INTRODUCTION

Circadian rhythms are 24 h oscillations within biochemical and cellular life processes [1]. The first mammalian clock gene, CLOCK, was identified in 1994 [2], and several mammalian clock genes (i.e., PER1, PER2, NR1D1, BMAL1) have been discovered since [3-5]. The mammalian cellular circadian clock is based on autonomous transcriptional and translational feedback loops comprising these clock genes. Additionally, the suprachiasmatic nucleus (SCN) of the hypothalamus is a mammalian master clock that generates and maintains physiological and behavioral oscillations, with SCN lesions affecting circadian temperature and rest-activity rhythms [6-8].

Diurnal rest-activity patterns are critical circadian rhythm outputs generated by the SCN. Several rest-activity pattern alterations have been reported with aging, including fragmented and blunted rest-activity rhythms [9]. Additionally, impacts on the advanced phase of rest-activity and sleep patterns are among the most well-known characteristics in older adults. Older adults tend to sleep earlier in the evening and to wake up earlier than desired [10]. However, controversy exists as to whether rest-activity pattern or circadian phase alterations are driven by normal physiological aging processes or by pathological neurodegenerative processes [11,12]. Reciprocal connections among circadian rhythm disruption and neurodegenerative processes also need to be considered. For example, recent animal studies using a genetic circadian rhythm deficit model suggest that circadian disruption in animals can accelerate neurodegenerative processes by affecting biological mechanisms associated with Alzheimer’s disease [13-16]. In contrast, neurodegeneration in rest-activity and sleep-regulating regions likewise presents a critical mechanism affecting rest-activity patterns or circadian phases. For example, the lo-
Circadian Rhythm in Alzheimer’s Disease

Circadian rhythm disruption and neurodegeneration [21]. Rest-activity pattern and circadian phase changes within various stages of neurodegenerative disease can be helpful in understanding the temporal and causal relationships between circadian rhythm disruption and neurodegeneration [21]. Rest-activity pattern and circadian phase alterations might serve not only as a biomarker for diagnosis but also as disease course or prognosis of Alzheimer’s disease. In addition, intervention to optimize or restore circadian function can be considered as a treatment option in patients with Alzheimer’s disease. The purpose of this article is to review the historical and recent evidence regarding potential associations of actigraphy-derived rest-activity pattern and circadian phase parameters with clinical or biomarker characteristics in patients with Alzheimer’s disease.

ACTIGRAPHY- Derived Rest-Activity Pattern and Circadian Phase: Nonparametric and Cosinor Analyses

Nonparametric analysis does not present a priori assumptions for the waveform of diurnal activity rhythm. Instead, this modality evaluates rest-activity and circadian phase based on raw activity counts [22]. Parameters for nonparametric analysis include 1) interdaily stability (IS, representing the strength of coupling with respect to rhythms and environmental zeitgebers), 2) intradaily variability (IV, representing rest-activity pattern fragmentation in one day), 3) relative amplitude (representing rest-activity rhythm amplitude), 4) the least active 5 h (L5) onset time, and 5) the most active 10 h (M10) onset time.

In contrast, cosinor analysis fits activity counts to cosine curves using least-square methods for assessing rest-activity and circadian phase [23]. Parameters for cosinor analysis include 1) robustness (i.e., goodness of fit for the cosine curve, representing the strength of rhythms within circadian activity), 2) midline estimation of rhythm statistics (representing the mean of the activity fitted curve), 3) amplitude (peak to nadir differences in activity, representing circadian activity amplitude), and 4) acrophase (timing of peak activity, representing the rest-activity phase).

