain and Mind Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2050, Australia.
** Corresponding author at: Healthy Brain Ageing Program, School of Psychology, Brain and Mind Centre and The Charles Perkins Centre, The University of Sydney, Sydney, NSW 2050, Australia.
E-mail addresses: yue.yang@sydney.du.au (Y. Yang), woojin.kim@sydney.edu.au (W.S. Kim), johannes.michaelian@sydney.edu.au (J.C. Michaelian), simon.lewis@sydney.edu.au (S.J.G. Lewis), c.phillips@mq.edu.au (C.L. Phillips), angela.drozario@sydney.edu.au (A.L. D'Rozario), pratishtha.chatterjee@mq.edu.au (P. Chatterjee), ralph.martins@mq.edu.au (R.N. Martins), ron.grunstein@sydney.edu.au (R. Grunstein), glenda.halliday@sydney.edu.au (G.M. Halliday), sharon.naismith@sydney.edu.au (S.L. Naismith).
[1] These authors contributed equally.

https://doi.org/10.1016/j.nbd.2023.106369
Received 7 August 2023; Received in revised form 30 November 2023; Accepted 1 December 2023
Available online 3 December 2023

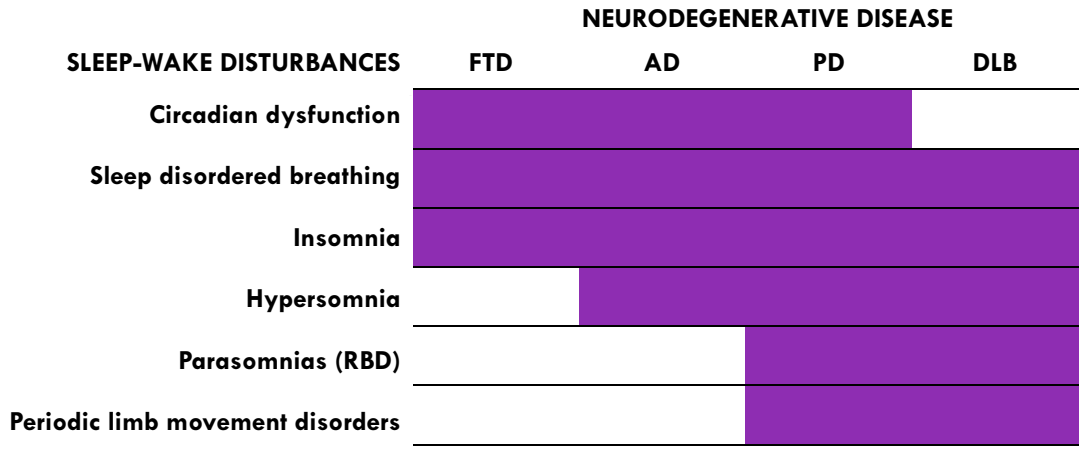


Fig. 1. Presence of sleep-wake disturbances in neurodegenerative diseases.
Sleep-wake disturbances are widely present in AD, PD, DLB, and FTD. The type of sleep-wake disturbances commonly encountered in these neurodegenerative diseases include circadian dysfunction, sleep disordered breathing, insomnia, hypersomnia, parasomnias (RBD), and periodic limb movement disorders.

potentially undergo longitudinal follow up and early intervention. Whilst various biomarkers have been assessed for this purpose, issues with accessibility and invasiveness have limited the utilization of some of these approaches.

In the present narration, we reviewed current biomarker studies that link sleep-wake disturbances with neurodegeneration, with a particular focus on biofluids. A systematic search was conducted in the PubMed database, using search terms – sleep-wake disturbances, sleep disorders, neurodegeneration, neurodegenerative diseases, biomarkers, serum, plasma, cerebrospinal fluid, and biofluids. We examined cohort, cross-sectional, longitudinal, and case-control studies, including clinical, epidemiological, and meta-analytic data. We covered major, as well as minor, neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, and frontotemporal dementia. We also compared the consistency of findings among different types of biofluids where available. Although reviews have been carried out on recent developments in separate explorations of fluid-based biomarkers in neurodegenerative diseases and sleep disturbances (Cocco et al., 2023; Giangrande et al., 2023; Pundir et al., 2022), these, however, do not extensively cover biofluid studies across interdisciplinary areas nor the link between sleep-wake disturbances and neurodegenerative diseases. We have addressed these shortfalls in our review. Synthesizing this work will help to inform strategies focused on the key fluid biomarkers that could identify people with sleep-wake disturbances, those at a greater risk of neurodegenerative disease, as well as those that can best monitor disease progression and response to interventions.

2. Sleep variation and sleep disorders

2.1. Sleep varies with age and sex

The nature of sleep varies with age and between the sexes. Ageing is commonly accompanied by changes in sleep macroarchitecture, such as more advanced sleep timing, longer sleep-onset latency, shorter overall sleep duration and increased sleep fragmentation (Li et al., 2018). Interestingly, whilst the duration of rapid eye movement (REM) sleep appears to be relatively stable before the age of 80 years (Mander et al., 2017; Ohayon et al., 2004), at the microstructural level, both the amplitude and density of slow wave sleep is reduced with advanced age (Dube et al., 2015). Sex is another factor impacting on sleep patterns with age. For instance, males over the age of 70 years present with more pronounced reductions in their percentage of slow wave sleep (stage 3–4 sleep) (average 3-fold lower), compared with age-matched females. In addition, males over the age of 70 years have shown a 50% reduction in their percentage of slow wave sleep compared with males at younger ages, whereas females do not show such significant changes with age (Redline et al., 2004).

2.2. Sleep-wake disturbances

Sleep-wake disturbances is an umbrella term that can be classified into seven major diagnostic sections, according to the International Classification of Sleep Disorders (ICSD)-3, namely insomnia, sleep-related breathing disorders including obstructive sleep apnea (OSA), central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias including REM sleep behavior disorder (RBD), sleep-related movement disorders including restless legs syndrome, and other sleep disorders. Furthermore, complaints of poor sleep quality are common in mild cognitive impairment (MCI) (McKinnon et al., 2014) and yet these may not meet criteria for a formal sleep disorder.

2.3. Difficulties in diagnosing sleep disorders

The clinical diagnosis of sleep disorders is commonly facilitated by questionnaires, wearable devices and polysomnography (PSG). PSG is the gold standard for diagnosing sleep disorders but is costly and not readily available. PSG can be carried out in the home environment but may be challenging for the older patient (Toedebusch et al., 2019) and may not capture all relevant aspects, such as REM Sleep Behavior Disorder. Moreover, measures of sleep microarchitecture relevant to ageing, cognition and neurodegeneration, such as slow wave activity and sleep spindles, are not currently routinely measured as they require more sophisticated power spectral analysis of the sleep electroencephalogram (EEG). Due to the complexity and cost of PSG measurements, these are typically conducted over a single night. For data collection over multiple nights, simpler wearable devices such as actigraphy and commercial activity monitors are used. These measure surrogates of objective sleep-wake activity using accelerometry over periods of at least 7 or 14 days (Ancoli-Israel et al., 2003) and are typically supplemented with a sleep diary. There is evidence that some commercial "sleep trackers" have greater correlation with PSG than actigraphy. For example, recent years have witnessed the development of contactless under bed mattresses that can measure sleep apnea and sleep movements over longer time periods (Chinoy et al., 2021; Edouard et al., 2021). Actigraphy and contactless devices have the greatest capacity to achieve ecological validity and to be scalable within the community, but the cut-offs and interpretations of these measures in relation to areas of clinical concern, are still variable and validation data is limited, particularly in older samples and those at risk of neurodegenerative diseases. Whilst the simplest to deploy and score, self-report measures are not well utilized in clinical dementia settings, as they are subject to recall bias (Lauderdale et al., 2008). There is also data to suggest that for some disorders, such as OSA, self-report measures are not effective in older people with cognitive impairment (Wilson et al., 2014). In addition, with increasing age, individuals are susceptible to an increasing risk of

comorbid medical and mental health conditions (along with medications), and sleep habits that may affect nocturnal sleep (Gulia and Kumar, 2018). Collectively, it therefore remains difficult to differentiate, at an individual level, those with sleep-wake disturbances who are at increased risk of developing specific neurodegenerative diseases, and further, which specific type of sleep disturbance is of most concern. This may in part be due to the issues outlined above, as well as a lack of longitudinal data in 'at risk' cohorts.

3. Relationship between sleep disorders and neurodegenerative diseases

Sleep disorders are increasingly considered to have a bidirectional relationship with neurodegenerative diseases. Of note, insomnia, OSA, RBD, and circadian changes are prominent in many neurodegenerative diseases and their prodromal stages (Lal et al., 2022; Naismith et al., 2011) (Fig. 1). Prospective epidemiological and meta-analytic data also support the notion that these sleep disorders increase dementia risk (Shi et al., 2018; Tranah et al., 2011; Yaffe et al., 2011), with more recent reports from ten years of National Health and Aging Trends Study data revealing that older adults with insomnia have a 51% increased dementia risk (hazard ratio = 1.51, 95% CI = 1.19, 1.90) (Wong and Lovier, 2023). A recent systematic review and meta-analysis of the association between OSA and levels of blood and CSF biomarkers of Alzheimer's disease (AD), comprising of 18 studies with 2804 patients, revealed that CSF amyloid-β40, blood total amyloid-β, blood amyloid-β40, blood amyloid-β42 and blood total-tau were significantly higher in OSA patients compared with healthy controls, indicating that OSA is associated with an elevation of some biomarkers of AD (Yeo et al., 2023). An animal model of AD revealed disrupted neurophysiological output of the suprachiasmatic nucleus (Fusilier et al., 2021), suggesting a potential link between disease mechanisms of AD and sleep disturbances. Whether identification of these sleep-wake disturbances in the absence of a change in cognition has the capability of accurately predicting the development of neurodegenerative diseases at an individual level in subsequent years remains to be further elucidated.

3.1. Alzheimer's disease and sleep disorders

Epidemiological and meta-analytic data shows that various sleep-wake disturbances are associated with an increased risk of cognitive impairment and AD (Hahn et al., 2014; Tranah et al., 2011; Yaffe et al., 2011) including insomnia (Shi et al., 2018; Wong and Lovier, 2023), OSA (Leng et al., 2017; Yaffe et al., 2011), short and long sleep duration (Cavailles et al., 2022; Chen et al., 2016) and poor sleep quality (Shi et al., 2018). Disturbances of sleep are also evident in people with MCI, a high-risk state for developing AD, whereby around 50% convert to dementia within 5 years (D'Rozario et al., 2020; Naismith et al., 2010).

Specifically, meta-analyses show that those with MCI have greater wake after sleep onset, lower sleep efficiency, reduced REM sleep, greater light sleep (stage 1), more nocturnal hypoxemia, as well as various other changes in macroarchitecture (D'Rozario et al., 2020). One study has also revealed advanced circadian phase, as determined by timing of melatonin secretion (Naismith et al., 2014). In addition, sleep disturbance in MCI also appears to be linked to structural and functional changes within the brain's default mode network (Luo et al., 2022; McKinnon et al., 2017), as well as to alterations in sleep microarchitecture (Naismith and Mowszowski, 2018).

In AD, there are exacerbations of the sleep-wake disturbances observed with normal ageing (Benca et al., 1992; Bliwise, 1993; Vitiello and Prinz, 1989), including prominent nocturnal awakenings, hypersomnia and daytime napping (Bubu et al., 2017; Moran et al., 2005). Circadian misalignment often manifests as sundowning, day-night reversal and nocturnal wandering (Ancoli-Israel et al., 1997; Andrade et al., 2018; Gaeta et al., 2020; Gallagher-Thompson et al., 1992; Gnanasekaran, 2016; Khachiyants et al., 2011; Martin et al., 2000; McCurry et al., 1999; Menegardo et al., 2019; van Someren et al., 1996; Vitiello et al., 1990; Volicer et al., 2001). While these clinical manifestations may reflect general degeneration of the suprachiasmatic nucleus (SCN), and reduced production and/or secretion of melatonin from the pineal gland (Stopa et al., 1999), recent in vivo findings also implicate the locus coeruleus (LC), a key component of the body's arousal system, with greater LC degeneration linked to higher odds for manifesting sleep-wakes disturbances in early stages of the disease (Dahl et al., 2019; Oh et al., 2022; Van Egroo et al., 2022; Van Egroo et al., 2021). Moreover, it has been hypothesized that increased sleep disruption (higher awakenings, non-REM N1 sleep and lower sleep maintenance) observed across AD subtypes (amnestic/typical, non-amnestic/atypical) is being driven by a dysfunctional arousal system of LC wake-promoting neurons (Falgàs et al., 2023). However, despite the wealth of data available in this field, thresholds for sleep disturbance that signify high risk remain to be determined and there remains a lack of sleep microarchitecture data to provide insights into key neural oscillations that may be pivotal to this process. This is particularly pertinent due to the recently recognized role of the glymphatic system, that clears Aβ and other toxic metabolic waste products, from the brain during sleep, a process that is maximal during the deeply restorative slow wave sleep (Nedergaard and Goldman, 2020).

3.2. Synucleinopathies and sleep disorders

Synucleinopathies are a group of neurodegenerative diseases characterized by abnormal deposition of α-synuclein, and include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). The association between synucleinopathies and idiopathic/isolated RBD (iRBD) has been extensively studied (Boeve et al., 2013; Chan et al., 2018; Fereshtehnejad et al., 2019; Ferman et al., 2011; Fernandez-Arcos et al., 2019; Gagnon et al., 2002; Hogl et al., 2018; Iranzo et al., 2014; Jozwiak et al., 2017; Postuma et al., 2009; Schenck et al., 2013; Si et al., 2022), and iRBD is considered a prodromal form of synucleinopathy (Iranzo et al., 2014), which has also been confirmed pathologically (Boeve et al., 2013). The A35T *SNCA* transgenic mouse model presented key feature of RBD from 5 months of age, and hyposmia when phosphorylated α-synuclein accumulated at 9 months of age (Taguchi et al., 2020), further suggested an association between the protein and sleep disturbances. Whether earlier changes in sleep before the onset of iRBD may predict progression to iRBD and the subsequent synucleinopathy remains to be determined. Although iRBD may appear decades before the onset of synucleinopathy-specific symptoms (Fereshtehnejad et al., 2019; Iranzo et al., 2014; Postuma et al., 2009; Schenck et al., 2013), its presence cannot yet accurately differentiate or predict progression to a specific synucleinopathy subtype. The amount of increased tonic chin electromyography (EMG) activity during REM sleep does seem to favor progression to PD (Postuma et al., 2010), but could not be used alone to accurately differentiate a subtype. It has also been demonstrated that MCI is three-fold greater in PD with RBD, compared to PD without RBD (Jozwiak et al., 2017), indicating a potential link between RBD and cognitive decline in synucleinopathies. A recent review expounded that patients with limited or prodromal forms of synucleinopathies, i.e. iRBD, were at high risk of developing motor and/or cognitive deficits over time and thereby "phenoconvert" to one of these conditions with established motor and/or cognitive deficits, and high risk of developing synucleinopathy that is associated with PD, MSA and DLB (Singer, 2022).

