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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 (mPFC). Additionally, the accompanying breakdown of hippocampal-mPFC 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

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1. Prologue

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 of 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 accumulation. Importantly, this conceptual approach of attractor system breakdown elucidates one possible mechanism through which early tau pathology can lead to subsequent cortical amyloid-β accumulation, which is currently a poorly understood relationship.

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 amyloid-β deposition. In closing, we discuss comorbid pathologic associations and therapeutic considerations on the basis of the above 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 non-rapid eye movement sleep (NREM), and medial prefrontal cortical metabolism (mPFC) dominates during REM sleep (Fig. 1) [17,18]. This fronto-hippocampal 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], though 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 (SPW-R) bursts, a functional reflection of activity replay during memory consolidation [8,9,15]. Furthermore, SPW-R 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, while hippocampal theta rhythms increase in power [8,9,15,20,31]. This fronto-hippocampal 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], though 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, as well as molecular pathways of long-term potentiation also abide to ultradian modulation during wakefulness [34–38]. Additionally, resting-state 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 above 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, while 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 above. 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 REM sleep [40]. These are in turn modulated by higher order nuclei, such as the VLPO, lateral hypothalamus, and locus coeruleus. Under healthy conditions, neurophysiological activity patterns within states remain relatively stable and discrete from other states, and driven by subcortical projections.

A conceptual approach in describing these network-states is through mutually inhibitory attractor networks (Fig. 2). Attractors were first defined in the fields of mathematics and physics to describe those special states of a system that are dynamically invariant (i.e. quasi-stationary over a period of time) and towards which the system tends to gravitate over time as it is "attracted" around a basin of attraction (i.e. a prototypical stationary state) [41,42]. The latter condition explains observations where mild to moderate deviations from quasi-stationarity are only transient, and thus allows the system to behave in a robust and relatively predictable manner. It also explains why the term *attractor* is more appropriate than *state* when describing systems with stable behavior that are not significantly affected by mild to moderate disruptions. It is also useful to highlight that attractors represent patterns of dynamic behavior rather than static or structural elements of a system. Attractors come in several types, and combinations of attractors that have linear or non-linear dynamics can bring forth more complex attractors. A single attractor, though, is conventionally defined as the smallest set of attractor states that cannot be decomposed into other attractors [42]. In biological systems, most attractors present in clusters of two or more, as systems tend to alternate between mutually inhibitory attractors, each one facilitating specific processes. This is also the case when describing brain function through attractor dynamics.

Considering that brain function serves the processing and retention of information through the dynamic interplay between functional states, attractor dynamics are a useful conceptual approach in understanding and describing brain function and, by extension, its disruption. Since attractors represent a dynamic pattern of activity, any measure of brain function that reveals such a pattern (e.g., neuronal firing rates, local field potentials, encephalographic measures, and serial behavioral measures) could be approached on the basis of attractor dynamics. Brain-wide attractor states, however, are derived in a bottom-up manner from self-organized stable neuronal activity patterns of the brainstem and hypothalamus, which in turn serve as brain state-generators and coordinate activity across the brain. As such, brainstem-hypothalamic activity patterns reflect a brain's dominant attractors, whereas core features of cortical activity patterns are derivatives of subcortical attractor activity, as represented through endophenotypic measures of neurophysiology (e.g., local field potentials, encephalography, or fMRI networks) and their phenotypic behavioral-cognitive expressions. In addition to brain-wide attractor dynamics, studies also support the co-existence of local intracortically-generated attractors, each one reflective of specific cognitive processes [41,43–47], in keeping with findings that attractor dynamics are an inherent feature of mature neuronal network organization [48,49]. These local attractors, however, are weak and unstable compared to those coordinated by subcortical state-generators, since they are modulated by both subcortical activity and by perceptual and praxis systems that interact on a moment-to-moment basis with the environment [50]. In contrast, brainstem and hypothalamic attractors are robust and hierarchically modulate the processing and retention of information in a brain-wide manner through sleep-wake and ultradian rhythms. Specifically, activity of sleep-promoting and wakefulness-promoting

brainstem and hypothalamic nuclei form two attractors, whereas ultradian rhythms (e.g., NREM-REM) represent two different attractors, each pair of attractors being partially independent to the other and following non-linear dynamics (Fig. 2) [32,33,51].