REST-ACTIVITY PATTERN AND CIRCADIAN PHASE ALTERATIONS IN PRECLINICAL ALZHEIMER’S DISEASE OR MILD COGNITIVE IMPAIRMENT

In the study profiled here, participants with preclinical Alzheimer’s disease were identified as cognitively normal individuals with Alzheimer’s-associated brain biomarkers, such as amyloid deposition in the brain identified via positron emission tomography (PET), as well as Alzheimer’s-associated tau and amyloid protein levels measured in the cerebrospinal fluid [24]. These findings suggest that Alzheimer’s disease starts long before various symptoms become apparent. Although participants at the preclinical Alzheimer’s disease stage are usually identified only in research settings, Musiek et al. [25] carefully assessed rest-activity alterations and circadian phase markers in 189 cognitively normal older adults via PET; this study enrolled 50 older adults positive for amyloid deposition in the brain. The researchers showed that increased IV, indicating rest-activity pattern fragmentation, was associated with an increased cerebrospinal fluid phosphorylated-tau to amyloid beta-42 ratio. Additionally, the researchers found that aging was associated with several circadian rest-activity parameters independent of preclinical Alzheimer’s disease pathology, especially in men. Another study performed in the Republic of Korea demonstrated that participants with preclinical Alzheimer’s disease present with an earlier circadian phase upon actigraphy [26]. In this study, the researchers suggested that preclinical Alzheimer’s disease made the effects of age-associated phase advance more prominent. However, the patients, who were clinically diagnosed with Alzheimer’s disease, exhibited a later circadian phase on actigraphy. As of the current review, the above two results are the only evidence to date suggesting possible associations of preclinical Alzheimer’s disease pathology with rest-activity pattern and circadian phase in patients in the preclinical stage of the disease.

Mild cognitive impairment (MCI) due to Alzheimer’s disease is a stage between preclinical Alzheimer’s disease and dementia due to Alzheimer’s disease [27]. Patients with MCI usually have objective cognitive impairment but do not have difficulties in activities of daily functioning [28]. Several reports have assessed rest-activity pattern and circadian phase alterations within MCI. For example, in 2014, Ortiz-Tudela et al. [29] assessed rest-activity and temperature rhythms in 21 participants with MCI via actigraphy and found that participants with MCI present with phase advances in both activity and temperature rhythms as compared with healthy controls. Another study performed in Hong Kong demonstrated different results [30]. In this study, Lee et al. [30] recruited 174 older adults (including 123 older adults with normal cognition and 51 patients with MCI). There were no statistically significant baseline differences in rest-activity pattern or circadian phase when comparing cognitively normal older adults and patients with MCI in this study. However, multinomial logistic regression suggested that participants showing delayed acro-
phase upon cosinor analysis were more likely to present with worse cognitive function. Another study conducted in the Republic of Korea that enrolled 70 participants with MCI and 30 with mild dementia suggested that amyloid-positive participants had a later L5 onset time on nonparametric analysis as compared with their amyloid-negative counterparts [31]. However, these researchers did not evaluate rest-activity pattern or circadian phase in cognitively normal older adults or in healthy controls. Finally, in 2020, Li et al. [32] published study results regarding longitudinal associations of rest-activity patterns and circadian phase parameters with clinical conversion of normal cognition to MCI or Alzheimer’s dementia. This study enrolled 1,401 older adults (aged >59 years) from within the Rush Memory and Aging Project and found that an increased risk of Alzheimer’s dementia conversion among patients with MCI can be predicted via lower amplitude, higher IV, and lower IS. Additionally, the researchers also found that circadian amplitude, acrophase, and IS decreased with aging and that IV increased with aging in the older adult population. This study suggests a potential bidirectional relationship and common underlying pathophysiological mechanisms between circadian rhythm disruption and Alzheimer’s disease progression.

**REST-ACTIVITY PATTERN AND CIRCADIAN PHASE ALTERATIONS IN DEMENTIA DUE TO ALZHEIMER’S DISEASE**

Rest-activity pattern and circadian phase alterations have also been evaluated in patients with dementia occurring due to Alzheimer’s disease. One historical report was published in 1996 by van Someren et al. [33]. This study assessed 34 patients with Alzheimer’s disease who were living at home or in a nursing home and showed that changes in rest-activity patterns were stronger in the institutionalized patients. Additionally, this study assessed the possible associations of rest-activity patterns and circadian phase parameters with daytime activity and environmental light exposure; daytime activity and environmental light exposure were found to be meaningful predictive factors. Another critical report was published by Hatfield et al. [34] in 2004. In this study, patients with moderate Alzheimer’s disease presented with decreased IS, increased IV, and decreased amplitude upon actigraphy. However, the degree of disruption for each parameter was not specifically correlated with dementia severity.

