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From Animal Models to At-Home Monitoring: The Translational Potential of Sleep Spindles as Non-invasive Biomarkers for Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is becoming more common and putting serious pressure on global health. Current Amyloid-β (Aβ) deposition and tau protein hyperphosphorylation are two main biomarkers of AD. Clinical diagnostic approaches depend on invasive detection of amyloid-β (Aβ) deposition and tau protein hyperphosphorylation through cerebrospinal fluid (CSF) analysis, positron emission tomography (PET) imaging or blood-based biomarker (BBM) testing. Evidence showed by recent studies have identified that slow-wave-sleep spindle coupling as potential non-invasive biomarkers of neurodegeneration for AD patients. Yet, the causality between spindle disruption and cognitive decline remains unknown. This paper examines the evidences from human, rodent models, and nonhuman primate (NHP) models of recent studies. This study presents how slow wave-spindle coupling reflects prefrontal-hippocampal, thalamocortical function. And it evaluates the contributions of NHPs researches for understanding the causal mechanisms. The findings provide supportive evidence that slow-wave-spindle activity is a reliable marker of thalamocortical integrity and prefrontal-hippocampal function correlating with cognitive decline for AD. Study shows the non-rapid eye movement (NREM) spindle and slow oscillation (SO) activity are predictive and non-invasive biomarkers for AD. The disruption of spindle-SO coupling is associated with Aβ deposits of AD. This predictive biomarker of AD points toward future directions for early detection and clinical interventions. These findings enable standardized predictive detection, home-based electroencephalography (EEG) monitoring and closed-loop stimulation techniques that could strengthen the clinical translation.

Keywords: Alzheimer's disease, Sleep spindles, Slow wave-spindle coupling, Electroencephalography (EEG)

1. Introduction

In 2023, adults aged 60 and over accounted for more than 14% of the global population. This figure will increase to over 20% by year 2050 [1]. As the population ages, neurodegenerative diseases like AD and other dementias are becoming more common. This is putting serious pressure on society [2]. AD has ranked as the second leading cause of disability-adjusted life years (DALYs) among

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adults aged 60 and over [3]. A critical question exists for early detection of AD and other dementias. The reliable predictive, non-invasive biomarkers for this purpose are essential. The current approaches of diagnostic are cerebrospinal fluid (CSF) analysis, positron emission tomography (PET) imaging, or blood-based biomarker (BBM) testing. These approaches are limited by their invasive nature. Their high cost and restricted accessibility make it difficult for large-scale screening in older adults. These challenges highlight the urgent need for precise AD biomarkers for early detection and scalable clinical interventions.

Recent researches show that spindle activity predicts long-term cognitive readouts, which suggests that spindle may serve as a non-invasive biomarker. The study by Páez and his colleagues [4] shows that NREM sleep spindle and SO activity constitute predictive and non-invasive biomarkers of neurodegeneration and mild cognitive impairment (MCI) in AD. The result shows the higher spindle activity predicted a better cognitive performance in 36 months [4]. Spindles are generated by thalamocortical circuits. It is closely linked to synaptic plasticity, memory consolidation, and cognitive function. Yet, researches show correlative evidence between spindle-SO coupling with cognitive decline, but not the causal mechanisms. This is why studies from NHP models become essential. By studying female macaques, Davis et al. [5] showed neuroendocrine changes during aging, perturbed sleep-wake cycles, and cognitive decline. With NHPs models, it can implement invasive neurophysiological recordings and causal manipulations that are not possible in human studies. Their neuroanatomical proximity to humans makes them the most relevant translational model for human's neural circuits studying.

This study addresses the predictive and non-invasive biomarker question by reviewing evidence from researches on sleep spindles of AD. It is including human, rodents model, and NHPs model studies on prefrontal-hippocampal circuit dysfunction in cognitive decline.

2. Sleep spindles: as biomarkers of prefrontal-hippocampal function in AD

2.1. Sleep spindles and slow wave-spindle coupling in AD

Sleep spindles are brief bursts of 11-16 Hz oscillatory activity generated by thalamocortical circuits. They are tightly linked to synaptic plasticity and memory consolidation. During NREM sleep, spindles interact with slow oscillations (SOs) and theta bursts, which facilitate the short-term memory transferring from hippocampal to neocortical storage then become long-term memory. This cross-regional coordination depends on the precise temporal coupling of these rhythms. Any disruptions to this coupling can cause impairment in memory consolidation.

The coupling of spindles and SO is particularly essential to AD patients. Wunderlin et al. [6] analyzed 47 older adults across three clinical trials. They found that slow-wave-spindle coupling was the best predictor of baseline plasma Aβ levels and cognitive function. The study shows that better Aβ levels linked to spindle-SO coupling patterns seen in a younger brain [6]. The study by Wei et al. [7] studied 93 individuals across the AD spectrum. They observed spindle-SO coupling frequency decreased from cognitively normal to mild cognitive impairment (MCI), and further declined from MCI to AD dementia [7]. The medial prefrontal cortex atrophy was specifically associated with disruption of SO-spindle coupling [7]. In turn, this disruption also predicted accelerated cognitive decline over two years' time. Furthermore, integrating sleep EEG with CSF and magnetic resonance imaging (MRI) has been shown to enhance the predictive accuracy for AD. This shows the evidence that sleep rhythms could serve as essential biomarkers for clinical intervention [7].