Brain rhythms satisfy attractor dynamics criteria since they reveal quasi-stationary features (i.e., stable activity patterns within states of sleep or wakefulness, or within ultradian states) and their activity gravitates towards a basin of attraction even if they are transiently deviated from their quasi-stationary steady-state. Additionally, brain rhythm attractor pairs (sleep-wake or ultradian) reveal mutually inhibitory mechanisms that allow between-state transition through flip-flop switches [40], perhaps through spatiotemporal saturation of neural capacitor circuits [52], a common feature of attractor systems. Attractor networks can balance state robustness and between-state agility through degrees of connectivity that prevent the system from being trapped within an aberrant attractor [53]. Studies also indicate that strengthening one attractor in an attractor pair subsequently entrains patterns in its counterpart. For example, sleep deprivation and light therapy increase subsequent deep sleep [54,55], and enhanced fast activity of specific cortical networks during wakefulness associates with increased local SWS afterwards [56]. Furthermore, attractor state dynamics can be derived from multiple constituent networks, as in the case of sleep and wakefulness where both homeostatic and circadian processes are involved in deriving attractor states [40]. Their complementarity and partial redundancy can serve as a possible mechanism for attractor robustness and agility. Implementing attractor dynamics in explaining brain rhythms allows for a hierarchical model of state generation, where integrating sleep-wake and ultradian patterns gives rise to specific brain states (Fig. 2), and can further account for the dynamic mechanisms involved in synaptic plasticity and memory consolidation. Such mechanisms are difficult to elucidate when approaching brain rhythms purely within-states or through circadian and homeostatic processes. An attractor model of brain rhythms further allows for a more economic organization of brain states. Through such a model, state-generators do not require unique activity patterns for each state, but rather only a few patterns to define the cardinal attractor dimensions (Fig. 2). This allows for an exponential degree of possible brain states, 2^n where n is the number of attractor pairs, and raises the possibility that in addition to sleep-wake and ultradian rhythms, other brain rhythm attractor pairs can be defined and integrated in such a model, possibly being subordinate to the two cardinal attractor pairs. This, however, remains speculative and requires further evidence. According to the above model, the processing and retention of information is hierarchically dependent on robust brain-wide rhythm attractors that are generated by brainstem and hypothalamic nuclear activity. Since early pathologic changes in certain degenerative diseases originate in the brainstem and hypothalamus (e.g., AD, synucleinopathies, progressive supranuclear palsy), modeling brain rhythm attractors and their breakdown in degenerative diseases may allow for earlier diagnosis, prognosis and potentially treatment response, as analyzed below for the case of Alzheimer’s disease.

3. Alzheimer's pathology and sleep disorders: pre-cognitive symptoms and bidirectional relationships

Increasing evidence points to comorbid associations between Alzheimer's pathology and sleep disorders. Presence of neurodegeneration or pathologic protein accumulation in critical sleep regulatory centers leads to sleep disorders. In turn, interfering with sleep increases the risk of pathologic amyloid-β aggregation and worsened cognitive performance. Currently, causal associations are better established in transgenic animal models of AD, but supportive evidence is also present in humans.

There is increased frequency of sleep disorders in cognitively intact people who eventually develop Alzheimer's dementia. The observed changes reflect circadian rhythm breakdown, extremes of sleep duration (less than six hours or more than nine), daytime napping, and nighttime awakenings [57–64]. Sleep disordered breathing, which is a risk factor for subsequent dementia [65,66], mostly shows an association with vascular pathology, rather than AD or synuclein pathology [67]. Presence of these clinical findings has an additive effect on cognitive decline, especially in working memory and executive function, and some of these symptoms increase prospective risk of AD by more than 50% within six years [60,62–64,68]. Sleep disruptions are also reflected in sleep architecture changes during aging, with gradual decreases in REM and slow wave sleep (SWS), degraded sleep spindle morphology, and increased periods of wakefulness after sleep onset [69,70], which in turn can contribute to worsened memory consolidation [19,71–73]. In contrast, during restful wake periods, EEG in AD shows a leftward power shift with increased power in lower frequencies and decreased power in higher frequencies [74–76]. Encephalographic changes during restful wakefulness are associated with worse cognitive performance and impaired intracortical network function [77].