Apart from iRBD, other sleep-wake disturbances, such as periodic limb movement disorder, insomnia, hypersomnia, and sleep-disordered breathing, are also frequently observed in PD and DLB (Azmin et al., 2013; Bhalsing et al., 2013; Bhattacharya et al., 2020; Boddy et al., 2007; Cagnin et al., 2017; Calzetti et al., 2014; Chung et al., 2013; Cochen De Cock, 2019; Gjerstad et al., 2006; Gjerstad et al., 2007; Loo and Tan, 2008; Neikrug et al., 2013; Nomura et al., 2013; Norlinah et al., 2009; Porter et al., 2008; Poryazova et al., 2010; Prudon et al., 2014; Rana et al., 2013; Suzuki et al., 2008; Terzaghi et al., 2013; Tse et al., 2005; Verbaan et al., 2010; Verbaan et al., 2008; Wong et al., 2014).

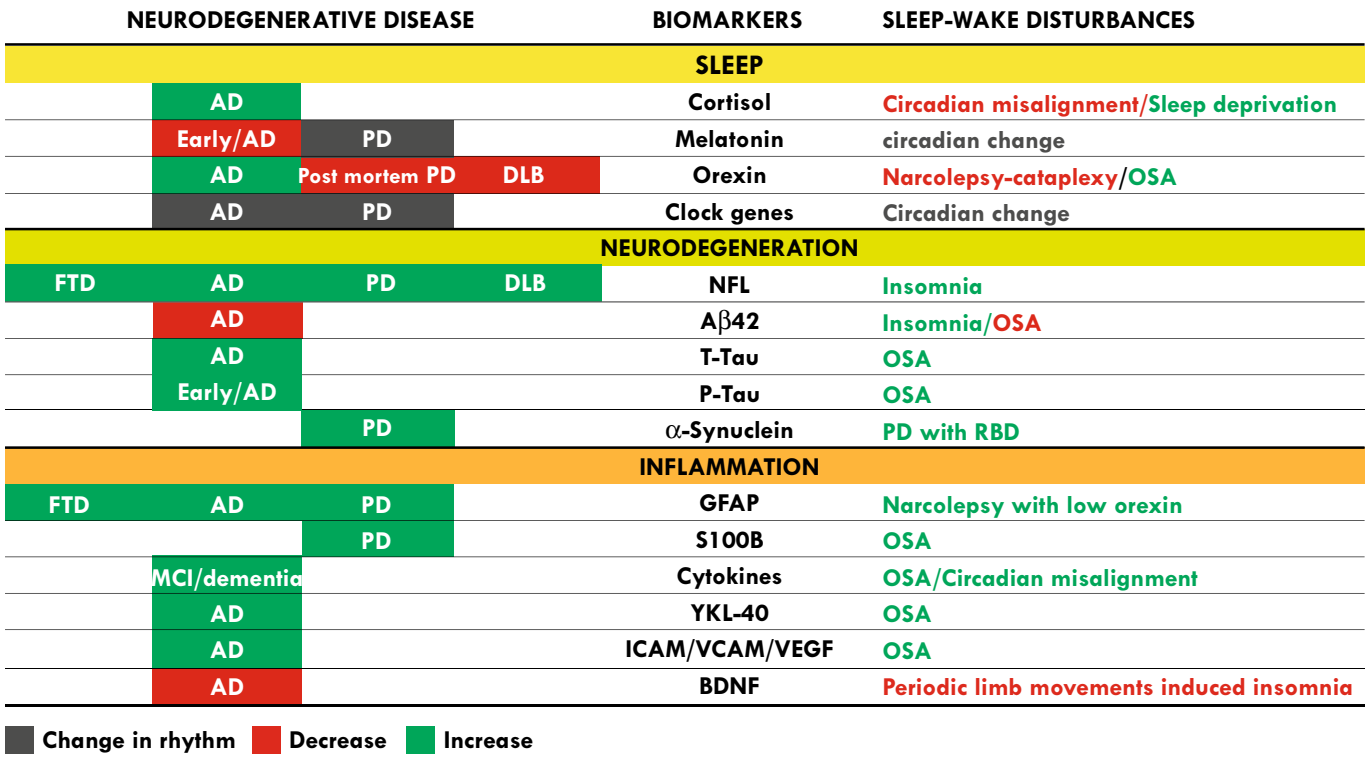


Fig. 2. Fluid-based biomarkers measured in sleep-wake disturbances and neurodegenerative diseases.
Though in limited number of studies and usually in small cohorts, given the bidirectional relationship between sleep disturbances and neurodegenerative diseases, various fluid-based biomarkers have been evaluated for increase, decrease, or rhythmic change in the overlapping field. These include sleep-related biomarkers, neurodegeneration-related biomarkers, as well as inflammatory biomarkers. These markers have been analyzed both in sleep disturbances and neurodegenerative diseases, and may be further validated for utilization as a screening marker in future studies.

Whether the presence of these sleep-wake disturbances are associated with disease progression remains to be determined.

3.3. Other neurodegenerative diseases and sleep disorders

Though small in numbers, studies are emerging that evaluate sleep-wake disturbances in other neurodegenerative diseases, such as frontotemporal dementia (FTD). Previous questionnaire-based studies have revealed a 30% prevalence of sleep-wake disturbances in FTD (Fernandez Martinez et al., 2008), with examples such as insomnia and sleep disordered breathing being previously reported in this type of neurodegenerative disease (McCarter et al., 2016). In addition, there appears to be greater fragmentation of rest-activity rhythms in FTD as measured by actigraphy (Anderson et al., 2009).

4. Fluid biomarkers for sleep and circadian rhythms

Various hormones and genes play essential roles in maintaining or reflecting sleep/wake cycles and circadian rhythms. However, little is known as to whether these biomarkers could be used alone or in combination with neurodegeneration biomarkers (see below) to predict onset to or progression of neurodegenerative diseases (Fig. 2).

4.1. Melatonin

Melatonin is a methoxyindole secreted by the pineal gland that can be measured in cerebrospinal fluid (CSF), blood and saliva, and dim light melatonin onset (DLMO) is considered to be the single most accurate circadian phase marker (Lewy, 1999; Pandi-Perumal et al., 2007). Both post-mortem CSF and blood serum studies have shown that melatonin levels are decreased significantly in AD compared to controls (Liu et al., 1999; Mishima et al., 1999), and were inversely correlated with increases in the Braak neuritic stage of AD (Zhou et al., 2003). Of importance, the rhythm of melatonin secretion is affected in AD (Mishima et al., 1999), with a lack of suppression in serum level of melatonin with light exposure occurring in AD patients (Ohashi et al., 1999) and the night-time peak of melatonin level in both serum and tissues decreased in AD compared with age-matched controls (Mishima et al., 1999; Wu et al., 2003). Importantly, the decrease in melatonin starts at a very early stage of disease (Zhou et al., 2003), and changes to the timing of melatonin secretion are evident in MCI (Naismith et al., 2014). This indicates that longitudinal monitoring of a change in melatonin rhythm or absolute amounts of the hormone may serve as a suitable early biomarker in people with sleep disorders at risk of future AD or for disease tracking.

Limited melatonin studies have been conducted in PD, of which it appears that patients have blunted circadian rhythms of melatonin secretion in saliva, serum and plasma, as well as changes in response to dopaminergic medication and motor fluctuations (Bolitho et al., 2014; Bordet et al., 2003; Breen et al., 2014; Fertl et al., 1993; Videnovic et al., 2014). At present, it is unknown if changes in melatonin level occur in other neurodegenerative diseases such as FTD. Whether the amplitude or pattern of the circadian change in melatonin differs with sleep-wake disturbances more in individuals at risk for neurodegeneration compared to those without risk remains unknown.

4.2. Cortisol

Cortisol is a glucocorticoid hormone that plays a crucial role in the stress response. Like melatonin, cortisol can be measured in CSF, blood and saliva (Pena-Bautista et al., 2019), and the secretion of cortisol follows a diurnal circadian pattern that is inverted compared to melatonin. Previous studies have shown that acute total sleep deprivation increases cortisol levels, while chronic circadian misalignment reduces cortisol levels (Wright Jr. et al., 2015).

Cortisol has also been evaluated in prodromal and clinical AD. CSF and serum levels of cortisol are significantly higher in clinical AD

compared with controls and those with prodromal AD (Popp et al., 2009; Swanwick et al., 1998). In addition, morning CSF cortisol levels increase in both prodromal and clinical AD compared with controls and prodromes of other dementias, and longitudinally, higher baseline CSF cortisol level is associated with faster cognitive decline in prodromal AD (Popp et al., 2015). The circadian fluctuation of cortisol was slightly less marked in AD compared to controls (Giubilei et al., 2001). Therefore, the change in cortisol levels could be used in combination with other markers to predict the rate of progression of AD.

4.3. Orexin

Orexins, which consist of orexin A and orexin B, are hypothalamic neuropeptides essential for the homeostasis of energy metabolism and sleep/wake cycles (Nixon et al., 2015). It has been widely accepted that orexin is associated with arousal, and it is reduced significantly in narcolepsy-cataplexy (Nishino et al., 2000). Orexin A is a specific and sensitive CSF biomarker for the diagnosis of narcolepsy type 1, which is characterized by sleepiness, cataplexy, disrupted nocturnal sleep, sleep-related hallucinations, and sleep paralysis (Barateau et al., 2023). Paradoxically, CSF levels of orexin increase with partial sleep deprivation in healthy adults (Olsson et al., 2018). Changes in orexin levels in other sleep-wake disturbances are less clear, although CSF levels of orexin are higher in OSA patients compared with AD (Liguori et al., 2019). In AD, CSF orexin levels are inversely correlated with daytime sleep fragmentation (Friedman et al., 2007) but positively correlated with sleep fragmentation in prodromal AD (Liguori et al., 2016). The overall levels are increased in AD compared to controls (Liguori et al., 2019), with higher levels observed in moderate-severe AD compared to mild AD (Liguori et al., 2014) and in general these increases are associated with cognitive dysfunction in AD (Shimizu et al., 2020). In addition, the CSF level of orexin has also been shown to increase in MCI, particularly in those with sleep complaints, with levels similar to AD (Gabelle et al., 2017; Liguori et al., 2016). In cognitively normal older adults, orexin A levels correlate with phosphorylated tau-181 (P-Tau181) levels (Osorio et al., 2016), indicating that the increase in orexin is associated with the onset of this specific biomarker for AD (see below). It is not yet clear why increases in this wake promoting peptide appear early in the disease course. This may well be a compensatory mechanism (i.e. to mitigate against other sedating signals) or may reflect early dysfunction of orexin neurons of the perifornical area and hypothalamus, and/or their widespread brain projections. Overall, whilst still requiring further evaluation, CSF levels of orexin show some promise as a biomarker for AD, and there is great interest in the role of orexin antagonists to target sleep disturbance in neurodegeneration (McCleery and Sharpley, 2020).

There are only a limited number of small cohort studies of orexin levels in PD, DLB or FTD. One study showed that CSF levels of pro-orexin are increased in FTD, but to a lesser extent compared to AD (Heywood et al., 2018). In contrast, CSF orexin levels have been shown to be comparable between PD and controls (Compta et al., 2009), but at post-mortem the levels were lower in PD (Fronczek et al., 2007), suggesting a change over time. In a study examining DLB, AD, and controls, CSF orexin levels were lower in DLB compared to both AD and controls (Wennstrom et al., 2012). Though the number of studies remain limited, orexin levels appear to relate more to dementia status than parkinsonism, and the impact on the orexin system may differ between AD and Lewy body diseases, which requires further confirmation by studies with larger and well characterized cohorts. Given that orexin is involved in the homeostasis of circadian rhythm, it remains of interest whether a change in the level of orexin may serve as a useful tool for predicting the progression to either AD or Lewy body dementia.

4.4. CLOCK genes

Circadian rhythm is present in most cells, with the SCN in the hypothalamus being the core regulation center. The light input synchronizes the core clock machinery in SCN neurons, which in turn synchronize cellular clocks throughout the human body (Leng et al., 2019). At the cellular level, the core circadian clock consists of proteins that form transcriptional-translation feedback loops. The clock proteins brain and muscle Arnt-like protein-1 (BMAL1) forms a heterodimer with other transcription factors including circadian locomotor output cycles kaput (CLOCK) or neuronal Per-Arnt-Sim (PAS) domain protein 2 (NPAS2). The heterodimer subsequently drives the transcription of clock-controlled genes, including its negative feedback regulators period 1 (PER1), period 2 (PER2) and period 3 (PER3), as well as cryptochrome 1 (CRY1) and cryptochrome 2 (CRY2), which in turn translocate to the nucleus and suppress transcription mediated by BMAL1:CLOCK or BMAL1:NPAS2 heterodimers (Huang et al., 2012a; Matsumura et al., 2013). In addition, BMAL1:CLOCK also activates transcription of the nuclear receptors REV-ERBα and REV-ERBβ, which competitively bind and negatively regulate BMAL1 transcription (Cox and Takahashi, 2019; Yin et al., 2007). Together, these core clock machineries maintain the 24-h cellular circadian rhythms.

Deletion of the *BMAL1* gene has been shown to attenuate rhythm of sleep and wakefulness in animal models (Laposky et al., 2005), and mutation of human *PER2* (*hPER2*) phosphorylation site has been shown to associate with variant in human sleep behavior (Toh et al., 2001), suggesting a correlation between clock genes and sleep. In addition, animal studies have shown that sleep deprivation increased cortical expression of clock genes such as *BMAL1*, *CLOCK*, *NPAS2*, *CRY2*, and *PER2* (Curie et al., 2015; Franken et al., 2007; Wisor et al., 2008), some of which return to normal upon recovery of sleep (Franken et al., 2007), as well as reduced DNA-binding of *CLOCK* and *BMAL1* to the clock genes (Mongrain et al., 2011), suggesting a bidirectional correlation between clock genes and sleep.

