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Deepen into sleep and wake patterns across Alzheimer's disease phenotypes

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Abstract

Although, the clinical variants of Alzheimer's disease (AD) show distinct patterns of cognitive and behavioral decline, disease progression, and neuropathological features, it is unclear if this clinical heterogeneity extends to sleep-wake patterns. Sleep and wake disturbances are frequent in typical AD, often preceding memory loss and negatively impacting the quality of life of patients and caregivers alike. Still, sleep and wake disorders are often misdiagnosed and undertreated in typical AD. Better characterization of sleep-wake features in AD clinical variants is an unmet gap of high importance because these differing patterns may require tailored treatment strategies. Moreover, as wake-promoting neurons are located in subcortical nuclei and degenerate early in typical AD, contrasting the profiles of sleep-wake patterns in typical and atypical AD aids diagnosis and brings a unique opportunity to uncover the mechanisms underlying AD clinical variants at the subcortical level and mechanisms for selective neuronal vulnerability.

Open-Peer Commentary:

Atypical variants of Alzheimer's Disease (AD) manifest predominantly with non-memory complaints, including visuospatial (posterior cortical atrophy), language (logopenic variant of primary progressive aphasia), motor (cortico-basal syndrome), executive or cognitive behavioral patterns. Compared to typical (amnestic) AD, these atypical profiles are

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characterized by faster rates of cognitive decline, higher regional cortical burden of neurofibrillary tangles, and syndrome-specific atrophy patterns [1,2].

Sleep-wake disorders, as nighttime awakenings and daytime sleepiness, are common symptoms in patients manifesting typical AD. Sleep disturbance in typical AD is thought to involve exaggeration of age-related increase in nocturnal awakenings, along with a prominent decrease in slow-wave sleep (SWS), but a modest decline in total sleep and REM sleep time, and an increased propensity for daytime sleep [3]. Worsening sleep disruption along with the disease course is associated with greater cognitive decline, negatively impacts quality of life, and increases caregiver burden, and causes early institutionalization [4]. Although confluent evidence supports that sleep disturbances manifest early in the disease course, even preceding cognitive decline, misdiagnosis and undertreatment are frequent [3,5]. Moreover, evidence supporting the efficacy of the current pharmacological and non-pharmacological treatments for sleep disturbance in dementia is poor and, the balance of benefits and risks associated with these conventional treatments are still in question (daytime sedation, confusion, risk of falls, cardiac events) [5]. Altogether, it indicates that further studies aiming to improve diagnostic and therapeutic frameworks are needed.

All these factors have led to increased research efforts to elucidating the pathogenetic role of sleep disturbances in AD in the last years. Sleep loss, particularly SWS, and sleep fragmentation, may contribute causally to AD by increasing amyloid-beta (Aβ) deposition [6]. Still, Aβ alone appears insufficient to explain all causal mechanisms linking disordered sleep to AD clinical manifestations [7]. More recently, converging evidence from human sleep and neuropathological studies corroborate a primary, novel role of tau-related neurodegeneration in driving the sleep-wake dysregulation in AD [8,9].

Arousal is mediated by the ascending reticular activating system (ARAS) [10]. Several key ARAS nuclei start accumulating AD-type tau from the very early stages of the neurodegenerative process in AD, even preceding accumulation of AD-tau in the entorhinal cortex, the first cortical area to accumulate neurofibrillary tangles in AD [11, 12]. Such tau accumulation is associated with early neuronal loss and higher odds of developing neuropsychiatric symptoms, including sleep-wake disturbances [9 ,12, 13]. Among the components of ARAS, the noradrenergic *locus coeruleus* (LC), the orexinergic neurons of the lateral hypothalamic area (LHA), and histaminergic neurons of the tuberomammillary nucleus (TMN) lose from 60 to 80% of their neurons in AD [9]. The widespread affection of these subcortical nuclei by AD-tau cytoskeletal pathology has been demonstrated from the early stages of the disease (Braak and Braak AD 0 and I), before the AD-related changes occur in the mediobasal temporal lobe [14]. This observation has risen as a potential central explanation for sleep-wake dysregulation in AD. Interestingly, integrity of the LC has been demonstrated to modulate memory performance in older adults [15]. Orexin A (hypocretin 1), a neuropeptide produced by the LHA neurons, promotes arousal by activating the wake-monoaminergic systems. An essential part of the arousing effect of orexin is in turn, modulated by histaminergic projections to the posterior hypothalamus (i.e., tuberomammillary nucleus) [16]. The imbalance between these network systems leads towards the upregulation of the orexigenic function, which could be at least in part, responsible for impaired nocturnal sleep in AD as well [3]. Similarly, other areas regulating

circadian rhythms such as the suprachiasmatic nucleus are affected in AD, suggesting that a circadian component could also contribute to the disruption of sleep-wake patterns in AD [17].

Although it is plausible that mechanisms of arousal dysregulation might be different in AD variants, this hypothesis remains underexplored. Most sleep-related studies in AD, investigated typical AD cases, neglecting atypical variants [3, 18]. Therefore, whether the pattern of sleep-wake dysfunction is different among AD clinical variants and, how it is different, remains unclear.