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2.2. Frequency specificity and cross-disease evidence

Spindles have specific frequency and location. Fast spindles (13-15 Hz, in centroparietal regions) and slow spindles (11-13 Hz, in frontal regions) are generated by different thalamocortical circuits. AD and MCI patients show a significant parietal fast spindle density decrease, correlated with cognitive decline severity [7]. The evidence shows that fast spindles may be more sensitive to AD pathology than slow spindles. But spindle density and duration may be more sensitive biomarkers than frequency. These differences may be because fast and slow spindles reflect different aspects of prefrontal-hippocampal integrity. They may be selectively affected by different pathologies. Castelnovo et al. [8] observed similar abnormalities in patients with disorders of arousal. This suggests a broader role for spindle alterations across diseases with thalamocortical dysfunction.

2.3. Mechanistic evidence from animal models and translational relevance

Animal studies provided the evidence for mechanisms of spindle alterations. SO, sleep spindles and their coupling are consistently reduced in both AD patients and AD mouse models [9]. In control mice, spindles-SO coupling is strengthened during post-task sleep. This coupling is associated with next-day performance. Katsuki et al. [9] studied SO (0.1-1Hz), sleep spindles (8-15Hz), and their coupling during NREM sleep in AD mouse models. The coupling is consistently reduced in all AD mouse models. However, the timing and level of these alterations depend on the specific pathophysiology and animal model studied. Cushing et al. [10] found that hippocampal-cortical interactions during sleep are impaired in the 3xTg-AD mouse model. The impairment is associated with deficits in spatial reorientation learning and memory. These findings further helped to explain the link between spindle-SO coupling and AD with cross-species models.

The spindle activity readout reflects the prefrontal-hippocampal integrity. These regions are functionally interacted via shared circuits that generate and modulate spindles. The hippocampus modulates spindle activity through its connections with the medial prefrontal cortex (mPFC). This is not a one-way relationship. The hippocampus influences cortical slow oscillations. This oscillatory activity in turn synchronizes to form spindle waves. If hippocampal function is impaired, this coordination is disrupted. Meanwhile, if prefrontal cortex is dysfunctional, spindle activity is also affected. Therefore, the density, amplitude, frequency, and topography of spindle reflect the functional state of this circuit. In AD, early pathological features are primarily localized to the hippocampus and medial temporal lobe regions [11]. It explains why the abnormality of spindle waves also appear in early stage of the disease. This makes spindle waves a highly valuable potential biomarker for early detection.

There are several limitations are needed for further consideration. Most of the human studies rely on nocturnal polysomnography conducted in a laboratory setting rather than natural sleep patterns. There are significant differences in the spindle detection algorithms used across studies, which cause complicated comparisons of their study results. The reliable measurement of early fast spindles especially for higher-frequency spindles in posterior recordings is also the technical limitation. Whilst there is an association between spindle abnormalities and neurodegenerative diseases. The nature of the causal relationship remains unclear. A translational gap between animal models and human applications still exists. The changes in spindles in rodents may reflect not only pathological features specific to Alzheimer's, but also general age-related cognitive decline, fragmented sleep, or comorbid conditions. The question is whether the changes in spindle occur before or after Aβ. It remains to be addressed in further longitudinal studies.

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Although with these limitations, the evidence provided by studies still suggests that spindle activity offers a non-invasive readout of prefrontal-hippocampal functional integrity. This is interpreted by observations of thalamocortical circuits regulating on spindles, association between spindle abnormalities and cognitive decline in AD, and converging evidence from animal models. However, to address the gap between this evidence and causal mechanisms the non-human primate (NHP) models become particularly valuable. NHPs are expected to provide further evidence that human studies and rodent models cannot provide. This will help to identify a clearer mechanism.

3. The value and limitations of NHP models in translational sleep research

Normally, post-mortem brain tissue is used to validate hypotheses from animal or human studies. But, SO-spindle coupling does not exist in post-mortem brain tissues. This makes NHPs more valuable for verifying SO-spindle coupling correlation with AD cognition decline.

