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Mechanisms of Sleep Spindle-Mediated Memory Dysfunction in Alzheimer's Disease and Clinical Translation Directions

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory loss. AD is the most common type of dementia, accounting for about 60% to 80% of all dementia cases. Typical pathological features include extracellular β -amyloid protein (Aβ) deposition to form senile plaques, and intracellular hyperphosphorylated tau protein aggregation to form neurofibrillary tangles, and these pathological changes usually begin decades before clinical symptoms appear. More and more evidence shows that sleep disorder appears in the prodromal stage of AD. Sleep spindle wave during NREM sleep is an important electrophysiological oscillation, which is helpful to memory consolidation. This paper systematically integrates the existing research evidence, links the dysfunction of sleep spindle wave with cognitive decline, and introduces the physiological generation of sleep spindle wave and its core role in memory consolidation. We further summarized the characteristic decrease of fast spindle density, duration and σ power in patients with mild cognitive impairment and Alzheimer's disease, and clarified how Aβ deposition, tau protein pathology and neuroinflammation interfere with thalamic-cortical circuits, thus causing spindle abnormalities. In addition, this paper also introduces the experimental neural regulation strategy for sleep spindle. This study emphasized the transformation potential of sleep spindle as a non-invasive early biomarker, and provided theoretical support for developing a new dry pre-target for sleep-related Alzheimer's disease.

Keywords: Alzheimer's disease, sleep spindle, β -amyloid protein, non-rapid eye movement

1. Introduction

With the acceleration of global population aging, Alzheimer's disease (AD) has become one of the most serious public health burdens in the world. AD is characterized by gradual memory loss and irreversible neuronal damage caused by amyloid-β plaque and tau neurofibrillary tangles. Clinical diagnosis is usually made after obvious cognitive dysfunction, at which time a lot of pathological changes have accumulated. Traditional detection methods, such as cerebrospinal fluid detection and amyloid PET imaging, are limited because of their high invasiveness and high cost, so it is urgent to develop accessible biomarkers for early screening [1].

Growing studies have confirmed bidirectional interactions between AD pathology and sleep dysfunction. Sleep microstructure disorders precede overt cognitive symptoms, and non-rapid eye movement sleep participates in the clearance of toxic protein aggregates in the brain [2]. Sleep

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spindles originating from thalamo-cortical loops are critical for memory consolidation. Recent clinical cohorts observed significant spindle parameter declines in asymptomatic AD high-risk populations and mild cognitive impairment individuals. Nevertheless, existing literatures lack systematic sorting of the causal chain connecting AD pathological proteins, spindle oscillation damage and memory dysfunction. Moreover, the biomarker value and intervention potential of sleep spindles have not been comprehensively summarized [3, 4].

In order to fill this research gap, this paper first expounds the physiological basis of sleep spindle and its mechanism in memory consolidation. Secondly, the phenotypic changes of parasomnia spindle in pedigree disorder of Alzheimer's disease and its potential mechanism were analyzed. Finally, this review discusses the experimental intervention measures for the sleep spindle and the obstacles in the related transformation research. The purpose of this framework is to clarify how the sleep spindle connects the pathology and memory dysfunction of Alzheimer's disease, and to provide inspiration for the subsequent transformational research.

2. The physiological basis of sleep spindles

2.1. The basic characteristics of sleep spindles

Sleep spindle wave mainly affects the central area and parietal lobe area of the brain, showing a roughly symmetrical and synchronous pattern in both hemispheres, and has observable amplitude modulation. Its amplitude is usually less than 100 microvolts, rarely more than 150 microvolts, and it will not last. External stimuli, such as sound or pain, may terminate sleep spindle waves or induce K complex waves. According to frequency, spindle waves can be divided into two subtypes: slow spindle waves (9–12 Hz) and fast spindle waves (12–15 Hz). During the development process, the sleep spindle wave first appeared at about the seventh week after birth, and stabilized after two months. If the spindle wave can't be detected until three months old, it indicates that the EEG activity is mature and abnormal [5].

2.2. The mechanism of sleep spindles generation

Sleep spindle wave originates from synchronous neuronal oscillation in thalamus, and its coordination is realized by the interaction between thalamus, thalamic reticular nucleus (TRN) and cerebral cortex. Isolated thalamic brain slices can independently generate spindle wave oscillation [6]. Sleep spindle wave originates from the explosive discharge of TRN neurons and thalamic cortical transmission neurons, forming a typical oscillation activity transmitted along thalamic-cortical pathway. The inhibitory output from TRN neurons will strongly depolarize thalamic-cortical transmission cells. After depolarization, the activation of non-selective cation current Ih depolarizes thalamic-cortical neurons, opens T-type calcium channels, and triggers the rebound action potential burst when the inhibitory postsynaptic potential terminates. The inhibitory signal diffuses from TRN to thalamic transmission nucleus, thus starting the sequential spindle wave. Calcium-mediated signal transduction transmits excitement back to TRN neurons and closes the oscillation circuit. Thalamic-cortical afferent fibers activate pyramidal cells in the fourth layer of cortex, induce excitatory postsynaptic potentials, and maintain the continuous oscillation of spindle waves. Although the thalamus itself can produce spindle activity, its synchronization and wide spread in the whole cortex depend on the feedback mechanism in the thalamus-cortex circuit [6].