In addition to their validated role in the maintenance of cellular circadian rhythm (Turek, 2016), researchers have started to examine clock genes in neurodegenerative diseases. Using fibroblast culture from AD patients compared with controls, it has been shown that the peak of *BMAL1* transcription is delayed (rhythm offset), and the rhythmic DNA methylation of *BMAL1* is significantly dysregulated in the brain early in AD (Cronin et al., 2017). Previous studies on newly diagnosed PD using blood samples revealed a lack of time-dependent variation in *BMAL1* but not *PER2* expression, which was accompanied by increased serum cortisol and decreased melatonin levels compared with controls (Breen et al., 2014). In addition, administration of melatonin in PD patients for three months resulted in elevation of *BMAL1* levels in peripheral blood (Delgado-Lara et al., 2020), suggesting a potential link between melatonin and clock gene expression. How a change in clock genes contributes to the pathophysiology of neurodegenerative diseases remains unknown, however animal studies have shown that deletion of *BMAL1* induces synaptic degeneration and glial fibrillary acidic protein (GFAP) activation (Musiek et al., 2013) and an increase in amyloid-beta (Aβ) peptides induces degradation of the circadian clock regulator cAMP-regulated-enhancer (CRE) binding protein (CBP), and transcription factor *BMAL1* (Song et al., 2015). Whether such dysregulation of clock genes is the 'chicken or the egg' mechanistically for neurodegeneration, they could certainly be positioned as additional therapeutic targets. Changes in the rhythmic transcription and expression of these clock genes in people with sleep-wake disturbances could also be used to predict progression in particular neurodegenerative diseases.

5. Neurodegeneration biomarkers for sleep disorders

Fluid biomarkers of neurodegeneration have been widely studied in the prodromal stages of neurodegenerative diseases (Fig. 2). These have been measured mostly in the CSF with more recent studies replicating these initial findings in blood samples. Given that these neurodegenerative biomarkers are frequently assessed at prodromal stages of neurodegeneration, it remains unclear as to whether individuals with sleep-wake disturbances without cognitive decline also have biomarker changes indicative of neuropathology. Such correlations may provide a useful tool for predicting individuals with sleep-wake disturbances at

risk of developing specific neurodegenerative diseases and may also provide viable surrogate endpoints for use in clinical trials.

5.1. Neurofilament light chain

The intermediate filaments specific to neurons include the neurofilament triplet proteins - light chain (NFL), medium chain (NFM) and heavy chain (NFH). These are located in the cytoplasm and dendrites of certain neurons and are crucial for the maintenance of structural stability of neurons. Under physiological conditions, NFL is released by neurons in small amounts (Disanto et al., 2017; Khalil et al., 2020), which increases with age (Khalil et al., 2020).

The increase of NFL release has long been considered a biomarker for neuroaxonal damage and neurodegeneration. Studies showed that both CSF and blood levels of NFL increase in synucleinopathies, tauopathies, and AD (Bacioglu et al., 2016). Longitudinal neuroimaging studies in prodromal and clinical AD patients compared with controls revealed that CSF levels of NFL were elevated at baseline in the cohorts with neurodegeneration, regardless of their levels of Aβ42 and P-Tau (Mattsson et al., 2019). This indicates that NFL represents a screening marker for overall neurodegeneration (Mattsson et al., 2019; Pilotto et al., 2021a; Pilotto et al., 2021b; Silva-Spinola et al., 2022). Importantly, given that changes in NFL in the blood closely reflect those in the CSF, it could be argued that the assessment of plasma NFL could potentially serve as a convenient screening biomarker for identifying those people who are at risk of developing a neurodegenerative disease.

It remains unclear how NFL levels change longitudinally in individuals with sleep-wake disturbances. In one study, individuals with chronic insomnia had higher serum levels of NFL compared to controls (Zhang et al., 2018), suggestive of neurodegeneration. Few longitudinal studies have been performed on the sustained or increased levels of NFL and their potential predictive value for subsequent neurodegeneration in people with isolated sleep-wake disturbances. In individuals with a parent diagnosed with sporadic AD, CSF levels of NFL were not associated with subjective sleep quality (Sprecher et al., 2017), and similarly, in a cohort of 4712 middle-aged to elderly non-demented individuals, plasma levels of NFL were not associated with self-rated sleep-wake disturbances measured by the Pittsburgh Sleep Quality Index and 24 h-rhythm actigraphy (Lysen et al., 2020). However, these results should be interpreted with caution, given that these patients were not screened for definitive AD biomarkers nor undertook a formal sleep study to objectively clarify the cause of self-reported or actigraphy determined poor sleep. A study using PSG revealed that the CSF level of NFL was negatively correlated with slow wave sleep in mild to moderate AD (Targa et al., 2021), and higher self-report sleepiness scores were associated with increased CSF NFL (Carvalho et al., 2022) in cognitively unimpaired older adults. In addition, inclusion of the plasma level of NFL with orthostatic hypotension (OH) and RBD may better predict motor progression in PD (Pilotto et al., 2021b). In summary, NFL appears to be a non-specific marker for neurodegeneration and needs further examination in relation to sleep disturbances.

5.2. Phosphorylated tau and total tau

Tau is a microtubule-binding protein that promotes the assembly and stability of microtubules (Weingarten et al., 1975). Hyperphosphorylation of tau leads to abnormal aggregation of tau into neurofibrillary tangles (Uchihara, 2014).

Changes in total tau (T-Tau) in the CSF have been considered as a response to neuronal injury (Jack Jr. et al., 2018), and have been shown to increase in different diseases including AD (Blennow and Zetterberg, 2018; Lew et al., 2021; Zetterberg, 2017). P-Tau has long been considered to be a more specific marker of AD. Mass spectrometry analysis of CSF from familial, non-familial prodromal and clinical AD has revealed that P-Tau at amino acid position 217 (P-Tau217) increases approximately two decades before the estimated symptom onset in dominantly inherited AD, followed by P-Tau at position 181 (P-Tau181) and then other P-Tau proteins (Barthelemy et al., 2020), with similar findings in sporadic AD. Interestingly, increases in P-Tau217 and P-Tau181 waned close to symptom onset (Barthelemy et al., 2020), suggesting that the change in these P-Tau proteins may not only present as an early biomarker, but also a predictor of progression into clinical disease. Importantly, analyses of P-Tau181 and P-Tau217 in blood were consistent to those of CSF, suggesting that these proteins are capable of differentiating AD from other types of dementia (Janelidze et al., 2020; Karikari et al., 2020; Palmqvist et al., 2020), and may possibly identifying prodromal forms of AD.

T-Tau and P-Tau are starting to be also used to evaluate people with sleep-wake disturbances. In cognitively normal elderly people, increased CSF levels of T-Tau and P-Tau181 are associated with decreased spindle density during the N2 sleep stage (Kam et al., 2019), and higher CSF levels of P-Tau181/Aβ42 are associated with inferior subjective sleep quality and daytime somnolence in cognitively normal adults with a parental history of AD (Sprecher et al., 2017). In addition, higher CSF levels of T-Tau and P-Tau181 are negatively correlated with sleep efficiency, and positively correlated with wakefulness after sleep onset in OSA patients (Liguori et al., 2017). However, CSF levels of T-Tau and P-Tau did not appear to be altered in chronic insomnia and controls in middle-aged to elderly individuals (Chen et al., 2018).

Few studies have assessed the plasma levels of T-Tau and P-Tau181, but OSA patients have been shown to present with increased plasma levels of T-Tau (Motamedi et al., 2018) and increased serum levels of P-Tau181 (Bu et al., 2015) compared with controls. However, these cohorts only consisted of middle-aged individuals, and whether these measures are elevated in older cohorts with a range of sleep-wake disturbances remain to be determined. Given their potential predictive value for progression to AD, identifying the longitudinal change in these markers in cohorts of people with sleep-wake disturbances will be important, as such measures may assist with disease tracking longitudinally or may even be suitable as scalable, cost effective and feasible biomarkers for evaluating responsiveness to interventions.

5.3. Amyloid-β42 and amyloid-β40

Aβ42 and Aβ40 peptides are generated by cleavage of the amyloid precursor protein (APP) by β- and γ-secretases (Hook et al., 2008). Amyloid-β42 is considered to be more neurotoxic and prone to aggregation (Kim and Hecht, 2005; Yan and Wang, 2006). Animal studies have shown that Aβ peptides in interstitial fluids fluctuate in a diurnal pattern, and significantly correlate with the extent of wakefulness (Kang et al., 2009). This is supported by human studies with serial CSF sampling showing that the levels of Aβ42 and Aβ40 fluctuate between 1.5 and 4 fold over a 36 h period of time (Bateman et al., 2007).

The National Institute on Aging and Alzheimer's Association (NIA-AA) recommends a classification system for neurodegeneration (ATN system) composed of the severity of Aβ deposition (A), pathologic tau (T), and atrophy on neuroimaging (N). Within this scheme, Aβ deposition is defined by Aβ positron emission tomography (PET) ligand binding or a decrease in CSF levels of Aβ42 or the Aβ42/Aβ40 ratio (Jack Jr. et al., 2018). The diagnostic value of measuring Aβ peptides in blood remains uncertain due to the lack of a distinguishable difference in their levels between AD and controls, as reported by some (Feinkohl et al., 2020), as well as correlation studies showing highly variable levels using plasma versus CSF samples (Hanon et al., 2018; Huang et al., 2012b; Janelidze et al., 2016; Teunissen et al., 2018).

Changes in Aβ levels appear sensitive to sleep-wake disturbances, as one night's sleep deprivation in healthy adults increases Aβ burden in the hippocampus and thalamus assessed by ^{18}F-florbetaben PET imaging (Shokri-Kojori et al., 2018), and counteracts the overnight decrease of Aβ42 in CSF expected from unrestricted sleep (Ooms et al., 2014). Also, CSF levels of Aβ42 are increased in middle aged to elderly individuals with insomnia (Chen et al., 2018), but CSF Aβ peptide levels are decreased in OSA patients compared with controls (Ju et al., 2016; Liguori et al., 2017). This supports the link between OSA and neurodegeneration, which is

consistent with the annual rate of decrease in CSF Aβ42 levels associated with the severity of OSA (Sharma et al., 2018). Also, cognitively impaired individuals with co-existing OSA have a more rapid decrease in CSF levels of Aβ42 (Bubu et al., 2019). However, measurement of Aβ42 levels in the blood of young people showed no change in those with OSA (Motamedi et al., 2018), while middle-aged OSA samples showed increases in Aβ42 (Bu et al., 2015), indicating that the effect of OSA on Aβ could be age-dependent. More research is required on the impact of different sleep-wake disturbances on measurable Aβ peptide levels.

5.4. α-Synuclein

Alpha-synuclein (α-synuclein) is a neuronal protein that is abundant in presynaptic nerve terminals, and abnormal aggregation of the protein forms the characteristic inclusions found in a group of diseases collectively called synucleinopathies. α-Synuclein is present in various biofluids, including CSF, plasma and saliva (Chahine et al., 2020). A study revealed that plasma levels of α-synuclein were significantly higher in PD compared with controls (Lin et al., 2017). Importantly, they were higher in PD with dementia (PDD) compared to PD patients with either MCI or normal cognition. In particular, plasma levels of α-synuclein were negatively correlated with MMSE scores (Lin et al., 2017). These results indicate that α-synuclein may serve not only as a differentiation marker in prodromal cases, but also in predicting cognitive decline and dementia in synucleinopathies. Little is known about whether α-synuclein levels are affected by sleep-wake disturbances. One study revealed that the CSF and serum levels of oligomeric α-synuclein were higher in PD with probable RBD compared with PD without probable RBD (Hu et al., 2015). However, it remains unknown whether the change occurs before clinical diagnosis of iRBD, and whether it could differentiate iRBD progression to PD or DLB. It also remains unknown whether the change could be of predictive value for progression to PDD from PD.

6. Inflammatory biomarkers for sleep disorders

6.1. Astrocyte biomarkers

6.1.1. Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is the intermediate filament maintaining the structure of astrocytes. Astrocytes are one of the three main types of glia in the brain required to maintain normal neural functions by providing supportive structural scaffolding, neurotrophic factors, metabolic regulation, synaptogenesis, maintenance of the blood brain barrier and the glymphatic system (Sofroniew and Vinters, 2010; Sunkaria and Bhardwaj, 2022; Verkhratsky and Nedergaard, 2018). Activated astrocytes increase their levels of GFAP that are observed in most neurodegenerative diseases (Phatnani and Maniatis, 2015; Xiao et al., 2022). Analyses of increased GFAP levels in biofluids from patients with neurodegenerative diseases indicate activation and degeneration (Xiao et al., 2022). One study in AD and one in PD have shown that the CSF levels of GFAP increased in both of these diseases (Jesse et al., 2009; Santaella et al., 2020). Another study in FTD also showed that plasma levels of GFAP were increased compared with controls (Marelli et al., 2020). In addition, in cognitively normal older adults, plasma levels of GFAP were increased in individuals with higher Aβ load as determined by PET compared with those with lower Aβ load (Chatterjee et al., 2021). The CSF levels of GFAP has been found to be higher in narcolepsy patients that presented lower levels of orexin A, suggesting an interplay between these pathologies (Feneberg et al., 2013). While in young males the plasma levels of GFAP remain unchanged following acute sleep loss (Benedict et al., 2020), there is a lack of studies evaluating GFAP levels in people with sleep-wake disturbances, warranting further work in this field.

6.1.2. S100 calcium-binding protein B

S100 calcium-binding protein B (S100B) is a calcium binding protein in perivascular astrocytes. The protein increases with injury and is released into serum via disruption to the blood brain barrier (Kanner et al., 2003; Kapural et al., 2002). Animal studies have shown that S100B can also be released via glymphatic drainage (Plog et al., 2015). Limited studies have measured CSF levels of S100B but it is increased in PD compared with controls (Papuc and Rejdak, 2020). Only one study has measured serum levels of S100B in OSA and this showed increases compared with controls (Braga et al., 2006). More research on the change in this protein in people with different sleep-wake disturbances is required.

6.2. Inflammatory cytokines

6.2.1. Inflammatory markers

Inflammatory markers, such as tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP) / high-sensitivity CRP (hsCRP), interleukin-6 (IL-6), interleukin 1 beta (IL-1β), interleukin-8 (IL-8), and interleukin-10 (IL-10), have been consistently increased in biofluids from people with circadian misalignment and sleep loss (Clinton et al., 2011; Wright Jr. et al., 2015), as well as OSA (Baril et al., 2018; Bozic et al., 2018; Canto Gde et al., 2015; Montesi et al., 2012; Nadeem et al., 2013). They have also been shown to be increased in MCI and dementia (Brosseron et al., 2018; Darweesh et al., 2018; Havekes et al., 2019; Swardfager et al., 2010), and also cognitively unimpaired older adults with higher self-reported sleepiness scores (Carvalho et al., 2022). However, since cytokines increase ubiquitously across various diseases, it is difficult to define a threshold to predict progression towards a specific disease trajectory.