Although sleep disorders have only partially overlapping pathophysiology between them, there is an early common pathologic process in AD that helps explain homeostatic, circadian and sleep architecture disorders in cognitively intact patients who subsequently develop AD. Specifically, the very first stages of AD are characterized by neurofibrillary tangle pathology in the isodendritic core of the brainstem and basal forebrain [78–80]. Tau aggregation in cells leads to presynaptic dysfunction, even prior to structural changes and neuronal loss [81]. Characteristic nuclei involved in early AD pathology that also play a role in sleep regulation are the locus coeruleus, the raphe nuclei, and the nucleus basalis of Meynert. Additionally, VLPO cell numbers are fewer in patients with Alzheimer's pathology but are not significantly fewer with aging alone [82]. It remains to be shown whether early-life tau pathology at the isodendritic core is directly related to cell loss at that early stage. Pathology studies in more advanced AD have shown conflicting results on the association between neurofibrillary tangle burden and cell loss, possibly a combination of cell loss leading to clearance of intracellular tau and non-linear neurofibrillary tangle accumulation and cell loss with advancing disease [83]. Nonetheless, early tau pathology relates to morphological and biochemical changes in isodendritic core nuclei (see [78] for review), supportive of early disrupted function of these nuclear formations. Whether early pathology is restricted to brainstem nuclei, or further involves hypothalamic centers that modulate homeostatic and

circadian processes through VLPO (i.e. GABA and galanin), lateral hypothalamic (i.e. orexin) and SCN activity (e.g., vasoactive intestinal peptide), remains to be clarified pathologically. It is clear, however, that these formations are affected during AD progression [82,84]. Interestingly, early symptoms due to SCN involvement may reflect desynchronized neuronal activity prior to neuronal loss [85], further influencing other neuronal populations through disrupted timing of both intracellular molecular pathways and neuronal firing patterns. Inferentially, since brainstem neurofibrillary tangle accumulation precedes cortical pathology in AD and thus cognitive decline, presence of sleep disorders is a risk factor for subsequent disease progression and cognitive impairment, allowing for earlier diagnosis and therapy.

Conversely, mounting evidence points to increased amyloid-β accumulation linked to disrupted sleep-wake cycles and neuronal hyperactivity. At baseline, studies in both humans and transgenic mice revealed that amyloid-β levels fluctuate across the sleep wake cycle, supporting the hypothesis that amyloid-β clearance increases during deeper sleep [86–88]. Clarifying these findings, a study using the Tg2576 mouse model, which overexpresses human amyloid precursor protein (APP) with a mutation linked to AD, showed that chemical or physiological neuronal hyperactivity led to increasing interstitial amyloid-β levels [89]. Additionally, manipulating sleep duration in APP/presenilin 1 (PS1) transgenic mice revealed increased amyloid-β deposition during sleep deprivation and decreased deposition with increasing SWS [90]. In cognitively normal older adults, an association has been shown between decreased SWS and increased mPFC amyloid positron emission tomography (PET) tracer uptake [71]. Furthermore, overnight hippocampal-dependent memory consolidation was worse in those individuals with decreased SWS [71]. A definite causal association in humans, however, is still lacking.

4. The twilight zone of Alzheimer’s disease as a breakdown of brain attractor dynamics

Combining the above information under the rubric of attractor dynamics, evidence supports that breakdown of discrete attractor networks occurs in AD. A few mechanistic processes can be considered: (a) state gravitation towards an attractor is decreased, (b) mutually inhibitory attractor mechanisms are defective, or (c) a combination of the two (Fig. 3). In the case of AD, there is behavioral and neurophysiological attenuation of rhythm fluctuations between two extremes of attractor dynamics, conceptually termed as the twilight zone (Fig. 4), with evidence stemming from both sleep-wake attractor and ultradian attractor dynamics. Specifically, characteristic findings from encephalographic studies, with slower rhythms during wakefulness and inability to maintain SWS [69,70,74,76,91], support attenuation of functional variability between full wakefulness and deep sleep. Patients gradually enter a twilight zone where they are never fully awake or deeply asleep, and their cortex is always active in the background. This attenuated functional variability is also accompanied by attenuated range of amyloid-β clearance with disease progression in both humans with presenilin mutations and APP/PS1 mice [92]. Encephalographic studies also indicate that a second attractor system is also affected with disease progression, this time within sleep. As mentioned above, the mutual separation between NREM and REM sleep is affected, but also