Thalamus plays a key role in transmitting sensory input to cortex. Specific thalamic nuclei mediate point-to-point sensory projection, while non-specific reticular input regulates the

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excitability of the whole cortex. Cortical activity will be fed back to thalamus, which dynamically regulates the excitability of cortical neuron population.

3. Sleep spindles and memory consolidation

3.1. Sleep and memory

Sleep is an indispensable physiological basis for memory consolidation, and playing a synergistic role in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages is conducive to the long-term storage of different types of memories [7]. NREM sleep mainly promotes the development of declarative memory [7]. The core mechanism of NREM sleep is the reactivation of hippocampal sharp wave rippling (SPW-R) coupled neuronal clusters, which form a three-phase coupling with cortical slow oscillations and spindle waves to realize information transmission between the hippocampus and neocortex, and reshape memory traces through plasticity changes in synaptic transmission (such as long-term potentiation) [7]. At the same time, the specific pathways are enhanced through "upscaling" in the context of global synaptic "downscaling" [7]. REM sleep focuses on the consolidation of emotional memory, social memory and procedural memory, and its mechanism involves long-term reactivation of specific neurons, selective pruning and strengthening of dendritic spines, and the regulation of hippocampal activity by hypothalamic SuM, MCH and other neurons, and even active forgetting of irrelevant information [7]. The two phases do not operate in isolation, but complement each other through sequential alternating -- NREM stage marks and transmits memory information, while REM stage performs synaptic pruning and fine modification to maintain the homeostasis and efficiency of synaptic network [7]. Under pathological conditions (such as sleep deprivation or Alzheimer's disease), impaired NREM reactivation or abnormal SPW-R directly lead to impaired memory consolidation, suggesting that the mechanism of sleep regulation of memory has important translational medical significance [7]. How sleep mediates the contradiction between global downscaling and local upscaling, the role of glial cells in this process, and whether the brain regions controlling sleep phases are directly involved in memory regulation are still needed to fully understand the neural circuit mechanism of sleep promoting memory consolidation [7].

3.2. Mechanisms by which sleep spindles promote memory consolidation

Related behavioral and electrophysiological studies show that the density, quantity and intensity of sleep spindle waves are positively correlated with declarative memory tasks (such as word pairing associative learning) and the consolidation of procedural memory. The decrease of spindle wave activity is consistent with memory impairment in aging, schizophrenia and Alzheimer's disease [8]. Causal intervention experiment further verified its function. Enhancing spindle wave oscillation by transcranial alternating current stimulation or GABA-A receptor modulator (such as zopiclone) can improve memory performance. On the contrary, the suppression of TRN inhibitory neurons by photogenetics or the reduction of spindle wave intensity by drugs will damage memory consolidation, and the impact is limited to the cortical area activated by tasks, indicating that spindle wave matches the local plasticity demand [8].

At the synaptic level, spindle frequency stimulation synchronized with presynaptic discharge induces long-term enhancement of cortical pyramidal neurons by activating L-type calcium channels and promoting the influx of dendritic calcium ions. Asynchronous stimulation can't produce the same effect. Dendritic calcium signal further promotes the formation of new dendritic spines [8]. At

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the system level, the accurate slow oscillation-spindle-ripple coupling creates a time window for the replay and redistribution of hippocampus memory to neocortex network. Therefore, sleep spindles are not only an incidental phenomenon of memory consolidation, but also can actively regulate declarative memory and procedural memory by realizing synchronization-dependent synaptic plasticity, support system-level memory playback, and promote the remodeling of neural structure [8].

4. Abnormal sleep spindles in AD and possible mechanisms

4.1. Changes in sleep spindles in AD patients

Mild cognitive impairment (MCI) is a transitional stage between normal aging and Alzheimer's disease (AD), which is characterized by good daily life function, but impaired semantic memory, thus affecting situational memory and working memory. In MCI patients and asymptomatic tau protein positive elderly people, the microstructure changes such as sleep spindle wave have changed significantly, and gradually increased with time, and finally developed into AD.

