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Perspective

Brain rhythm attractor breakdown in Alzheimer's disease: Functional and pathologic implications

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Abstract This perspective binds emerging evidence on the bidirectional relationship between Alzheimer's disease (AD) and sleep disorders through a model of brain rhythm attractor breakdown. This approach explains behavioral-cognitive changes in AD across the sleep-wake cycle and supports a causal association between early brainstem tau pathology and subsequent cortical amyloid β accumulation. Specifically, early tau dysregulation within brainstem-hypothalamic nuclei leads to breakdown of sleep-wake attractor networks, with patients displaying an attenuated range of behavioral and electrophysiological activity patterns, a "twilight zone" of constant activity between deep rest and full alertness. This constant cortical activity promotes activity-dependent amyloid β accumulation in brain areas that modulate their activity across sleep-wake states, especially the medial prefrontal cortex. In addition, the accompanying breakdown of hippocampal–medial prefrontal cortex interplay across sleep stages could explain deficient memory consolidation through dysregulation of synaptic plasticity. Clinical implications include the potential therapeutic benefit of attractor consolidation (e.g., slow-wave sleep enhancers) in delaying AD progression.

Keywords: Sleep; Neurofibrillary tangles; Amyloid β; Memory consolidation; Frontohippocampal; Default mode network; Attractor systems

1. Introduction

Alzheimer's disease (AD) symptoms are associated with pathologic protein accumulation and neurodegenerative changes in critical brain areas involved in specific cognitive functions [1]. Several mechanisms have been proposed to explain degenerative patterns within selectively vulnerable neural networks, from transneuronal spread of misfolded proteins, to metabolic demands in coactive areas, to shared nodal vulnerability or trophic failure [2]. These mechanisms are supported by clinicopathologic associations, but they do not fully consider temporal variations in dynamic brain states as contributors to symptoms and pathologic progression in AD. Sleep and wakefulness represent two extremes of brain states that are the behavioral expressions of brain state attractors—dynamically invariant neuronal activity patterns that broadly coordinate activity across the brain in a bottom-up and self-organized manner [3]. This perspective outlines, through a theoretical model of sleep-wake attractor system breakdown in AD, a mechanism for the observed attenuated rhythm fluctuations, a "twilight zone," which in turn contributes to poor memory consolidation and cortical amyloid β (Aβ) accumulation. Importantly, this conceptual approach of attractor system breakdown elucidates one possible mechanism through which early tau pathology can lead to subsequent cortical Aβ accumulation, which is currently a poorly understood relationship.

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In what follows, memory consolidation and sleep-wake architecture are explained through attractor network temporal dynamics. This background is supplemented by current evidence on the bidirectional relationship between sleep disorders and AD pathology. These concepts are subsequently combined to explain, through the breakdown of brain attractor dynamics, the attenuated behavioral and neurophysiological responses observed in AD and their implications in memory consolidation and Aβ deposition. In closing, we discuss comorbid pathologic associations and therapeutic considerations on the basis of the aforementioned framework.

2. Attractor networks in sleep-wake architecture and memory consolidation

Information processing in the brain is not a static linear process but involves serial, parallel, and feedback pathways that are differentially activated across circadian and ultradian cycles [4–11]. This dynamic process allows, through temporal binding of neuronal activity between areas, the integration and retrieval of multimodal information [12–14] but also allows the formation of memory engrams through strengthening and pruning of synapses [9,15]. Synaptic plasticity is a temporally recursive process that abides to rules characterized by sequential and cyclical activation of interconnected networks, with each temporal component differentially optimizing cognitive functions [15,16]. Such patterns of brain activations and their respective cognitive implications are well defined across sleep stages, where hippocampal metabolism dominates during nonrapid eye movement (NREM) sleep, and medial prefrontal cortex (mPFC) metabolism dominates during rapid eye movement (REM) sleep (Fig. 1) [17,18]. This frontohippocampal interplay is integral to the consolidation and retrieval of memories through direct or thalamically gated bottom-up and top-down mechanisms [19–23]. Furthermore, each state seems to mostly subserve specific types of memory, with NREM hippocampal-predominant periods consolidating episodic declarative memories and REM mPFC-predominant periods consolidating implicit procedural and emotional memories [24,25], although sequential and recursive involvement of both periods is likely required for most memories [8,26,27]. These elements are also reflected in unique neurophysiological signatures within NREM and REM sleep. Specifically, in NREM sleep, electroencephalography (EEG) shows large amplitude slow synchronous activity, reflecting a resting cortex mostly driven by thalamocortical pathways [28,29]. Concurrently, at the synaptic level, there is gradual strengthening of hippocampal synapses with occasional sharp-wave ripple bursts, a functional reflection of activity replay during memory consolidation [8,9,15]. Furthermore, sharp-wave ripples are often accompanied by a cortical counterpart in the form of sleep spindles, indicating mPFC-hippocampal information transmission [30]. In contrast, during REM sleep, the EEG resembles wakefulness with small amplitude fast desynchronized activity, reflecting increased cortical activity. Also during REM sleep, hippocampal synapses are gradually downscaled and eventually pruned, a process suggested through gradually decreasing neuronal firing rates, whereas hippocampal theta rhythms increase in power [8,9,15,20,31]. This frontohippocampal reciprocal communication allows for memory consolidation by strengthening synaptic engrams and pruning irrelevant synapses, thus economically optimizing brain function. Such a state-dependent pattern seems to also exist during wakefulness, with ultradian rhythms showing a similar duration to sleep cycles [4,32,33], although the lack of clear state separation makes individual state contributions to learning and memory consolidation less clear. Nonetheless, studies indicate that learning and memory consolidation, encephalographic activity, brainstem neurophysiological activity, and molecular pathways of long-term potentiation also abide to ultradian modulation during wakefulness [34–38]. In addition, resting-state functional magnetic resonance imaging (fMRI) experiments suggest ultradian modulation of functional brain networks [10,39]; however, these experiments are generally not prolonged and do not account for sleep intrusions. Overall, our understanding of ultradian mechanisms during wakefulness lags behind that of sleep.

The aforementioned features highlight the dynamic nature of brain function through separate, yet temporally related, functional states in the processing and retention of information. This between-state separation and switching is achieved through the differential activation of specific hypothalamic and brainstem neuronal populations and their mutual inhibition, both between sleep and wakefulness and between ultradian stages. Specifically, sleep-state is promoted by homeostatic and circadian elements, with increased ventrolateral preoptic nucleus (VLPO; also known as the intermediate nucleus of the preoptic area) GABAergic and galaninergic activity and melatonin levels playing a dominant role. In contrast during wakefulness, monoamine (locus coeruleus nucleus (n.); raphe n.; periaqueductal gray n.; tuberomammillary n.), orexin (lateral hypothalamic n.), glutamate (parabrachial n.; lateral hypothalamic n.), and acetylcholine (pedunculopontine tegmental n.; laterodorsal tegmental n.; basal forebrain n.) pathways are activated, whereas suprachiasmatic nucleus (SCN) activity operates as a timer for circadian wakefulness in part by suppressing melatonin secretion (see [40] for review). Ultradian rhythms, such as cycling between NREM and REM stages, are modulated by overlapping pathways described previously. In addition to laterodorsal and prepontine tegmental nuclei, the sublaterodorsal nucleus of the precoeruleus region functions as a REM-state promoter, whereas the ventrolateral periaqueductal gray and lateral pontine tegmental nuclei suppress