The human studies have confirmed that slow-wave spindle coupling can predict cognitive performance in patients with Alzheimer's disease [6, 7]. However, these findings are only correlational. They suggest that the disruption of coupling occurs concurrently with cognitive decline. Yet, they did not indicate causal relationship existing between slow-wave coupling and cognitive decline, where NHP model offers the possibility to fill the gap. Liu et al. [12] reported recordings from thalamic neurons in macaques during natural sleep. They found the thalamic bursts during NREM sleep were neither periodic nor highly synchronized. In contrast, the state-dependent thalamocortical dynamics involving spindle activity were able to suppress cortical arousal. This suggests that the thalamus actively shapes sleep oscillations, instead of only transferring signals. These findings are corresponded to the perception of spindle waves that observed in humans. Yazdanbakhsh et al. [13] conducted a study using computational modelling of thalamocortical loops in primates. They found that the spindles in primates are more homogeneous than those in rodents. This supports the view that NHP models are more reliable for capturing dynamic changes relevant to humans. Data from both humans and non-human primates point to the thalamocortical system as a key mechanism for cognitive and memory. However, it is not possible to conduct further invasive experiment in human to confirm the pattern found in NHP models due to ethical and technical limitations. NHP models offer unique advantages for studying sleep spindles. They enable invasive and causal manipulations, which are not feasible in humans. Therefore, human studies cannot provide causality alone. Liu et al. [12] demonstrated by inhibiting activity in the thalamic reticular nucleus of macaques not only reduced spindle density but also impaired subsequent performance on a delayed matching task. This provides direct evidence that spindle disruption causes cognitive deficits in NHPs.

Brennan-Saremski et al. [14] also compared spindles in humans, macaques, rats and mice. They identified significant morphological differences. Spindles presents in range of 12 to 16 Hz. as distinct and narrow-band events in humans. In macaques, spindles are less distinguishable and have a broader frequency range between 8 to 14 Hz. While in rats and mice, spindles are more diffuse and exhibit a much wider range of variation comparing to humans and macaques. Therefore, spindles in primates are closer to those in humans, but the two are not entirely the same. This evidence that findings from NHP species are more reliable than those from rodent species. However, the frequency ranges of spindles in NHP differ from those in humans. Findings from previous studies on NHP may not be entirely applicable to human biomarkers. These NHP studies typically involve small sample sizes which limits the statistical power of evidence. The ethical and practical constrains are more complex in NHPs models. And applying similar algorithmic assumptions for

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spindles detection not be appropriate for cross-species comparison. All these limitations restrict the translation of NHP research to clinical applications.

The guideline to improve the translation pathways is required. Standardized detection methods are needed to improve cross-species spindle algorithms. The NHP models closed-loop regulation can be used to test closed-loop interventions. It includes time-controlled acoustic and electrical stimulation such as wearable home-use EEG targeting the timing of spindle onset. The longitudinal studies (from healthy cohort to Alzheimer's) will help to identify which interventions are broadly applicable. Mechanisms which combining findings from NHPs and observational human data will strengthen the further evidence base. NHPs has evidenced that spindle activity reflects the function of thalamocortical circuits. The consistent findings in NHPs about slow-wave-spindle coupling and pathophysiology of AD reflects humans as well. Castelnovo's [14] research extends this concept to sleep disorders, revealing abnormal spindle activity in various conditions. With these advances, NHP models are expected to bridge the gap between mechanistic understanding and clinical application.

4. Conclusion

This study analyzed evidence from three mutually corroborating lines of research. Previous researches on humans and rodent studies have shown that slow-wave-spindle coupling is correlated with cognitive decline in AD patients. And the studies in NHPs have provided evidence that this coupling also reflects the operational function of thalamocortical circuits where produces spindles. Studies in human and rodents' have revealed a correlation, whilst NHPs models have established causation. Taken together, these studies identify sleep spindles as a non-invasive biomarker of integrity in the prefrontal-hippocampal region. These findings are essential for clinical applications. Due to current biomarkers has limitations of invasive and high cost, researches are also limited to small-scale screening. With predictive slow-wave-spindle coupling biomarker by using EEG, it provides the possibility of detecting AD in earlier stage for older adults than before. This is why NHPs studies are more essential for providing solid evidence for humans' trials and clinical applications. Yet, the spindle waves pattern in NHPs are differ from those in humans of frequency and morphology. And detection methods have not yet been fully standardized. Although with these limitations, NHPs provides more reliable evidence to further validate spindle activity as an AD biomarker.

Looking forward, standardized NHPs spindle detection algorithms need to be developed for different species. To address the credit of slow-wave-spindle coupling for AD biomarker, longitudinal NHPs studies are expected to provide temporal relationship evidence between spindle changes and Aβ deposition. The closed-loop modulation techniques in NHPs, such as synchronize the timing of spindle activity through auditory or electrical stimulation also worth for further studies. This will facilitate the early detection of AD and effective early clinical interventions, such as wearable EEG devices. The translation of NHP research findings to clinical application directs toward home-based monitoring. Now, sleep EEG can be performed with portable single-channel devices which are suitable for home use. Although, the translation of spindle-based biomarkers for home use faces numerous challenges. The signal quality from wearable EEG is lower than that from laboratory polysomnography. Automated spindle detection algorithms have to be validated under a variety of recording conditions. And the relationship between home-recorded spindle metrics and cognitive outcomes also needs to be established through longitudinal studies. These approaches could ultimately lead to wearable devices that enable early detection and intervention in older adults at risk of AD.

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