4.1.1. Changes in sleep spindles

Sleep spindle density is currently recognized as the sleep microstructure indicator most closely related to cognitive function. Multiple cross-sectional and longitudinal studies have consistently shown that the decline of fast spindle density is significantly associated with memory impairment and cognitive decline. In patients with Alzheimer's disease (AD) -induced and amnestic mild cognitive impairment (aMCI), the density of fast spindles, but not slow spindles, is significantly lower in parietal regions than in healthy controls and positively correlated with MMSE scores, suggesting that changes in fast spindles may occur very early in the disease [9, 10]. The density of fast spindles is further decreased in patients with dementia [1]. However, the spatial distribution patterns of fast spindles are different among different neurodegenerative diseases, suggesting that the simple reduction of the number of spindles lacks disease specificity, and the topographic distribution characteristics may provide clues for the differential diagnosis [1]. Mechanistically, disruption of the thalamus-hippocampa-neocortical memory consolidation pathway is considered to be an important basis for the decrease in density [1]. Notably, the spindle density in NREM 2 was negatively correlated with the levels of Aβ42, p-tau and t-tau in CSF, and positively correlated with the degree of cognitive decline, suggesting that this indicator may be used as A non-invasive biomarker for the early pathological process of AD [1]. In conclusion, fast spindle density is not only a sensitive marker for the deterioration of cognitive dysfunction, but also its spatiotemporal dynamic changes may provide valuable electrophysiological evidence for the identification and early warning of different neurodegenerative diseases [1].

4.1.2. Sleep spindle power

Sleep spindle power, typically measured as spectral power in the 12-14 Hz sigma band during NREM stage 2, is another electrophysiological measure of impaired spindle activity [1]. Existing studies have shown that in the AD -induced cognitive impairment spectrum, sigma power in the temporal region is lower than normal in the MCI stage, and the power in the occipital region further decreases in the AD stage, suggesting that the temporal lobe function is affected earlier, which is consistent with the early pathological changes of the medial temporal lobe [1]. Reduced sigma

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power in the parietal lobe was associated with thinner precuneus cortex [1]. However, the relationship between power measures and CSF T-tau levels was not consistent, and the initial sigma power change was not found to predict memory decline in follow-up studies [1]. In general, the decrease of sigma power is associated with the pathological progression of AD, especially in the parietal region, which is similar to the trend of density change. However, sigma power may be less sensitive than spindle density in the early stage or prognosis of AD [1].

4.1.3. Sleep spindle amplitude

In the quantitative analysis of EEG, the power spectrum and amplitude spectrum are related by the square root [1]. Therefore, the changes of EEG power and amplitude during sleep may be similar, but not identical, in AD patients [1]. The decrease of EEG power and amplitude is associated with the decrease of MMSE score and the increase of cognitive degradation risk, which may be used as an early warning indicator of SCD/MCI [1]. However, amplitude changes were less significant in AD/aMCI than in spindle density and duration, and were not clearly associated with CSF Aβ42 and tau levels [1]. In general, although the decreased amplitude has been repeatedly confirmed in AD patients, its diagnostic sensitivity and power are comparable, and it is not as good as the density and slow wave coupling indicators, so it can be used as an auxiliary reference in clinical evaluation [1].

4.1.4. Sleep spindle duration

The duration of sleep spindle wave is closely related to cognitive function. Studies have shown that the duration of spindle wave in patients with mild cognitive impairment (aMCI) and Alzheimer's disease (AD) is significantly shorter than that in the normal control group, and the degree of shortening the duration is positively correlated with the decline of MMSE and MoCA scores [1]. ROC curve analysis shows that this index is more sensitive than spindle density in distinguishing aMCI/AD from normal control group. In addition, the shortened duration is negatively correlated with the level of T-tau in cerebrospinal fluid, suggesting that it can be used as a sensitive EEG biomarker for cognitive impairment caused by early AD [1].

Among all the spindle parameters mentioned above, fast spindle density and spindle duration are highly sensitive to identify precursor AD, while σ power and amplitude can be used as auxiliary indicators. These electrophysiological abnormalities are supposed to originate from the interruption of thalamus-hippocampus-neocortex loop, thus establishing the physiological relationship between AD pathology and memory impairment.

4.2. Sleep spindles are correlated with pathological factors of AD

4.2.1. Sleep spindles and Aβ/Tau

Aβ and Tau proteins damage the formation and function of sleep spindle wave through independent and synergistic ways, and then participate in the pathological process of Alzheimer's disease. Aβ deposition impairs memory consolidation and amyloid clearance by interfering with slow-wave sleep, weakening spindle-slow oscillation phase coupling and thalamic-cortical rhythm synchronization, and reducing spindle density and frequency [2]. Tau protein directly inhibits spindle-related neuroplasticity through axonal injury and synaptic degeneration mediated by abnormal phosphorylation, and its CSF level is negatively correlated with N2 spindle density. The synergistic effect of Aβ and Tau is more significant: Aβ enhances the neuronal inhibitory effect of

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Tau, Tau aggravates the synaptic toxicity of Aβ, and promotes neuroinflammation by activating microglia to jointly destroy the thalamo-cortical circuit [2]. At the same time, Aβ/Tau co-deposition reduces the power of slow oscillation, and its mechanism involves the activation of MAPK/CaMK signaling pathway and the imbalance of calcium homeostasis, which leads to the damage of synaptic plasticity related to slow oscillation. This two-way pathological interaction eventually aggravates the abnormality of spindle and becomes an important neurophysiological basis for the early cognitive decline of AD [2].