state characteristics are less well defined, indicating additional breakdown of individual attractor characteristics. In sum, the mutual inhibition of attractor systems (sleep vs. wakefulness and NREM vs. REM promoting nuclei) is at least impaired. A weaker gravitational pull towards each attractor may also be present with disease progression, eventually reflecting either hypersomnia, insomnia, or more frequent transition between states (rhythm breakdown). When the overlap between attractor states is pronounced, new symptoms surface, such as visual hallucinations or sundowning, reflecting this dissociated state [93].

Certain implications stem from the above changes in attractor dynamics in AD. These can be grouped under short term and long term effects. Short term effects involve poor overnight memory consolidation as a result of deficient NREM and REM interplay [8,24,26,27,94], with a possible counterpart being ultradian rhythm breakdown and poor memory consolidation during wakefulness as well [34–36]. Neurophysiologically, these findings reflect poor synaptic plasticity within and between hippocampal and mPFC areas [9,15,20–23]. Additionally, the twilight zone can provide an alternative explanation to the decreased effective connectivity observed even in early AD during wakefulness. Specifically, transcranial magnetic stimulation (TMS) experiments in AD during wake states reveal dampened cortical spreading of evoked neuronal activity and findings have been interpreted as representations of decreased intracortical connectivity [95–97]. Furthermore, TMS-induced inhibition of motor evoked responses correlates with cerebrospinal fluid levels of total tau, hinting to a relationship between deficient connectivity and disease burden in AD [98]. Alternatively, the dampening of cortical spreading in TMS-EEG experiments is also reminiscent of patterns observed in sleep of healthy adults [99]. By extension, it is possible that decreased effective connectivity in early AD is not necessarily reflective of a primary breakdown of intracortical information transmission, and could be secondary to breakdown of attractor dynamics as coordinated by brainstem and hypothalamic nuclei. Further supportive of this hypothesis are the following. First, tau pathology, which best correlates with symptoms, presents at the isodendritic core prior to spreading in the cortex [78], second, improved cortical signal spread after modulation of the TMS stimulus correlated with improved cognition [95], implying that intracortical networks are relatively intact as long as global rhythms are not dampened, and, third, short-latency afferent inhibition is consistently decreased in TMS-EEG experiments in AD, a marker of possibly deficient cholinergic activity and dysregulation of subcortical-cortical integration [95]. Even though much of the neurophysiological evidence is derived from animal studies, and thus certain mechanisms remain speculative in humans, physiological dynamics have shown marked similarities between species [100]. Clinically, these short term effects of brain rhythm attractor breakdown may provide an explanation for day-to-day variability in AD patients, since cycling between sleep-wake and ultradian states is not stable or identical across days in patients. Nonetheless, even though learning and retrieval of recently acquired information may be impaired, it is presumably a reversible process in the short term. Long term effects of attractor system breakdown, though, can be far reaching and permanent as discussed below.

5. Linking two pathologies of Alzheimer's disease: from neurofibrillary tangles to amyloid-β aggregation

From the above perspective a unique theoretical model unfolds. Early involvement of neurofibrillary tangle pathology in brainstem nuclei can serve as the pathologic substrate for sleep disruption in early pre-cognitive stages of AD, prior to cortical amyloid-β accumulation. Considering, however, that patients who will develop AD enter a twilight zone of cortical activity, likely secondary to damage of the brainstem sleep-wake attractor networks with the brain never reaching full rest to allow synaptic pruning or full alertness to allow better synaptic potentiation, there is increased probability for subsequent amyloid-β aggregation in areas that maintain increased cortical activity over long periods of time [101]. This extracellular amyloid-β accumulation adds to downstream degeneration through excitotoxic mechanisms involving impairment of inhibitory interneurons and aberrant stimulation of extrasynaptic glutamate receptors [102]. Further downstream effects involve altered distribution and function of surface receptors and signaling molecules, changes in subcellular calcium dynamics, impairments in axonal transport, mitochondrial dysfunction, and alterations in immediate early gene expression (see [103] for review on amyloid-β downstream effects). In many of these processes, tau serves as a critical enabler of amyloid-β toxicity and contributes to aberrant neuronal activity [104]. The above processes outline a direct link between early brainstem neurofibrillary pathology and subsequent cortical amyloid-β deposition through early vulnerability of sleep-wake nuclei and the interim effect of a twilight zone of continuous, yet attenuated, cortical activity (Fig. 5).