The evidence of a faster cognitive and behavioral decline in atypical variants of AD led to a belief that sleep disturbances are more common in early-onset AD (EOAD) mainly because EOAD is enriched with atypical forms. Consequently, many studies have attempted to evaluate the differences in subjective sleep disturbances between early/late onset presentations (Table 1) or amnestic/non-amnestic variants [19, 20, 21]. Although in general advancing our understanding, these studies show discordant results, which might be explained by several methodological limitations. The use of inventories evaluating global behavioral assessment (i.e., Neuropsychiatric Inventory) instead of using more domain-specific sleep questionnaires (i.e., Insomnia Severity Index, Epworth Sleepiness Scale, sleep diary reports of time in bed and total sleep time) together with the subjective bias of caregiver-reported inventories and the potential inaccuracy of self-reported measures in individuals with memory impairment, could provide misleading information on sleep-wake dysfunction. Additionally, the variability in clinical disease staging, use of non-biomarker confirmed cohorts, and the lack of objective tools evaluating sleep and wake (i.e., polysomnography, multiple sleep latency tests, actigraphy) may have contributed to the inconsistent findings. Further studies consisting of well-characterized cohorts (i.e., biomarker-based or neuropathological diagnosis) and objective measures of sleep and wake assessment are still needed.

Identifying the differences in the sleep and wake patterns across AD clinical variants would be particularly relevant for clinicians to aid diagnosis and enable earlier detection and management. Further, the existence of specific sleep-wake profiles would suggest there are different degeneration patterns of the arousal system within AD phenotypes, which would open the door to uncover the selective vulnerability on subcortical structures for the first time.

It is plausible that heterogeneity in AD clinical variants found in many behavioral and cognitive aspects may extend to the subcortical structures and, consequently, to the sleep-wake patterns. A better understanding of the specific patterns and mechanisms for arousal disturbances within the AD clinical spectrum is an unmet need. The existence of differential sleep-wake profiles within AD variants would suggest a distinct selective vulnerability extending to the subcortical structures, requiring targeted symptomatic treatment through clinical phenotypes. Recent data show that the magnitude of degeneration of LC neurons is greater in EOAD than in late-onset AD [12]. Nevertheless, this research hypothesis is still in its infancy, and further studies, directly investigating the differences in neurobiological mechanisms underlying sleep-wake alterations across AD phenotypes, are needed. We

believe that to explore further, the differential involvement of sleep-related subcortical structures in the AD variants could reveal new potential genetic, neuronal, and molecular pathways underlying the AD heterogeneity. This would provide a better understanding of the disease itself and facilitating the identification of new targets for drug development.

Identifying the neural substrates associated with specific sleep-wake patterns is a crucial step to discover novel therapeutic avenues and promote targeted interventions for sleep disturbances in AD. Recently, we have seen this research approach succeed in the case of progressive supranuclear palsy (PSP). The detection of a profound disrupted pattern of sleep in PSP, featuring nighttime and daytime hyposomnia, along with the identification of the relative sparing of wake-regulating nuclei in the brainstem, led to the hypothesis that suppressing the wake-promoting centers with specific medications like Suvorexant, which indeed has been recently approved for the insomnia treatment, would be more beneficial to improve sleep quality in PSP individuals than the traditional approach of enhancing GABA effects using zolpidem [9, 22]. Based on this novel hypothesis, a clinical trial to test the efficacy of Suvorexant in PSP is currently ongoing (NCT04014387, Treatment of Disturbed Sleep in Progressive Supranuclear Palsy). We believe that taking a similar approach, like that used in the example in PSP, to define the differential sleep profiles in AD variants and exploring their association with specific patterns of neurodegeneration within the arousal system is a unique opportunity to develop more tailored treatment strategies for sleep disorders within the AD spectrum. Consequently, widening the options for proper treatment of arousal disorders in AD would definitively make a difference in models of care, increasing the quality of life of both patients and their families along the course of the disease.

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Table 1.

Studies evaluating differences in subjective sleep disturbances between early and late onset AD.

Article	Sample size	Assessment	Diagnostic criteria	Outcome
Baillon et al., 2019	80	NPI	NINCDS-ADRDA	EOAD worst
Ferreira et al., 2018	70	NPI	NIA-AA **	No differences
Mushtaq *et al.*, 2016	80	NPI	NINCDS-ADRDA	LOAD worst
Park *et al.*, 2014	870	NPI	NINCDS-ADRDA	No differences
Hori *et al.*, 2005	68	DBD	ICD-10	EOAD worst

*All participants have CT or MRI. A proportion of patients also had information available on CSF or FDG-PET.

NPI, Neuropsychiatric Inventory; DBD; Dementia Behavior Disturbance Scale; EOAD, early onset Alzheimer disease; LOAD, late onset Alzheimer disease; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; ICD-10, International Statistical Classification of Diseases and Related Health Problems, NIA-AA, National Institute on Aging/Alzheimer's Association