In 2015, a study conducted by Wang et al. [35] suggested a possible association between rest-activity patterns and vasoactive intestinal peptide-expressing SCN neuron neurodegeneration among older adults. In this study, the number of vasoactive intestinal peptide immunoreactive neurons in the SCN was positively associated with circadian rhythm amplitude with respect to motor activity in both patients with Alzheimer’s disease and in age-matched healthy controls. Additionally, patients with Alzheimer’s disease exhibited a delayed circadian phase as compared with healthy controls. In 2016, La Morgia et al. [36] reported that 16 participants with mild to moderate Alzheimer’s disease presented with reduced relative amplitude and daytime activities as compared with 10 healthy control participants. In this study, the researchers stated that rest-activity patterns and their dysfunctions appear to exhibit substantial variability between individuals. Our team presents similar results with respect to insights into the large individual variability among rest-activity patterns and circadian phase parameters in this regard. For example, in a prior paper, we extracted data on rest-activity patterns and circadian phase parameters from 100 patients with MCI or mild dementia enrolled in the Biobank Innovation for Chronic Cerebrovascular Disease with Alzheimer’s Disease Study and found that rest-activity patterns and circadian phase parameters were normally distributed with a large variance [31]. Additionally, recently published articles have evaluated not only sleep, rest-activity patterns, and circadian phase parameters, but have also investigated postmortem neocortical microglial marker gene expression with respect to measured cognitive function [37]. A total of 685 older adults (265 with Alzheimer’s dementia and 420 without) were evaluated in the latter study, although only a subset of study participants had postmortem neocortical gene expression data. This study demonstrated that greater sleep fragmentation upon actigraphy may be associated with higher neocortical microglial marker gene expression and worse cognitive function. However, the researchers did not find a statistically significant association between circadian rhythmicity (IS) and microglial marker gene expression levels. These findings suggest that microglial activation may be specifically associated with sleep fragmentation and not with circadian rhythmicity. However, caution is needed in the interpretation of these results, as this investigation did not evaluate other rest-activity or circadian phase variables, such as IV or amplitude.

Several additional studies have evaluated potential cross-sectional or longitudinal associations of rest-activity patterns and circadian phase parameters with clinical and biomarker characteristics in patients with dementia [38-42]. However, clinical or biomarker-based Alzheimer’s disease diagnoses were not performed in these investigations. Considering the potential moderating effects of cortical Alzheimer’s disease pathology on rest-activity pattern, and possible noise effects of resting tremors on rest-activity pattern parameters in patients with Lewy body dementia, future research should consider the specification of dementia clinical diagnoses, such as Alzheimer’s dementia, vascular dementia, frontotemporal dementia, and Lewy body dementia. Recently developed neuroimaging biomarkers and detailed clinical evaluations with structured neuropsychological tests need to be considered in future research as well.

**CONCLUSION**

This narrative review provides a comprehensive presentation with respect to actigraphy-derived rest-activity pattern and circadian phase alterations in patients with Alzheimer’s disease. To the best of our knowledge, only two previous studies have assessed
rest-activity patterns and circadian phase in the preclinical Alzheimer’s disease stage. These studies have shown inconsistent results. Additionally, several studies have assessed rest-activity patterns and circadian phase alterations among patients with Alzheimer’s dementia. The most replicated findings demonstrate delayed phase and increased activity fragmentation, represented as increased IV on actigraphy readings. Unfortunately, many studies assessing rest-activity patterns in dementia have not evaluated neuroimaging biomarkers and have not conducted structured neuropsychological examinations. This has limited the specification of dementia clinical diagnoses within many investigations. In addition, actigraphy-derived rest-activity pattern and circadian phase parameters are likely to be influenced by several confounding factors such as physical activity, mealtime, weekend, and seasonal effect. The influence of confounding factors can be minimized by using clinical and research guideline such as the Society of Behavioral Sleep Medicine guideline [43]. Future studies should consider a more comprehensive assessment of a range of clinical and biomarker characteristics among patients with dementia due to Alzheimer’s disease.

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Conflicts of Interest
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REFERENCES