4.2.2. Sleep spindles and neuroinflammation

Neuroinflammation and sleep spindles form a two-way vicious cycle in Alzheimer's disease. Microglia and astrocytes activate to release proinflammatory factors (such as IL-1β, IL-6, and TNF-α), which interfere with spontaneous firing and action potential patterns of neurons, inhibit the expression of spindles in the prefrontal cortex, reduce slow oscillation power, and impair synaptic transmission and neuroplasticity [2]. The reduction of spindles further weakens the function of the neural network and the efficiency of brain waste removal, leading to the accumulation of Aβ and Tau protein, triggering A stronger immune response, aggravating neuroinflammation and cognitive decline. The two promote each other and jointly promote the progression of the disease [2].

5. The value of sleep spindles in the clinical treatment of AD

The drug treatment of Alzheimer's disease (AD) currently mainly involves cholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, and hypnotic drugs. Studies have found that healthy volunteers taking gamma-aminobutyric acid (GABA) receptor agonists during the non-rapid eye movement (NREM) sleep phase show enhanced slow wave sleep spindle phase amplitude couplings, while non-verbal memory ability is also improved [11]. Although these drugs can improve the microstructure of sleep, they are usually only used as a last-line treatment in clinical practice because they may induce awakenings, cognitive impairment, and psychomotor adverse effects [1].

Several studies have confirmed that improving sleep quality and increasing the duration of slow wave sleep can help reduce the risk of Alzheimer's disease in the elderly [12]. Based on this, researchers are paying increasing attention to non-invasive brain stimulation techniques that are still in the experimental stage. These techniques have the advantages of being economical, non-invasive, individualized and adaptive. They mainly include transcranial magnetic stimulation (short magnetic pulses of high intensity generated by a coil on the scalp to induce shallow cortical currents). In turn, it causes neuronal axonal excitation or transsynaptic activation) and transcranial electrical stimulation (current delivered through scalp electrodes to regulate neuronal or axonal membrane polarization) [13]. In patients with mild cognitive impairment, transcranial direct current stimulation can significantly enhance the power and temporal synchrony of slow wave and sleep spindles, thereby improving visual declarative memory. Similar positive effects were also observed in the siesta test in healthy elderly people, and the mechanism was closely related to the enhancement of slow and fast spindle power in the frontal lobe. In addition, TMS induced slow wave activity during slow wave sleep, which was similarly observed to improve declarative memory. However, some studies have come to inconsistent conclusions that enhancing slow wave activity may not necessarily improve memory function in the elderly, which may be due to the differences in experimental subjects (there are essential differences in brain structure and function between pathological aging and normal aging) and experimental design, suggesting that non-invasive stimulation may only have a more definite effect on pathological states or napping situations. Future

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studies should focus on longitudinal observational trials to further explore the relationship between memory consolidation and sleep spindles, so as to further expand the application prospects of non-invasive stimulation therapy.

6. Conclusion

This paper systematically expounds how impaired sleep spindle oscillations mediate memory dysfunction in individuals along the Alzheimer's disease continuum. Sleep spindles generated by thalamo-cortical circuits actively facilitate memory consolidation through coupling with slow oscillations and hippocampal ripples. Multiple electrophysiological studies demonstrate that fast spindle density, duration and sigma power decrease significantly in prodromal AD stages, and these changes are closely associated with cerebral Aβ and tau load. Amyloid-β deposition, hyperphosphorylation of tau protein and persistent neuroinflammation jointly destroy the integrity of thalamic-cortical network, forming a vicious circle, aggravating spindle dysfunction and cognitive deterioration. At present, drug regulation and non-invasive brain stimulation can regulate spindle activity under experimental conditions, but there is still a lack of stable clinical programs.

This paper integrates multi-level evidence and proves that sleep spindle wave has good application value as a noninvasive early electrophysiological marker of AD. It should be admitted that there are several limitations. Most of the existing research results come from cross-sectional studies; At present, there is no unified EEG detection standard and large-scale longitudinal verification, and the causal relationship between spindle wave loss and AD progress needs to be confirmed. Future research needs to establish standardized spindle quantitative index and optimize closed-loop neural regulation scheme, so as to promote the transformation of sleep spindle related research into clinical practice.

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