6.2.2. YKL-40

YKL-40 is a glycoprotein produced by inflammation that has been reported to be increased in the CSF of patients with mild AD-type dementia compared to controls (Craig-Schapiro et al., 2010). In addition, CSF levels of YKL-40/Aβ42 appear to predict the risk of developing cognitive impairment, determined by CDR score (Craig-Schapiro et al., 2010). Furthermore, a previous study has shown that serum levels of YKL-40 are elevated in OSA, where it positively correlates with apnea hypopnea index (AHI) and the oxygen desaturation index (ODI) (Mutlu et al., 2017). Whether the increased levels of YKL-40 in OSA are linked to a progression to dementia remains to be determined.

6.3. Growth factors

Vascular related markers have been of interest in sleep-wake disturbances, particularly OSA (Baril et al., 2018; Nadeem et al., 2013). Intercellular adhesion molecule 1 (ICAM-1) is a cell surface glycoprotein robustly expressed in response to inflammation, and vascular cell adhesion molecule (VCAM) is an adhesion molecule expressed on activated endothelium. A recent study has shown that higher CSF levels of ICAM1 and VCAM1 occurs with advanced stages of the ATN scheme (Rauchmann et al., 2020), suggesting similar growth factor changes in OSA and AD. Vascular endothelial growth factor (VEGF) is vascular endothelial growth factor, and serum levels of VEGF are elevated in OSA, as well as in AD (Alvarez et al., 2018; Briancon-Marjollet et al., 2014). Brain-derived neurotrophic factor (BDNF) is an important neurotrophic factor, and serum levels of BDNF are decreased in periodic limb movements and restless legs syndrome induced insomnia compared with controls (Giese et al., 2014), as well as in AD (Ng et al., 2019). At present, limited studies have assessed these markers in biofluid studies of people with sleep-wake disturbances.

7. Conclusions

Sleep is often disrupted in neurodegenerative diseases either before or after the initiation of neurodegeneration. Fluid biomarkers are available for both sleep-wake disturbances and neurodegeneration, both with the potential to predict cognitive decline and dementia in individuals with sleep-wake disturbances (Fig. 3). Considering the difficulties in obtaining PET scans and CSF samples, blood and saliva are

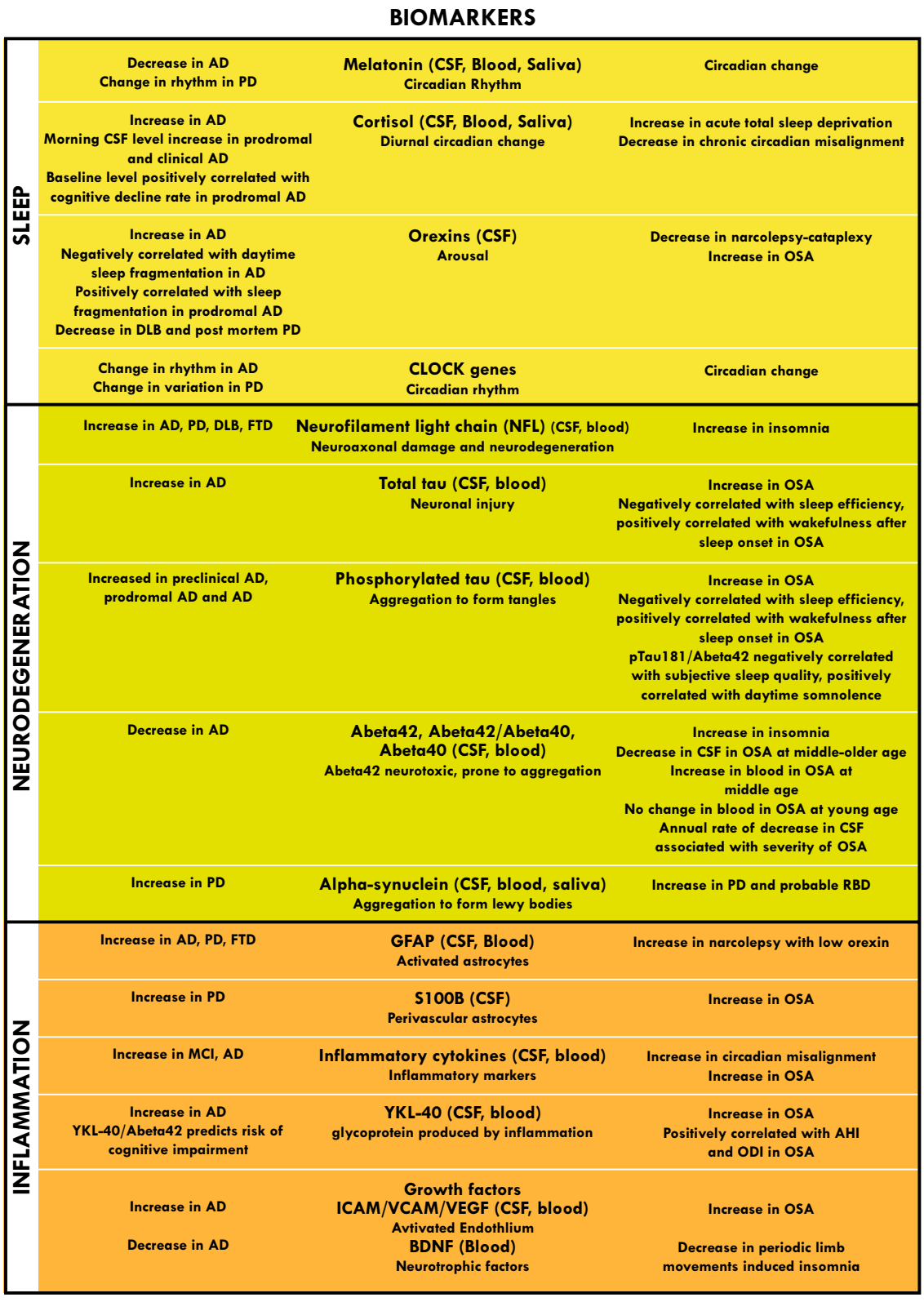


Fig. 3. Summary of biomarkers discussed in this review.
A summarization of biomarkers discussed in this review. These biomarkers include neurodegeneration-related biomarkers, sleep-related biomarkers, as well as other biomarkers such as inflammatory markers. These markers showed various changes and correlations in sleep-wake disturbances and neurodegenerative diseases, and some markers have been measured in different biofluids, such as CSF, blood and saliva. Of note, the number of studies are limited, and the study cohort is usually small. Gathering these data will guide future directions on exploration of potential biomarkers that may identify individuals with sleep-wake disturbances that are at increased risk of neurodegenerative diseases.

becoming more important for developing biomarkers, although studies using these biofluids are currently limited. With a better understanding of circadian biomarkers, their measurement in people with sleep-wake disturbances may assist with identifying early neurodegeneration and would seem to be particularly useful for the differentiation of the underlying pathologies involved. A biomarker strategy utilizing a combination of circadian and neurodegenerative biomarkers may increase sensitivity and specificity for predicting the type of sleep-wake disturbances and the potential to progress to a neurodegenerative disease. A long term prospective longitudinal study with records of clinical profiles, imaging and other assessment profiles as well as fluid-based biomarker profiles of healthy older people at risk, such as those with predisposed genetic variation and iRBD, may facilitate better understanding of utilization of these markers.

CRediT authorship contribution statement

Yue Yang: Conceptualization, Formal analysis, Investigation, Writing – original draft. **Woojin Scott Kim:** Conceptualization, Formal analysis, Investigation, Project administration, Writing – review & editing. **Johannes C. Michaelian:** Formal analysis, Writing – original draft, Writing – review & editing. **Simon J.G. Lewis:** Conceptualization, Funding acquisition, Writing – review & editing. **Craig L. Phillips:** Conceptualization, Funding acquisition, Writing – review & editing. **Angela L. D'Rozario:** Conceptualization, Funding acquisition, Writing – review & editing. **Pratishtha Chatterjee:** Conceptualization, Investigation, Writing – review & editing. **Ralph N. Martins:** Conceptualization, Funding acquisition, Writing – review & editing. **Ron Grunstein:** Conceptualization, Funding acquisition, Writing – review & editing. **Glenda M. Halliday:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Sharon L. Naismith:** Conceptualization, Funding acquisition, Writing – review & editing.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work is supported by the NHMRC Centre of Research Excellence to Optimize Brain Ageing in Neurodegeneration (CogSleep CRE). Dr. Yang and Dr. Michaelian are supported by a CogSleep CRE Fellowship. Prof Naismith and A/Prof Craig Phillips are supported by a Boosting Dementia Leadership Fellowship. Dr. D'Rozario is supported by an NHMRC-ARC Dementia Fellowship. Prof Lewis is supported by an NHMRC Leadership Fellowship. G.M.H. and R.G are supported by NHMRC Senior Leadership Fellowships. G.M.H. and W.S.K. are supported by funding to ForeFront, a collaborative research group dedicated to the study of frontotemporal dementia and motor neuron disease, from the National Health and Medical Research Council of Australia (NHMRC) program grant (#1037746). We thank Heidi Cartwright for figure preparation.

References

Alvarez, X.A., Alvarez, I., Aleixandre, M., Linares, C., Muresanu, D., Winter, S., Moessler, H., 2018. Severity-related increase and cognitive correlates of serum VEGF levels in Alzheimer's Disease ApoE4 carriers. J. Alzheimers Dis. 63, 1003–1013.

Ancoli-Israel, S., Klauber, M.R., Jones, D.W., Kripke, D.F., Martin, J., Mason, W., Pat-Horenczyk, R., Fell, R., 1997. Variations in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients. Sleep 20, 18–23.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., Pollak, C.P., 2003. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 26, 342–392.

Anderson, K.N., Hatfield, C., Kipps, C., Hastings, M., Hodges, J.R., 2009. Disrupted sleep and circadian patterns in frontotemporal dementia. Eur. J. Neurol. 16, 317–323.

Andrade, A.G., Bubu, O.M., Varga, A.W., Osorio, R.S., 2018. The relationship between obstructive sleep apnea and Alzheimer's Disease. J. Alzheimers Dis. 64, S255–S270.

Azmin, S., Khairul Anuar, A.M., Nafisah, W.Y., Tan, H.J., Raymond, A.A., Hanita, O., Shah, S.A., Norlinah, M.I., 2013. Restless legs syndrome and its associated risk factors in Parkinson's disease. Parkinsons Dis 2013, 535613.

Bacioglu, M., Maia, L.F., Preische, O., Schelle, J., Apel, A., Kaeser, S.A., Schweighauser, M., Eninger, T., Lambert, M., Pilotto, A., Shimshek, D.R., Neumann, U., Kahle, P.J., Staufenbiel, M., Neumann, M., Maetzler, W., Kuhle, J., Jucker, M., 2016. Neurofilament light chain in blood and CSF as marker of Disease progression in mouse models and in neurodegenerative diseases. Neuron 91, 56–66.

Barateau, L., Pizza, F., Chenini, S., Peter-Derex, L., Dauvilliers, Y., 2023. Narcolepsies, update in 2023. Rev. Neurol. (Paris) 179, 727–740.

Baril, A.A., Carrier, J., Lafreniere, A., Warby, S., Poirier, J., Osorio, R.S., Ayas, N., Dube, M.P., Petit, D., Gosselin, N., Canadian, S., Circadian, N., 2018. Biomarkers of dementia in obstructive sleep apnea. Sleep Med. Rev. 42, 139–148.

Barthelemy, N.R., Li, Y., Joseph-Mathurin, N., Gordon, B.A., Hassenstab, J., Benzinger, T. L.S., Buckles, V., Fagan, A.M., Perrin, R.J., Goate, A.M., Morris, J.C., Karch, C.M., Xiong, C., Allegri, R., Mendez, P.C., Berman, S.B., Ikeuchi, T., Mori, H., Shimada, H., Shoji, M., Suzuki, K., Noble, J., Farlow, M., Chhatwal, J., Graff-Radford, N.R., Salloway, S., Schofield, P.R., Masters, C.L., Martins, R.N., O'Connor, A., Fox, N.C., Levin, J., Jucker, M., Gabelle, A., Lehmann, S., Sato, C., Bateman, R.J., McDade, E., Alzheimer N., Dominantly Inherited, 2020. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat. Med. 26, 398–407.

Bateman, R.J., Wen, G., Morris, J.C., Holtzman, D.M., 2007. Fluctuations of CSF amyloid-beta levels: implications for a diagnostic and therapeutic biomarker. Neurology 68, 666–669.

Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, J.C., 1992. Sleep and psychiatric disorders. A meta-analysis. Arch. Gen. Psychiatry 49, 651–668 discussion 669-670.

Benedict, C., Blennow, K., Zetterberg, H., Cedernaes, J., 2020. Effects of acute sleep loss on diurnal plasma dynamics of CNS health biomarkers in young men. Neurology 94, e1181–e1189.

Bhalsing, K., Suresh, K., Muthane, U.B., Pal, P.K., 2013. Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. Parkinsonism Relat. Disord. 19, 426–430.

Bhattacharya, A., Lenka, A., Stezin, A., Kamble, N., Pal, P.K., 2020. Overview of sleep disturbances and their management in Parkinson plus disorders. J. Neurol. Sci. 415, 116891.

Blennow, K., Zetterberg, H., 2018. Biomarkers for Alzheimer's disease: current status and prospects for the future. J. Intern. Med. 284, 643–663.

Bliwise, D.L., 1993. Sleep in normal aging and dementia. Sleep 16, 40–81.

Boddy, F., Rowan, E.N., Lett, D., O'Brien, J.T., McKeith, I.G., Burn, D.J., 2007. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. Int. J. Geriatr. Psychiatry 22, 529–535.

Boeve, B.F., Silber, M.H., Ferman, T.J., Lin, S.C., Benarroch, E.E., Schmeichel, A.M., Ahlskog, J.E., Caselli, R.J., Jacobson, S., Sabbagh, M., Adler, C., Woodruff, B., Beach, T.G., Iranzo, A., Gelpi, E., Santamaria, J., Tolosa, E., Singer, C., Mash, D.C., Luca, C., Arnulf, I., Duyckaerts, C., Schenck, C.H., Mahowald, M.W., Dauvilliers, Y., Graff-Radford, N.R., Wszolek, Z.K., Parisi, J.E., Dugger, B., Murray, M.E., Dickson, D. W., 2013. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med. 14, 754–762.

Bolitho, S.J., Naismith, S.L., Rajaratnam, S.M., Grunstein, R.R., Hodges, J.R., Terpening, Z., Rogers, N., Lewis, S.J., 2014. Disturbances in melatonin secretion and circadian sleep-wake regulation in Parkinson disease. Sleep Med. 15, 342–347.