Of additional relevance to this hypothesis is the distribution of cortical amyloid-β deposition and how it may relate to the disruption of sleep-wake rhythms. Studies in cognitively normal humans indicate an association between decreased SWS and amyloid-β deposition in the mPFC [71], an area of the brain that is least active during SWS and more active during REM sleep [17,18]. Additionally, it is an integral part of the default mode network as revealed in functional MRI studies, which is active during resting wakefulness and decreases its activity as sleep gets deeper [105,106]. In vivo amyloid PET studies in humans reveal that the first area to have above-threshold amyloid-β deposition in the brain is the mPFC [107]. As AD progresses, there is additional amyloid-β accumulation in other areas of the default mode network, indicative of an association between cortical activity and amyloid-β deposition [101,107]. Interestingly, when dissecting the individual nodes of the default mode network according to signal intensity during deeper sleep, there is a preferential decrease of activity of the mPFC compared to other nodes, such as the precuneus or lateral parietal lobe [105], which further supports an association between decreased SWS and preferential mPFC amyloid-β deposition within the default mode network.

6. Comorbid and therapeutic implications

An interesting possibility from sleep-wake attractor breakdown is the association with epilepsy. The increased frequency of epileptiform activity during sleep is well established, with seizure threshold decreasing because of increased thalamocortical synchrony during deeper sleep [108]. At face value, decreased SWS should entail decreased seizures during

sleep in AD. Seizures, however, are more frequent in AD and are associated with earlier cognitive decline [109]. There are several pathways that one may consider to explain this dissonance. An enticing possibility relates to amyloid-β aggregates promoting hyperexcitable neuronal activity. As such, the presence of the AD brain in the twilight zone allows for both a constantly active neuronal state, as well as downstream neuronal hyperexcitability from amyloid-β aggregation. Notably, amyloid-β at picomolar concentrations enhances synaptic transmission, a likely favorable contribution of amyloid-β in memory consolidation [110]. Persistent neuronal activation, however, promotes amyloid-β aggregation, which can in turn be epileptogenic. The clinician can further appreciate this mechanism since sleep deprivation, an extreme example of a constantly active brain, reduces seizure threshold. The potential coexistence of seizures and sleep disorders in AD patients merits further investigation.

Another consideration of attractor state disruption is whether all degenerative disorders lead to an attenuated range of rhythms into the twilight zone, or whether other patterns can exist. A simple refutation involves fatal familial insomnia in which selective early damage of the thalamus leads to decreased SWS and agrypnia excitata (persistent wakefulness) [111], conceptually reflecting a preferentially damaged sleep-NREM attractor. A similar extrapolation could be made if elements of the sleep-promoting attractor (e.g., VLPO) are selectively affected, leading to hyperaroused behaviors. A reasonable corollary from the previous example is to consider whether in all hyperaroused states amyloid-β deposition should follow suit. This is unlikely to be the case, since amyloid-β does not accumulate in all humans with insomnia, indicating that a susceptible brain substrate is also required.

Finally, it is worth considering possible interventions on the basis of attractor network dynamics. Since attractor breakdown in AD could eventually lead to amyloid-β aggregation, aiming for better attractor state separation could prevent amyloid-β deposition, especially by strengthening SWS. This can be achieved through SWS enhancers, such as gabapentin, pregabalin, tiagabine, γ-hydroxybutyrate, mirtazapine, olanzapine, and trazodone [112]. Of these, trazodone is the only one to date studied through randomized controlled trials in AD showing both effectiveness in increasing total sleep time and SWS and lack of cognitive side effects [113]. In addition to possible long term effects of decreasing amyloid-β deposition, SWS enhancers could potentially help in sleep-mediated memory consolidation in AD by consolidating mPFC-hippocampal interplay. Studies to date have not been structured to evaluate such effects. The newly developed orexin receptor antagonists could also serve as SWS enhancers, though selective orexin-2-receptor antagonists may provide better SWS consolidation than dual-orexin-receptor antagonists [114]. From a public health perspective, SWS enhancers are further attractive in AD treatment because, in contrast to most of the current AD trials (i.e. anti-amyloid antibodies), they aim for prevention of amyloid-β accumulation rather than promoting clearance after accumulation, in a way reflecting primary rather than secondary prevention. As such, they can be significantly cost-effective both because of lower production costs but also because of potentially increased quality-adjusted life years. This latter benefit can be achieved by addressing the pathologic process at its infancy and allowing both decreased morbidity and mortality, and increased duration of independence from family and social resources. On the other end of the spectrum, wake consolidation, and by extension entrainment of faster brain rhythms, may also serve attractor