Bordet, R., Devos, D., Brique, S., Touitou, Y., Guieu, J.D., Libersa, C., Destee, A., 2003. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin. Neuropharmacol. 26, 65–72.

Bozic, J., Borovac, J.A., Galic, T., Kurir, T.T., Supe-Domic, D., Dogas, Z., 2018. Adropin and inflammation biomarker levels in male patients with obstructive sleep apnea: a link with glucose metabolism and sleep parameters. J. Clin. Sleep Med. 14, 1109–1118.

Braga, C.W., Martinez, D., Wofchuk, S., Portela, L.V., Souza, D.O., 2006. S100B and NSE serum levels in obstructive sleep apnea syndrome. Sleep Med. 7, 431–435.

Breen, D.P., Vuono, R., Nawarathna, U., Fisher, K., Shneerson, J.M., Reddy, A.B., Barker, R.A., 2014. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 71, 589–595.

Briancon-Marjollet, A., Henri, M., Pepin, J.L., Lemarie, E., Levy, P., Tamisier, R., 2014. Altered in vitro endothelial repair and monocyte migration in obstructive sleep apnea: implication of VEGF and CRP. Sleep 37, 1825–1832.

Brosseron, F., Traschutz, A., Widmann, C.N., Kummer, M.P., Tacik, P., Santarelli, F., Jessen, F., Heneka, M.T., 2018. Characterization and clinical use of inflammatory cerebrospinal fluid protein markers in Alzheimer's disease. Alzheimers Res. Ther. 10, 25.

Bu, X.L., Liu, Y.H., Wang, Q.H., Jiao, S.S., Zeng, F., Yao, X.Q., Gao, D., Chen, J.C., Wang, Y.J., 2015. Serum amyloid-beta levels are increased in patients with obstructive sleep apnea syndrome. Sci. Rep. 5, 13917.

Bubu, O.M., Brannick, M., Mortimer, J., Umasabor-Bubu, O., Sebastiao, Y.V., Wen, Y., Schwartz, S., Borenstein, A.R., Wu, Y., Morgan, D., Anderson, W.M., 2017. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and Meta-analysis. Sleep 40.

Bubu, O.M., Pirraglia, E., Andrade, A.G., Sharma, R.A., Gimenez-Badia, S., Umasabor-Bubu, O.Q., Hogan, M.M., Shim, A.M., Mukhtar, F., Sharma, N., Mbah, A.K., Seixas, A.A., Kam, K., Zizi, F., Borenstein, A.R., Mortimer, J.A., Kip, K.E., Morgan, D., Rosenzweig, I., Ayappa, I., Rapoport, D.M., Jean-Louis, G., Varga, A.W., Osorio, R.S., Alzheimer's Disease Neuroimaging, I., 2019. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. Sleep 42.

Cagnin, A., Fragiacomo, F., Camporese, G., Turco, M., Busse, C., Ermani, M., Montagnese, S., 2017. Sleep-wake profile in dementia with Lewy bodies, Alzheimer's Disease, and Normal aging. J. Alzheimers Dis. 55, 1529–1536.
Calzetti, S., Angelini, M., Negrotti, A., Marchesi, E., Goldoni, M., 2014. A long-term prospective follow-up study of incident RLS in the course of chronic DAergic therapy in newly diagnosed untreated patients with Parkinson's disease. J. Neural Transm. (Vienna) 121, 499–506.
Canto Gde, L., Pacheco-Pereira, C., Aydinoz, S., Major, P.W., Flores-Mir, C., Gozal, D., 2015. Biomarkers associated with obstructive sleep apnea: a scoping review. Sleep Med. Rev. 23, 28–45.
Carvalho, D.Z., St. Louis, E.K., Przybelski, S.A., Morgenthaler, T.I., Machulda, M.M., Boeve, B.F., Petersen, R.C., Jack, C.R., Graff-Radford, J., Vemuri, P., Mielke, M.M., 2022. Sleepiness in cognitively unimpaired older adults is associated with CSF biomarkers of inflammation and axonal integrity. Front. Aging Neurosci. 14.
Cavailles, C., Carriere, I., Wagner, M., Dartigues, J.F., Berr, C., Dauvilliers, Y., Jaussent, I., 2022. Trajectories of sleep duration and timing before dementia: a 14-year follow-up study. Age Ageing 51.
Chahine, L.M., Beach, T.G., Brumm, M.C., Adler, C.H., Coffey, C.S., Mosovsky, S., Caspell-Garcia, C., Serrano, G.E., Munoz, D.G., White 3rd, C.L., Crary, J.F., Jennings, D., Taylor, P., Foroud, T., Arnedo, V., Kopil, C.M., Riley, L., Dave, K.D., Mollenhauer, B., Sampling S., Systemic Synuclein, 2020. In vivo distribution of alpha-synuclein in multiple tissues and biofluids in Parkinson disease. Neurology 95, e1267–e1284.
Chan, P.C., Lee, H.H., Hong, C.T., Hu, C.J., Wu, D., 2018. REM sleep behavior disorder (RBD) in dementia with Lewy bodies (DLB). Behav. Neurol. 2018, 9421098.
Chatterjee, P., Pedrini, S., Stoops, E., Goozee, K., Villemagne, V.L., Asih, P.R., Verberk, I. M.W., Dave, P., Taddei, K., Sohrabi, H.R., Zetterberg, H., Blennow, K., Teunissen, C. E., Vanderstichele, H.M., Martins, R.N., 2021. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. Transl. Psychiatry 11, 27.
Chen, D.W., Wang, J., Zhang, L.L., Wang, Y.J., Gao, C.Y., 2018. Cerebrospinal fluid amyloid-beta levels are increased in patients with insomnia. J. Alzheimers Dis. 61, 645–651.
Chen, J.C., Espeland, M.A., Brunner, R.L., Lovato, L.C., Wallace, R.B., Leng, X., Phillips, L.S., Robinson, J.G., Kotchen, J.M., Johnson, K.C., Manson, J.E., Stefanick, M.L., Sarto, G.E., Mysiw, W.J., 2016. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimers Dement. 12, 21–33.
Chinoy, E.D., Cuellar, J.A., Huwa, K.E., Jameson, J.T., Watson, C.H., Bessman, S.C., Hirsch, D.A., Cooper, A.D., Drummond, S.P.A., Markwald, R.R., 2021. Performance of seven consumer sleep-tracking devices compared with polysomnography. Sleep 44.
Chung, S., Bohnen, N.I., Albin, R.L., Frey, K.A., Muller, M.L., Chervin, R.D., 2013. Insomnia and sleepiness in Parkinson disease: associations with symptoms and comorbidities. J. Clin. Sleep Med. 9, 1131–1137.
Clinton, J.M., Davis, C.J., Zielinski, M.R., Jewett, K.A., Krueger, J.M., 2011. Biochemical regulation of sleep and sleep biomarkers. J. Clin. Sleep Med. 7, S38–S42.
Cocco, C., Manai, A.L., Manca, E., Noli, B., 2023. Brain-biomarker changes in body fluids of patients with Parkinson's Disease. Int. J. Mol. Sci. 24.
Cochen De Cock, V., 2019. Therapies for restless legs in Parkinson's Disease. Curr. Treat. Options Neurol. 21, 56.
Compta, Y., Santamaria, J., Ratti, L., Tolosa, E., Iranzo, A., Munoz, E., Valldeoriola, F., Casamitjana, R., Rios, J., Marti, M.J., 2009. Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. Brain 132, 3308–3317.
Cox, K.H., Takahashi, J.S., 2019. Circadian clock genes and the transcriptional architecture of the clock mechanism. J. Mol. Endocrinol. 63, R93–R102.
Craig-Schapiro, R., Perrin, R.J., Roe, C.M., Xiong, C., Carter, D., Cairns, N.J., Mintun, M. A., Peskind, E.R., Li, G., Galasko, D.R., Clark, C.M., Quinn, J.F., D'Angelo, G., Malone, J.P., Townsend, R.R., Morris, J.C., Fagan, A.M., Holtzman, D.M., 2010. YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol. Psychiatry 68, 903–912.
Cronin, P., McCarthy, M.J., Lim, A.S.P., Salmon, D.P., Galasko, D., Masliah, E., De Jager, P.L., Bennett, D.A., Desplats, P., 2017. Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. Alzheimers Dement. 13, 689–700.
Crowley, K., 2011. Sleep and sleep disorders in older adults. Neuropsychol. Rev. 21, 41–53.
Curie, T., Maret, S., Emmenegger, Y., Franken, P., 2015. In vivo imaging of the central and peripheral effects of sleep deprivation and suprachiasmatic nuclei lesion on PERIOD-2 protein in mice. Sleep 38, 1381–1394.
Dahl, M.J., Mather, M., Düzel, S., Bodammer, N.C., Lindenberger, U., Kühn, S., Werkle-Bergner, M., 2019. Rostral locus coeruleus integrity is associated with better memory performance in older adults. Nat. Hum. Behav. 3, 1203–1214.
Darweesh, S.K.L., Wolters, F.J., Ikram, M.A., de Wolf, F., Bos, D., Hofman, A., 2018. Inflammatory markers and the risk of dementia and Alzheimer's disease: a meta-analysis. Alzheimers Dement. 14, 1450–1459.
Delgado-Lara, D.L., Gonzalez-Enriquez, G.V., Torres-Mendoza, B.M., Gonzalez-Usigli, H., Cardenas-Bedoya, J., Macias-Islas, M.A., de la Rosa, A.C., Jimenez-Delgado, A., Pacheco-Moises, F., Cruz-Serrano, J.A., Ortiz, G.G., 2020. Effect of melatonin administration on the PER1 and BMAL1 clock genes in patients with Parkinson's disease. Biomed. Pharmacother. 129, 110485.
Disanto, G., Barro, C., Benkert, P., Naegelin, Y., Schadelin, S., Giardiello, A., Zecca, C., Blennow, K., Zetterberg, H., Leppert, D., Kappos, L., Gobbi, C., Kuhle, J., Swiss Multiple Sclerosis Cohort Study, G, 2017. Serum Neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann. Neurol. 81, 857–870.
D'Rozario, A.L., Chapman, J.L., Phillips, C.L., Palmer, J.R., Hoyos, C.M., Mowszowski, L., Duffy, S.L., Marshall, N.S., Benca, R., Mander, B., Grunstein, R.R., Naismith, S.L., 2020. Objective measurement of sleep in mild cognitive impairment: a systematic review and meta-analysis. Sleep Med. Rev. 52, 101308.
Dube, J., Lafortune, M., Bedetti, C., Bouchard, M., Gagnon, J.F., Doyon, J., Evans, A.C., Lina, J.M., Carrier, J., 2015. Cortical thinning explains changes in sleep slow waves during adulthood. J. Neurosci. 35, 7795–7807.
Edouard, P., Campo, D., Bartet, P., Yang, R.Y., Bruyneel, M., Roisman, G., Escourrou, P., 2021. Validation of the Withings sleep analyzer, an under-the-mattress device for the detection of moderate-severe sleep apnea syndrome. J. Clin. Sleep Med. 17, 1217–1227.
Falgàs, N., Walsh, C.M., Yack, L., Simon, A.J., Allen, I.E., Kramer, J.H., Rosen, H.J., Joie, R.L., Rabinovici, G., Miller, B., Spina, S., Seeley, W.W., Ranasinghe, K., Vossel, K., Neylan, T.C., Grinberg, L.T., 2023. Alzheimer's disease phenotypes show different sleep architecture. Alzheimers Dement 19 (8), 3272–3282.
Feinkohl, I., Schipke, C.G., Kruppa, J., Menne, F., Winterer, G., Pischon, T., Peters, O., 2020. Plasma amyloid concentration in Alzheimer's Disease: performance of a high-throughput amyloid assay in distinguishing Alzheimer's Disease cases from controls. J. Alzheimers Dis. 74, 1285–1294.
Feneberg, E., Steinacker, P., Lehnert, S., Bohm, B., Mayer, G., Otto, M., 2013. Elevated glial fibrillary acidic protein levels in the cerebrospinal fluid of patients with narcolepsy. Sleep Med. 14, 692–694.
Fereshtehnejad, S.M., Yao, C., Pelletier, A., Montplaisir, J.Y., Gagnon, J.F., Postuma, R. B., 2019. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain 142, 2051–2067.
Ferman, T.J., Boeve, B.F., Smith, G.E., Lin, S.C., Silber, M.H., Pedraza, O., Wszolek, Z., Graff-Radford, N.R., Uitti, R., Van Gerpen, J., Pao, W., Knopman, D., Pankratz, V.S., Kantarci, K., Boot, B., Parisi, J.E., Dugger, B.N., Fujishiro, H., Petersen, R.C., Dickson, D.W., 2011. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 77, 875–882.
Fernandez Martinez, M., Castro Flores, J., Perez de las Heras, S., Mandaluniz Lekumberri, A., Gordejuela Menocal, M., Zarranz Imirizaldu, J.J., 2008. Prevalence of neuropsychiatric symptoms in elderly patients with dementia in Mungialde County (Basque Country, Spain). Dement. Geriatr. Cogn. Disord. 25, 103–108.
Fernandez-Arcos, A., Morenas-Rodriguez, E., Santamaria, J., Sanchez-Valle, R., Llado, A., Gaig, C., Lleo, A., Iranzo, A., 2019. Clinical and video-polysomnographic analysis of rapid eye movement sleep behavior disorder and other sleep disturbances in dementia with Lewy bodies. Sleep 42.
Fertl, E., Auff, E., Doppelbauer, A., Waldhauser, F., 1993. Circadian secretion pattern of melatonin in de novo parkinsonian patients: evidence for phase-shifting properties of l-dopa. J. Neural Transm. Park. Dis. Dement. Sect. 5, 227–234.
Franken, P., Thomason, R., Heller, H.C., O'Hara, B.F., 2007. A non-circadian role for clock-genes in sleep homeostasis: a strain comparison. BMC Neurosci. 8, 87.
Friedman, L.F., Zeitzer, J.M., Lin, L., Hoff, D., Mignot, E., Peskind, E.R., Yesavage, J.A., 2007. In Alzheimer disease, increased wake fragmentation found in those with lower hypocretin-1. Neurology 68, 793–794.
Fronczek, R., Overeem, S., Lee, S.Y., Hegeman, I.M., van Pelt, J., van Duinen, S.G., Lammers, G.J., Swaab, D.F., 2007. Hypocretin (orexin) loss in Parkinson's disease. Brain 130, 1577–1585.
Fusilier, A.R., Davis, J.A., Paul, J.R., Yates, S.D., McMeekin, L.J., Goode, L.K., Mokashi, M.V., Remiszewski, N., van Groen, T., Cowell, R.M., McMahon, L.L., Roberson, E.D., Gamble, K.L., 2021. Dysregulated clock gene expression and abnormal diurnal regulation of hippocampal inhibitory transmission and spatial memory in amyloid precursor protein transgenic mice. Neurobiol. Dis. 158, 105454.
Gabelle, A., Jaussent, I., Hirtz, C., Vialaret, J., Navucet, S., Grasselli, C., Robert, P., Lehmann, S., Dauvilliers, Y., 2017. Cerebrospinal fluid levels of orexin-a and histamine, and sleep profile within the Alzheimer process. Neurobiol. Aging 53, 59–66.
Gaeta, A.M., Benitez, I.D., Jorge, C., Torres, G., Dakterzada, F., Minguez, O., Huerto, R., Pujol, M., Carnes, A., Dalmases, M., Gibert, A., Farre, R., de la Torres, M.S., Barbe, F., Pinol-Ripoll, G., 2020. Prevalence of obstructive sleep apnea in Alzheimer's disease patients. J. Neurol. 267, 1012–1022.
Gagnon, J.F., Bedard, M.A., Fantini, M.L., Petit, D., Panisset, M., Rompre, S., Carrier, J., Montplaisir, J., 2002. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59, 585–589.
Gallagher-Thompson, D., Brooks 3rd, J.O., Bliwise, D., Leader, J., Yesavage, J.A., 1992. The relations among caregiver stress, "sundowning" symptoms, and cognitive decline in Alzheimer's disease. J. Am. Geriatr. Soc. 40, 807–810.
Giangrande, C., Delatour, V., Andreasson, U., Blennow, K., Gobom, J., Zetterberg, H., 2023. Harmonization and standardization of biofluid-based biomarker measurements for AT(N) classification in Alzheimer's disease. Alzheimers Dement (Amst) 15, e12465.
Giese, M., Unternahrer, E., Huttig, H., Beck, J., Brand, S., Calabrese, P., Holsboer-Trachsler, E., Eckert, A., 2014. BDNF: an indicator of insomnia? Mol. Psychiatry 19, 151–152.
Giubilei, F., Patacchioli, F.R., Antonini, G., Sepe Monti, M., Tisei, P., Bastianello, S., Monnazzi, P., Angelucci, L., 2001. Altered circadian cortisol secretion in Alzheimer's disease: clinical and neuroradiological aspects. J. Neurosci. Res. 66, 262–265.
Gjerstad, M.D., Alves, G., Wentzel-Larsen, T., Aarsland, D., Larsen, J.P., 2006. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology 67, 853–858.
Gjerstad, M.D., Wentzel-Larsen, T., Aarsland, D., Larsen, J.P., 2007. Insomnia in Parkinson's disease: frequency and progression over time. J. Neurol. Neurosurg. Psychiatry 78, 476–479.
Gnanasekaran, G., 2016. "Sundowning" as a biological phenomenon: current understandings and future directions: an update. Aging Clin. Exp. Res. 28, 383–392.

Gulia, K.K., Kumar, V.M., 2018. Sleep disorders in the elderly: a growing challenge. Psychogeriatrics 18, 155–165.
Hahn, E.A., Wang, H.X., Andel, R., Fratiglioni, L., 2014. A change in sleep pattern may predict Alzheimer disease. Am. J. Geriatr. Psychiatry 22, 1262–1271.
Hanon, O., Vidal, J.S., Lehmann, S., Bombois, S., Allinquant, B., Treluyer, J.M., Gele, P., Delmaire, C., Blanc, F., Mangin, J.F., Buee, L., Touchon, J., Hugon, J., Vellas, B., Galbrun, E., Benetos, A., Berrut, G., Paillaud, E., Wallon, D., Castelnovo, G., Volpe-Gillot, L., Paccalin, M., Robert, P.H., Godefroy, O., Dantoine, T., Camus, V., Belmin, J., Vandel, P., Novella, J.L., Duron, E., Rigaud, A.S., Schraen-Maschke, S., Gabelle, A., group, B.s, 2018. Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. Alzheimers Dement. 14, 858–868.
Havekes, R., Heckman, P.R.A., Wams, E.J., Stasiukonyte, N., Meerlo, P., Eisel, U.L.M., 2019. Alzheimer's disease pathogenesis: the role of disturbed sleep in attenuated brain plasticity and neurodegenerative processes. Cell. Signal. 64, 109420.
Heywood, W.E., Hallqvist, J., Heslegrave, A.J., Zetterberg, H., Fenoglio, C., Scarpini, E., Rohrer, J.D., Galimberti, D., Mills, K., 2018. CSF pro-orexin and amyloid-beta38 expression in Alzheimer's disease and frontotemporal dementia. Neurobiol. Aging 72, 171–176.
Hogl, B., Stefani, A., Videnovic, A., 2018. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. Nat. Rev. Neurol. 14, 40–55.
Hook, V., Schechter, I., Demuth, H.U., Hook, G., 2008. Alternative pathways for production of beta-amyloid peptides of Alzheimer's disease. Biol. Chem. 389, 993–1006.
Hu, Y., Yu, S.Y., Zuo, L.J., Cao, C.J., Wang, F., Chen, Z.J., Du, Y., Lian, T.H., Wang, Y.J., Chan, P., Chen, S.D., Wang, X.M., Zhang, W., 2015. Parkinson disease with REM sleep behavior disorder: features, alpha-synuclein, and inflammation. Neurology 84, 888–894.
Huang, N., Chelliah, Y., Shan, Y., Taylor, C.A., Yoo, S.H., Partch, C., Green, C.B., Zhang, H., Takahashi, J.S., 2012a. Crystal structure of the heterodimeric CLOCK: BMAL1 transcriptional activator complex. Science 337, 189–194.
Huang, Y., Potter, R., Sigurdson, W., Santacruz, A., Shih, S., Ju, Y.E., Kasten, T., Morris, J.C., Mintun, M., Duntley, S., Bateman, R.J., 2012b. Effects of age and amyloid deposition on Abeta dynamics in the human central nervous system. Arch. Neurol. 69, 51–58.
Iranzo, A., Fernandez-Arcos, A., Tolosa, E., Serradell, M., Molinuevo, J.L., Valldeoriola, F., Gelpi, E., Vilaseca, I., Sanchez-Valle, R., Llado, A., Gaig, C., Santamaria, J., 2014. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 9, e89741.
Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R. Contributors, 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14, 535–562.
Janelidze, S., Stomrud, E., Palmqvist, S., Zetterberg, H., van Westen, D., Jeromin, A., Song, L., Hanlon, D., Tan Hehir, C.A., Baker, D., Blennow, K., Hansson, O., 2016. Plasma beta-amyloid in Alzheimer's disease and vascular disease. Sci. Rep. 6, 26801.
Janelidze, S., Mattsson, N., Palmqvist, S., Smith, R., Beach, T.G., Serrano, G.E., Chai, X., Proctor, N.K., Eichenlaub, U., Zetterberg, H., Blennow, K., Reiman, E.M., Stomrud, E., Dage, J.L., Hansson, O., 2020. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat. Med. 26, 379–386.
Jesse, S., Steinacker, P., Cepek, L., von Arnim, C.A., Tumani, H., Lehnert, S., Kretzschmar, H.A., Baier, M., Otto, M., 2009. Glial fibrillary acidic protein and protein S-100B: different concentration pattern of glial proteins in cerebrospinal fluid of patients with Alzheimer's disease and Creutzfeldt-Jakob disease. J. Alzheimers Dis. 17, 541–551.
Jozwiak, N., Postuma, R.B., Montplaisir, J., Latreille, V., Panisset, M., Chouinard, S., Bourgouin, P.A., Gagnon, J.F., 2017. REM sleep behavior disorder and cognitive impairment in Parkinson's Disease. Sleep 40.
Ju, Y.E., Finn, M.B., Sutphen, C.L., Herries, E.M., Jerome, G.M., Ladenson, J.H., Crimmins, D.L., Fagan, A.M., Holtzman, D.M., 2016. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. Ann. Neurol. 80, 154–159.
Kam, K., Parekh, A., Sharma, R.A., Andrade, A., Lewin, M., Castillo, B., Bubu, O.M., Chua, N.J., Miller, M.D., Mullins, A.E., Glodzik, L., Mosconi, L., Gosselin, N., Prathamesh, K., Chen, Z., Blennow, K., Zetterberg, H., Bagchi, N., Cavedoni, B., Rapoport, D.M., Ayappa, I., de Leon, M.J., Petkova, E., Varga, A.W., Osorio, R.S., 2019. Sleep oscillation-specific associations with Alzheimer's disease CSF biomarkers: novel roles for sleep spindles and tau. Mol. Neurodegener. 14, 10.
Kang, J.E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., Holtzman, D.M., 2009. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326, 1005–1007.
Kanner, A.A., Marchi, N., Fazio, V., Mayberg, M.R., Koltz, M.T., Siomin, V., Stevens, G. H., Masaryk, T., Aumayr, B., Vogelbaum, M.A., Barnett, G.H., Janigro, D., 2003. Serum S100beta: a noninvasive marker of blood-brain barrier function and brain lesions. Cancer 97, 2806–2813.
Kapural, M., Krizanac-Bengez, L., Barnett, G., Perl, J., Masaryk, T., Apollo, D., Rasmussen, P., Mayberg, M.R., Janigro, D., 2002. Serum S-100beta as a possible marker of blood-brain barrier disruption. Brain Res. 940, 102–104.
Karikari, T.K., Pascoal, T.A., Ashton, N.J., Janelidze, S., Benedet, A.L., Rodriguez, J.L., Chamoun, M., Savard, M., Kang, M.S., Therriault, J., Scholl, M., Massarweh, G., Soucy, J.P., Hoglund, K., Brinkmalm, G., Mattsson, N., Palmqvist, S., Gauthier, S., Stomrud, E., Zetterberg, H., Hansson, O., Rosa-Neto, P., Blennow, K., 2020. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. 19, 422–433.
Khachiyants, N., Trinkle, D., Son, S.J., Kim, K.Y., 2011. Sundown syndrome in persons with dementia: an update. Psychiatry Investig. 8, 275–287.
Khalil, M., Pirpamer, L., Hofer, E., Voortman, M.M., Barro, C., Leppert, D., Benkert, P., Ropele, S., Enzinger, C., Fazekas, F., Schmidt, R., Kuhle, J., 2020. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat. Commun. 11, 812.
Kim, W., Hecht, M.H., 2005. Sequence determinants of enhanced amyloidogenicity of Alzheimer a{beta}42 peptide relative to a{beta}40. J. Biol. Chem. 280, 35069–35076.
Lal, C., Ayappa, I., Ayas, N., Beaudin, A.E., Hoyos, C., Kushida, C.A., Kaminska, M., Mullins, A., Naismith, S.L., Osorio, R.S., Phillips, C.L., Parekh, A., Stone, K.L., Turner, A.D., Varga, A.W., 2022. The link between obstructive sleep apnea and neurocognitive impairment: an official American Thoracic Society workshop report. Ann. Am. Thorac. Soc. 19, 1245–1256.
Laposky, A., Easton, A., Dugovic, C., Walisser, J., Bradfield, C., Turek, F., 2005. Deletion of the mammalian circadian clock gene BMAL1/Mop3 alters baseline sleep architecture and the response to sleep deprivation. Sleep 28, 395–409.
Lauderdale, D.S., Knutson, K.L., Yan, L.L., Liu, K., Rathouz, P.J., 2008. Self-reported and measured sleep duration: how similar are they? Epidemiology 19, 838–845.
Leng, Y., McEvoy, C.T., Allen, I.E., Yaffe, K., 2017. Association of Sleep-Disordered Breathing with Cognitive Function and Risk of cognitive impairment: a systematic review and Meta-analysis. JAMA Neurol. 74, 1237–1245.
Leng, Y., Musiek, E.S., Hu, K., Cappuccio, F.P., Yaffe, K., 2019. Association between circadian rhythms and neurodegenerative diseases. Lancet Neurol. 18, 307–318.
Lew, C.H., Petersen, C., Neylan, T.C., Grinberg, L.T., 2021. Tau-driven degeneration of sleep- and wake-regulating neurons in Alzheimer's disease. Sleep Med. Rev. 60, 101541.
Lewy, A.J., 1999. The dim light melatonin onset, melatonin assays and biological rhythm research in humans. Biol. Signals Recept. 8, 79–83.
Li, J., Vitiello, M.V., Gooneratne, N.S., 2018. Sleep in Normal Aging. Sleep Med. Clin. 13, 1–11.
Liguori, C., Romigi, A., Nuccetelli, M., Zannino, S., Sancesario, G., Martorana, A., Albanese, M., Mercuri, N.B., Izzi, F., Bernardini, S., Nitti, A., Sancesario, G.M., Sica, F., Marciani, M.G., Placidi, F., 2014. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol. 71, 1498–1505.
Liguori, C., Nuccetelli, M., Izzi, F., Sancesario, G., Romigi, A., Martorana, A., Amoroso, C., Bernardini, S., Marciani, M.G., Mercuri, N.B., Placidi, F., 2016. Rapid eye movement sleep disruption and sleep fragmentation are associated with increased orexin-a cerebrospinal-fluid levels in mild cognitive impairment due to Alzheimer's disease. Neurobiol. Aging 40, 120–126.
Liguori, C., Mercuri, N.B., Izzi, F., Romigi, A., Cordella, A., Sancesario, G., Placidi, F., 2017. Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's Disease biomarkers changes. Sleep 40.
Liguori, C., Mercuri, N.B., Nuccetelli, M., Izzi, F., Cordella, A., Bernardini, S., Placidi, F., 2019. Obstructive sleep apnea may induce orexinergic system and cerebral beta-amyloid metabolism dysregulation: is it a further proof for Alzheimer's disease risk? Sleep Med. 56, 171–176.
Lin, C.H., Yang, S.Y., Horng, H.E., Yang, C.C., Chieh, J.J., Chen, H.H., Liu, B.H., Chiu, M. J., 2017. Plasma alpha-synuclein predicts cognitive decline in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 88, 818–824.
Liu, R.Y., Zhou, J.N., van Heerikhuize, J., Hofman, M.A., Swaab, D.F., 1999. Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype. J. Clin. Endocrinol. Metab. 84, 323–327.
Loo, H.V., Tan, E.K., 2008. Case-control study of restless legs syndrome and quality of sleep in Parkinson's disease. J. Neurol. Sci. 266, 145–149.
Luo, Y., Qiao, M., Liang, Y., Chen, C., Zeng, L., Wang, L., Wu, W., 2022. Functional brain connectivity in mild cognitive impairment with sleep disorders: A study based on resting-state functional magnetic resonance imaging. Front. Aging Neurosci. 14.
Lysen, T.S., Ikram, M.A., Ghanbari, M., Luik, A.I., 2020. Sleep, 24-h activity rhythms, and plasma markers of neurodegenerative disease. Sci. Rep. 10, 20691.
Mander, B.A., Winer, J.R., Walker, M.P., 2017. Sleep and Human Aging. Neuron 94, 19–36.
Marelli, C., Hourregue, C., Gutierrez, L.A., Paquet, C., Menjot de Champfleur, N., De Verbizier, D., Jacob, M., Dubois, J., Maleska, A.M., Hirtz, C., Navucet, S., Bennys, K., Dumurgier, J., Cognat, E., Berr, C., Magnin, E., Lehmann, S., Gabelle, A., 2020. Cerebrospinal fluid and plasma biomarkers do not differ in the Presenile and late-onset behavioral variants of frontotemporal dementia. J. Alzheimers Dis. 74, 903–911.
Martin, J., Marler, M., Shochat, T., Ancoli-Israel, S., 2000. Circadian rhythms of agitation in institutionalized patients with Alzheimer's disease. Chronobiol. Int. 17, 405–418.
Matsumura, R., Matsubara, C., Node, K., Takumi, T., Akashi, M., 2013. Nuclear receptor-mediated cell-autonomous oscillatory expression of the circadian transcription factor, neuronal PAS domain protein 2 (NPAS2). J. Biol. Chem. 288, 36548–36553.
Mattsson, N., Cullen, N.C., Andreasson, U., Zetterberg, H., Blennow, K., 2019. Association between longitudinal plasma Neurofilament light and neurodegeneration in patients with Alzheimer Disease. JAMA Neurol. 76, 791–799.
McCarter, S.J., St Louis, E.K., Boeve, B.F., 2016. Sleep disturbances in frontotemporal dementia. Curr. Neurol. Neurosci. Rep. 16, 85.
McCleery, J., Sharpley, A.L., 2020. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database Syst. Rev. 11, CD009178.
McCurry, S.M., Logsdon, R.G., Teri, L., Gibbons, L.E., Kukull, W.A., Bowen, J.D., McCormick, W.C., Larson, E.B., 1999. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J. Geriatr. Psychiatry Neurol. 12, 53–59.

McKinnon, A., Terpening, Z., Hickie, I.B., Batchelor, J., Grunstein, R., Lewis, S.J., Naismith, S.L., 2014. Prevalence and predictors of poor sleep quality in mild cognitive impairment. J. Geriatr. Psychiatry Neurol. 27, 204–211.
McKinnon, A.C., Duffy, S.L., Cross, N.E., Terpening, Z., Grunstein, R.R., Lagopoulos, J., Batchelor, J., Hickie, I.B., Lewis, S.J., Shine, J.M., Naismith, S.L., 2017. Functional connectivity in the default mode network is reduced in association with nocturnal awakening in mild cognitive impairment. J. Alzheimers Dis. 56, 1373–1384.
Menegardo, C.S., Friggi, F.A., Scardini, J.B., Rossi, T.S., Vieira, T.D.S., Tieppo, A., Morelato, R.L., 2019. Sundown syndrome in patients with Alzheimer's disease dementia. Dement Neuropsychol 13, 469–474.
Mishima, K., Tozawa, T., Satoh, K., Matsumoto, Y., Hishikawa, Y., Okawa, M., 1999. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking. Biol. Psychiatry 45, 417–421.
Mongrain, V., La Spada, F., Curie, T., Franken, P., 2011. Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. PLoS One 6, e26622.
Montesi, S.B., Bajwa, E.K., Malhotra, A., 2012. Biomarkers of sleep apnea. Chest 142, 239–245.
Moran, M., Lynch, C.A., Walsh, C., Coen, R., Coakley, D., Lawlor, B.A., 2005. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med. 6, 347–352.
Motamedi, V., Kanefsky, R., Matsangas, P., Mithani, S., Jeromin, A., Brock, M.S., Mysliwiec, V., Gill, J., 2018. Elevated tau and interleukin-6 concentrations in adults with obstructive sleep apnea. Sleep Med. 43, 71–76.
Musiek, E.S., Lim, M.M., Yang, G., Bauer, A.Q., Qi, L., Lee, Y., Roh, J.H., Ortiz-Gonzalez, X., Dearborn, J.T., Culver, J.P., Herzog, E.D., Hogenesch, J.B., Wozniak, D. F., Dikranian, K., Giasson, B.I., Weaver, D.R., Holtzman, D.M., Fitzgerald, G.A., 2013. Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. J. Clin. Invest. 123, 5389–5400.
Mutlu, L.C., Tulubas, F., Alp, R., Kaplan, G., Yildiz, Z.D., Gurel, A., 2017. Serum YKL-40 level is correlated with apnea hypopnea index in patients with obstructive sleep apnea sindrome. Eur. Rev. Med. Pharmacol. Sci. 21, 4161–4166.
Nadeem, R., Molnar, J., Madbouly, E.M., Nida, M., Aggarwal, S., Sajid, H., Naseem, J., Loomba, R., 2013. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J. Clin. Sleep Med. 9, 1003–1012.
Naismith, S.L., Mowszowski, L., 2018. Sleep disturbance in mild cognitive impairment: a systematic review of recent findings. Curr. Opin. Psychiatry 31, 153–159.
Naismith, S.L., Rogers, N.L., Hickie, I.B., Mackenzie, J., Norrie, L.M., Lewis, S.J., 2010. Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. J. Geriatr. Psychiatry Neurol. 23, 123–130.
Naismith, S.L., Lewis, S.J., Rogers, N.L., 2011. Sleep-wake changes and cognition in neurodegenerative disease. Prog. Brain Res. 190, 21–52.
Naismith, S.L., Hickie, I.B., Terpening, Z., Rajaratnam, S.M., Hodges, J.R., Bolitho, S., Rogers, N.L., Lewis, S.J., 2014. Circadian misalignment and sleep disruption in mild cognitive impairment. J. Alzheimers Dis. 38, 857–866.
Nedergaard, M., Goldman, S.A., 2020. Glymphatic failure as a final common pathway to dementia. Science 370, 50–56.
Neikrug, A.B., Maglione, J.E., Liu, L., Natarajan, L., Avanzino, J.A., Corey-Bloom, J., Palmer, B.W., Loredo, J.S., Ancoli-Israel, S., 2013. Effects of sleep disorders on the non-motor symptoms of Parkinson disease. J. Clin. Sleep Med. 9, 1119–1129.
Ng, T.K.S., Ho, C.S.H., Tam, W.W.S., Kua, E.H., Ho, R.C., 2019. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with Alzheimer's Disease (AD): a systematic review and Meta-analysis. Int. J. Mol. Sci. 20.
Nishino, S., Ripley, B., Overeem, S., Lammers, G.J., Mignot, E., 2000. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 355, 39–40.
Nixon, J.P., Mavanji, V., Butterick, T.A., Billington, C.J., Kotz, C.M., Teske, J.A., 2015. Sleep disorders, obesity, and aging: the role of orexin. Ageing Res. Rev. 20, 63–73.
Nomura, T., Inoue, Y., Kobayashi, M., Namba, K., Nakashima, K., 2013. Characteristics of obstructive sleep apnea in patients with Parkinson's disease. J. Neurol. Sci. 327, 22–24.
Norlinah, M.I., Afidah, K.N., Noradina, A.T., Shamsul, A.S., Hamidon, B.B., Sahathevan, R., Raymond, A.A., 2009. Sleep disturbances in Malaysian patients with Parkinson's disease using polysomnography and PDSS. Parkinsonism Relat. Disord. 15, 670–674.
Oh, J.Y., Walsh, C.M., Ranasinghe, K., Mladinov, M., Pereira, F.L., Petersen, C., Falgàs, N., Yack, L., Lamore, T., Nasar, R., Lew, C., Li, S., Metzler, T., Coppola, Q., Pandher, N., Le, M., Heuer, H.W., Heinsen, H., Spina, S., Seeley, W.W., Kramer, J., Rabinovici, G.D., Boxer, A.L., Miller, B.L., Vossel, K., Neylan, T.C., Grinberg, L.T., 2022. Subcortical neuronal correlates of sleep in neurodegenerative diseases. JAMA Neurol. 79, 498–508.
Ohashi, Y., Okamoto, N., Uchida, K., Iyo, M., Mori, N., Morita, Y., 1999. Daily rhythm of serum melatonin levels and effect of light exposure in patients with dementia of the Alzheimer's type. Biol. Psychiatry 45, 1646–1652.
Ohayon, M.M., Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27, 1255–1273.
Olsson, M., Arlig, J., Hedner, J., Blennow, K., Zetterberg, H., 2018. Sleep deprivation and cerebrospinal fluid biomarkers for Alzheimer's disease. Sleep 41.
Ooms, S., Overeem, S., Besse, K., Rikkert, M.O., Verbeek, M., Claassen, J.A., 2014. Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial. JAMA Neurol. 71, 971–977.
Osorio, R.S., Ducca, E.L., Wohlleber, M.E., Tanzi, E.B., Gumb, T., Twumasi, A., Tweardy, S., Lewis, C., Fischer, E., Koushyk, V., Cuartero-Toledo, M., Sheikh, M.O., Pirraglia, E., Zetterberg, H., Blennow, K., Lu, S.E., Mosconi, L., Glodzik, L., Schuetz, S., Varga, A.W., Ayappa, I., Rapoport, D.M., de Leon, M.J., 2016. Orexin-a is associated with increases in cerebrospinal fluid phosphorylated-tau in cognitively Normal elderly subjects. Sleep 39, 1253–1260.
Palmqvist, S., Janelidze, S., Quiroz, Y.T., Zetterberg, H., Lopera, F., Stomrud, E., Su, Y., Chen, Y., Serrano, G.E., Leuzy, A., Mattsson-Carlgren, N., Strandberg, O., Smith, R., Villegas, A., Sepulveda-Falla, D., Chai, X., Proctor, N.K., Beach, T.G., Blennow, K., Dage, J.L., Reiman, E.M., Hansson, O., 2020. Discriminative accuracy of plasma Phospho-tau217 for Alzheimer Disease vs other neurodegenerative disorders. JAMA 324, 772–781.
Pandi-Perumal, S.R., Smits, M., Spence, W., Srinivasan, V., Cardinali, D.P., Lowe, A.D., Kayumov, L., 2007. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31, 1–11.
Papuc, E., Rejdak, K., 2020. Increased cerebrospinal fluid S100B and NSE reflect neuronal and glial damage in Parkinson's Disease. Front. Aging Neurosci. 12, 156.
Pena-Bautista, C., Baquero, M., Ferrer, I., Hervas, D., Vento, M., Garcia-Blanco, A., Chafer-Pericas, C., 2019. Neuropsychological assessment and cortisol levels in biofluids from early Alzheimer's disease patients. Exp. Gerontol. 123, 10–16.
Phatnani, H., Maniatis, T., 2015. Astrocytes in Neurodegenerative Disease. Cold Spring Harb Perspect Biol, p. 7.
Pilotto, A., Imarisio, A., Carrarini, C., Russo, M., Masciocchi, S., Gipponi, S., Cottini, E., Aarsland, D., Zetterberg, H., Ashton, N.J., Hye, A., Bonanni, L., Padovani, A., 2021a. Plasma Neurofilament light chain predicts cognitive progression in prodromal and clinical dementia with Lewy bodies. J. Alzheimers Dis. 82, 913–919.
Pilotto, A., Imarisio, A., Conforti, F., Scalvini, A., Masciocchi, S., Nocivelli, S., Turrone, R., Gipponi, S., Cottini, E., Borroni, B., Rizzetti, M.C., Pizzi, M., Bonanni, L., Sturchio, A., Espay, A.J., Zetterberg, H., Ashton, N.J., Hye, A., Padovani, A., 2021b. Plasma NfL, clinical subtypes and motor progression in Parkinson's disease. Parkinsonism Relat. Disord. 87, 41–47.
Plog, B.A., Dashnaw, M.L., Hitomi, E., Peng, W., Liao, Y., Lou, N., Deane, R., Nedergaard, M., 2015. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. J. Neurosci. 35, 518–526.
Popp, J., Schaper, K., Kolsch, H., Cvetanovska, G., Rommel, F., Klingmuller, D., Dodel, R., Wullner, U., Jessen, F., 2009. CSF cortisol in Alzheimer's disease and mild cognitive impairment. Neurobiol. Aging 30, 498–500.
Popp, J., Wolfsgruber, S., Heuser, I., Peters, O., Hull, M., Schroder, J., Moller, H.J., Lewczuk, P., Schneider, A., Jahn, H., Luckhaus, C., Perneczky, R., Frolich, L., Wagner, M., Maier, W., Wiltfang, J., Kornhuber, J., Jessen, F., 2015. Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. Neurobiol. Aging 36, 601–607.
Porter, B., Macfarlane, R., Walker, R., 2008. The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. Eur. J. Neurol. 15, 50–54.
Poryazova, R., Benninger, D., Waldvogel, D., Bassetti, C.L., 2010. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. Eur. Neurol. 63, 129–135.
Postuma, R.B., Gagnon, J.F., Vendette, M., Fantini, M.L., Massicotte-Marquez, J., Montplaisir, J., 2009. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 72, 1296–1300.
Postuma, R.B., Gagnon, J.F., Rompre, S., Montplaisir, J.Y., 2010. Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 74, 239–244.
Prudon, B., Duncan, G.W., Khoo, T.K., Yarnall, A.J., Anderson, K.N., 2014. Primary sleep disorder prevalence in patients with newly diagnosed Parkinson's disease. Mov. Disord. 29, 259–262.
Pundir, M., Papagerakis, S., De Rosa, M.C., Chronis, N., Kurabayashi, K., Abdulmawjood, S., Prince, M.E.P., Lobanova, L., Chen, X., Papagerakis, P., 2022. Emerging biotechnologies for evaluating disruption of stress, sleep, and circadian rhythm mechanism using aptamer-based detection of salivary biomarkers. Biotechnol. Adv. 59, 107961.
Rana, A.Q., Siddiqui, I., Mosabbir, A., Athar, A., Syed, O., Jesudasan, M., Hafez, K., 2013. Association of pain, Parkinson's disease, and restless legs syndrome. J. Neurol. Sci. 327, 32–34.
Rauchmann, B.S., Sadlon, A., Perneczky, R., Alzheimer's Disease Neuroimaging, I., 2020. Soluble TREM2 and inflammatory proteins in Alzheimer's Disease cerebrospinal fluid. J. Alzheimers Dis. 73, 1615–1626.
Redline, S., Kirchner, H.L., Quan, S.F., Gottlieb, D.J., Kapur, V., Newman, A., 2004. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch. Intern. Med. 164, 406–418.
Santaella, A., Kuiperij, H.B., van Rumund, A., Esselink, R.A.J., Bloem, B.R., Verbeek, M. M., 2020. Cerebrospinal fluid myelin basic protein is elevated in multiple system atrophy. Parkinsonism Relat. Disord. 76, 80–84.
Schenck, C.H., Boeve, B.F., Mahowald, M.W., 2013. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med. 14, 744–748.
Sharma, R.A., Varga, A.W., Bubu, O.M., Pirraglia, E., Kam, K., Parekh, A., Wohlleber, M., Miller, M.D., Andrade, A., Lewis, C., Tweardy, S., Buj, M., Yau, P.L., Sadda, R., Mosconi, L., Li, Y., Butler, T., Glodzik, L., Fieremans, E., Babb, J.S., Blennow, K., Zetterberg, H., Lu, S.E., Badia, S.G., Romero, S., Rosenzweig, I., Gosselin, N., Jean-Louis, G., Rapoport, D.M., de Leon, M.J., Ayappa, I., Osorio, R.S., 2018. Obstructive sleep apnea severity affects amyloid burden in cognitively Normal elderly. A longitudinal study. Am. J. Respir. Crit. Care Med. 197, 933–943.
Shi, L., Chen, S.J., Ma, M.Y., Bao, Y.P., Han, Y., Wang, Y.M., Shi, J., Vitiello, M.V., Lu, L., 2018. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. Sleep Med. Rev. 40, 4–16.
Shimizu, S., Takenoshita, N., Inagawa, Y., Tsugawa, A., Hirose, D., Kaneko, Y., Ogawa, Y., Serisawa, S., Sakurai, S., Hirao, K., Kanetaka, H., Kanbayashi, T., Imanishi, A., Sakurai, H., Hanyu, H., 2020. Positive association between cognitive

function and cerebrospinal fluid orexin a levels in Alzheimer's Disease. J. Alzheimers Dis. 73, 117–123.
Shokri-Kojori, E., Wang, G.J., Wiers, C.E., Demiral, S.B., Guo, M., Kim, S.W., Lindgren, E., Ramirez, V., Zehra, A., Freeman, C., Miller, G., Manza, P., Srivastava, T., De Santi, S., Tomasi, D., Benveniste, H., Volkow, N.D., 2018. beta-amyloid accumulation in the human brain after one night of sleep deprivation. Proc. Natl. Acad. Sci. U. S. A. 115, 4483–4488.
Si, X., Guo, T., Wang, Z., Fang, Y., Gu, L., Cao, L., Yang, W., Gao, T., Song, Z., Tian, J., Yin, X., Guan, X., Zhou, C., Wu, J., Bai, X., Liu, X., Zhao, G., Zhang, M., Pu, J., Zhang, B., 2022. Neuroimaging evidence of glymphatic system dysfunction in possible REM sleep behavior disorder and Parkinson's disease. NPJ Parkinsons Dis 8, 54.
Silva-Spinola, A., Lima, M., Leitao, M.J., Duraes, J., Tabuas-Pereira, M., Almeida, M.R., Santana, I., Baldeiras, I., 2022. Serum neurofilament light chain as a surrogate of cognitive decline in sporadic and familial frontotemporal dementia. Eur. J. Neurol. 29 (1), 36–46.
Singer, W., 2022. Recent advances in establishing fluid biomarkers for the diagnosis and differentiation of alpha-synucleinopathies - a mini review. Clin. Auton. Res. 32, 291–297.
Sofroniew, M.V., Vinters, H.V., 2010. Astrocytes: biology and pathology. Acta Neuropathol. 119, 7–35.
van Someren, E.J., Hagebeuk, E.E., Lijzenga, C., Scheltens, P., de Rooij, S.E., Jonker, C., Pot, A.M., Mirmiran, M., Swaab, D.F., 1996. Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol. Psychiatry 40, 259–270.
Song, H., Moon, M., Choe, H.K., Han, D.H., Jang, C., Kim, A., Cho, S., Kim, K., Mook-Jung, I., 2015. Abeta-induced degradation of BMAL1 and CBP leads to circadian rhythm disruption in Alzheimer's disease. Mol. Neurodegener. 10, 13.
Sprecher, K.E., Koscik, R.L., Carlsson, C.M., Zetterberg, H., Blennow, K., Okonkwo, O.C., Sager, M.A., Asthana, S., Johnson, S.C., Benca, R.M., Bendlin, B.B., 2017. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. Neurology 89, 445–453.
Stopa, E.G., Volicer, L., Kuo-Leblanc, V., Harper, D., Lathi, D., Tate, B., Satlin, A., 1999. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. J. Neuropathol. Exp. Neurol. 58, 29–39.
Sunkaria, A., Bhardwaj, S., 2022. Sleep disturbance and Alzheimer's Disease: the glial connection. Neurochem. Res. 47, 1799–1815.
Suzuki, K., Miyamoto, T., Miyamoto, M., Okuma, Y., Hattori, N., Kamei, S., Yoshii, F., Utsumi, H., Iwasaki, Y., Iijima, M., Hirata, K., 2008. Excessive daytime sleepiness and sleep episodes in Japanese patients with Parkinson's disease. J. Neurol. Sci. 271, 47–52.
Swanwick, G.R., Kirby, M., Bruce, I., Buggy, F., Coen, R.F., Coakley, D., Lawlor, B.A., 1998. Hypothalamic-pituitary-adrenal axis dysfunction in Alzheimer's disease: lack of association between longitudinal and cross-sectional findings. Am. J. Psychiatry 155, 286–289.
Swardfager, W., Lanctot, K., Rothenburg, L., Wong, A., Cappell, J., Herrmann, N., 2010. A meta-analysis of cytokines in Alzheimer's disease. Biol. Psychiatry 68, 930–941.
Taguchi, T., Ikuno, M., Hondo, M., Parajuli, L.K., Taguchi, K., Ueda, J., Sawamura, M., Okuda, S., Nakanishi, E., Hara, J., Uemura, N., Hatanaka, Y., Ayaki, T., Matsuzawa, S., Tanaka, M., El-Agnaf, O.M.A., Koike, M., Yanagisawa, M., Uemura, M.T., Yamakado, H., Takahashi, R., 2020. Alpha-Synuclein BAC transgenic mice exhibit RBD-like behaviour and hyposmia: a prodromal Parkinson's disease model. Brain 143, 249–265.
Targa, A., Dakterzada, F., Benitez, I., Lopez, R., Pujol, M., Dalmases, M., Arias, A., Sanchez-de-la-Torre, M., Zetterberg, H., Blennow, K., Pamplona, R., Jove, M., Barbe, F., Pinol-Ripoll, G., 2021. Decrease in sleep depth is associated with higher cerebrospinal fluid neurofilament light levels in patients with Alzheimer's disease. Sleep 44.
Terzaghi, M., Arnaldi, D., Rizzetti, M.C., Minafra, B., Cremascoli, R., Rustioni, V., Zangaglia, R., Pasotti, C., Sinforiani, E., Pacchetti, C., Manni, R., 2013. Analysis of video-polysomnographic sleep findings in dementia with Lewy bodies. Mov. Disord. 28, 1416–1423.
Teunissen, C.E., Chiu, M.J., Yang, C.C., Yang, S.Y., Scheltens, P., Zetterberg, H., Blennow, K., 2018. Plasma amyloid-beta (Abeta42) correlates with cerebrospinal fluid Abeta42 in Alzheimer's Disease. J. Alzheimers Dis. 62, 1857–1863.
Toedebusch, C.D., McLeland, J.S., Schaibley, C.M., Banks, I.R., Boyd, J., Morris, J.C., Holtzman, D.M., Lucey, B.P., 2019. Multi-modal home sleep monitoring in older adults. J. Vis. Exp. 26, 143.
Toh, K.L., Jones, C.R., He, Y., Eide, E.J., Hinz, W.A., Virshup, D.M., Ptacek, L.J., Fu, Y.H., 2001. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 291, 1040–1043.
Tononi, G., Cirelli, C., 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81, 12–34.
Tranah, G.J., Blackwell, T., Stone, K.L., Ancoli-Israel, S., Paudel, M.L., Ensrud, K.E., Cauley, J.A., Redline, S., Hillier, T.A., Cummings, S.R., Yaffe, K., Group, S.O.F.R., 2011. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann. Neurol. 70, 722–732.
Tse, W., Liu, Y., Barthlen, G.M., Halbig, T.D., Tolgyesi, S.V., Gracies, J.M., Olanow, C.W., Koller, W.C., 2005. Clinical usefulness of the Parkinson's disease sleep scale. Parkinsonism Relat. Disord. 11, 317–321.
Turek, F.W., 2016. Circadian clocks: not your grandfather's clock. Science 354, 992–993.
Uchihara, T., 2014. Pretangles and neurofibrillary changes: similarities and differences between AD and CBD based on molecular and morphological evolution. Neuropathology 34, 571–577.
Van Egroo, M., van Hooren, R.W.E., Jacobs, H.I.L., 2021. Associations between locus coeruleus integrity and nocturnal awakenings in the context of Alzheimer's disease plasma biomarkers: a 7T MRI study. Alzheimers Res. Ther. 13, 159.
Van Egroo, M., Koshmanova, E., Vandewalle, G., Jacobs, H.I.L., 2022. Importance of the locus coeruleus-norepinephrine system in sleep-wake regulation: implications for aging and Alzheimer's disease. Sleep Med. Rev. 62, 101592.
Verbaan, D., van Rooden, S.M., Visser, M., Marinus, J., van Hilten, J.J., 2008. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. Mov. Disord. 23, 35–41.
Verbaan, D., van Rooden, S.M., van Hilten, J.J., Rijsman, R.M., 2010. Prevalence and clinical profile of restless legs syndrome in Parkinson's disease. Mov. Disord. 25, 2142–2147.
Verkhratsky, A., Nedergaard, M., 2018. Physiology of Astroglia. Physiol. Rev. 98, 239–389.
Videnovic, A., Noble, C., Reid, K.J., Peng, J., Turek, F.W., Marconi, A., Rademaker, A.W., Simuni, T., Zadikoff, C., Zee, P.C., 2014. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 71, 463–469.
Vitiello, M.V., Prinz, P.N., 1989. Alzheimer's disease. Sleep and sleep/wake patterns. Clin. Geriatr. Med. 5, 289–299.
Vitiello, M.V., Prinz, P.N., Williams, D.E., Frommlet, M.S., Ries, R.K., 1990. Sleep disturbances in patients with mild-stage Alzheimer's disease. J. Gerontol. 45, M131–M138.
Volicer, L., Harper, D.G., Manning, B.C., Goldstein, R., Satlin, A., 2001. Sundowning and circadian rhythms in Alzheimer's disease. Am. J. Psychiatry 158, 704–711.
Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W., 1975. A protein factor essential for microtubule assembly. Proc. Natl. Acad. Sci. U. S. A. 72, 1858–1862.
Wennstrom, M., Londos, E., Minthon, L., Nielsen, H.M., 2012. Altered CSF orexin and alpha-synuclein levels in dementia patients. J. Alzheimers Dis. 29, 125–132.
Wilson, G., Terpening, Z., Wong, K., Grunstein, R., Norrie, L., Lewis, S.J., Naismith, S.L., 2014. Screening for sleep apnoea in mild cognitive impairment: the utility of the multivariable apnoea prediction index. Sleep Disord. 2014, 945287.
Wisor, J.P., Pasumarthi, R.K., Gerashchenko, D., Thompson, C.L., Pathak, S., Sancar, A., Franken, P., Lein, E.S., Kilduff, T.S., 2008. Sleep deprivation effects on circadian clock gene expression in the cerebral cortex parallel electroencephalographic differences among mouse strains. J. Neurosci. 28, 7193–7201.
Wong, J.C., Li, Y., Schwarzschild, M.A., Ascherio, A., Gao, X., 2014. Restless legs syndrome: an early clinical feature of Parkinson disease in men. Sleep 37, 369–372.
Wong, R., Lovier, M.A., 2023. Sleep disturbances and dementia risk in older adults: findings from 10 years of National U.S. prospective data. Am. J. Prev. Med. 64 (6), 781–787.
Wright Jr., K.P., Drake, A.L., Frey, D.J., Fleshner, M., Desouza, C.A., Gronfier, C., Czeisler, C.A., 2015. Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. Brain Behav. Immun. 47, 24–34.
Wu, Y.H., Feenstra, M.G., Zhou, J.N., Liu, R.Y., Torano, J.S., Van Kan, H.J., Fischer, D.F., Ravid, R., Swaab, D.F., 2003. Molecular changes underlying reduced pineal melatonin levels in Alzheimer disease: alterations in preclinical and clinical stages. J. Clin. Endocrinol. Metab. 88, 5898–5906.
Xiao, S.-Y., Liu, Y.-J., Lu, W., Sha, Z.-W., Xu, C., Yu, Z.-H., Lee, S.-D., 2022. Possible neuropathology of sleep disturbance linking to Alzheimer's Disease: astrocytic and microglial roles. Front. Cell. Neurosci. 16.
Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., Takano, T., Deane, R., Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. Science 342, 373–377.
Yaffe, K., Laffan, A.M., Harrison, S.L., Redline, S., Spira, A.P., Ensrud, K.E., Ancoli-Israel, S., Stone, K.L., 2011. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 306, 613–619.
Yan, Y., Wang, C., 2006. Abeta42 is more rigid than Abeta40 at the C terminus: implications for Abeta aggregation and toxicity. J. Mol. Biol. 364, 853–862.
Yeo, B.S.Y., Koh, J.H., Ng, A.C.W., Loh, S., See, A., Seow, D.C.C., Toh, S.T., 2023. The association of obstructive sleep apnea with blood and cerebrospinal fluid biomarkers of Alzheimer's dementia - a systematic review and meta-analysis. Sleep Med. Rev. 70, 101790.
Yin, L., Wu, N., Curtin, J.C., Qatanani, M., Szwergold, N.R., Reid, R.A., Waitt, G.M., Parks, D.J., Pearce, K.H., Wisely, G.B., Lazar, M.A., 2007. Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. Science 318, 1786–1789.
Zetterberg, H., 2017. Review: tau in biofluids - relation to pathology, imaging and clinical features. Neuropathol. Appl. Neurobiol. 43, 194–199.
Zhang, P., Tan, C.W., Chen, G.H., Ge, Y.J., Xu, J., Xia, L., Wang, F., Li, X.Y., Kong, X.Y., 2018. Patients with chronic insomnia disorder have increased serum levels of neurofilaments, neuron-specific enolase and S100B: does organic brain damage exist? Sleep Med. 48, 163–171.
Zhou, J.N., Liu, R.Y., Kamphorst, W., Hofman, M.A., Swaab, D.F., 2003. Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. J. Pineal Res. 35, 125–130.