separation and even facilitate amyloid-β clearance during sleep, since more active cortical areas during wakefulness for example display more pronounced slow wave activity in subsequent sleep periods [56]. Such a mechanism may also be a framework through which certain cognitive-training paradigms [115] could help clear amyloid-β from specific cortical areas, though their effectiveness remains to be established. Attractor separation by consolidating wakefulness is more likely to be achieved, instead, through well-established interventions that target circadian (e.g., light therapy and melatonin) or homeostatic processes (e.g., coffee and transcranial current stimulation possibly involving adenosine pathways) [116–119]. In the case of transcranial current stimulation, attractor separation could be also pursued through SWS consolidation using different stimulation parameters [118,120–122]. As for light therapy and melatonin use in AD, research has shown conflicting results on their separate use, but results are more promising from combined use [119,123,124].

7. Novelty and comparison to other models

Alternative models have been proposed to describe the bidirectional relationship between sleep disruptions and AD [100,125,126]. These models share a common logic, approaching this relationship on the basis of pathophysiological findings observed in AD patients and animal models. Specifically, they place neuronal loss and AD pathology on one hand and sleep disorders on the other, and link the two through pathways supported by research studies, also summarized in Section 3 above. These models hold their own merit, as they explain clinical and pathologic findings observed in patients with sleep disorders and, vice versa, sleep disruptions in patients who have pathologic evidence of AD. They allow for example to integrate evidence, some more speculative, linking sleep disruptions to AD pathology through the following pathways: primarily (a) increased neuronal activity through decreased SWS leading to increased amyloid-β production and aggregation, and (b) decreased SWS further decreasing amyloid-β clearance, but also (c) increased neuronal metabolism during sleep deprivation leading to immune system disruption, oxidative stress, and subsequent neuronal death, (d) sleep disruption affecting blood-brain barrier integrity that could be a possible mechanism of decreased amyloid-β clearance, and (e) possible circadian misalignment leading to neuronal damage. Conversely, these models indicate that neuronal damage from AD pathology in sleep-wake centers is causal to the observed sleep disruption. They further explain the distribution of amyloid-β deposition across the the default mode network, though they fail to clarify regional network differences, and also link worse sleep to worse cognitive performance in a non-specific manner. Finally, they provide a basis in studying SWS enhancers for amyloid-β clearance.

The brain rhythm attractor model follows a different conceptual approach. Specifically, the premise of the model considers the brain as a dynamic machine in which information is processed and stored through serial, parallel and feedback pathways, and that information being hierarchically organized through brain rhythm attractors, allowing for within-state robustness, between-state agility, and organizational economy (see Section 2). As such, the model accounts for the structural-functional association between brain architecture and its main function, transmission of information, for which structural elements are facilitators, including amyloid-β in low concentrations.

A more general framework, thus, emerges in representing deviations from normality across disease states through brain rhythm attractor breakdown, providing insight into both cognitive and pathologic findings while identifying unique functional disease patterns. First, the model presents a characteristic pattern of brain rhythm attractor breakdown that can be observed in AD, the twilight zone, which in turn could help in early diagnosis, prognosis and even treatment response. This pattern is distinct from that of preferential strengthening or weakening of an attractor (Fig. 3), which is noted for example in progressive supranuclear palsy where hyperarousal patterns predominate across the sleep-wake cycle [127,128]. The inverse, a pattern of hypersomnolence dominance is observed in early stages of synucleinopathies, especially dementia with Lewy bodies, and is accompanied by a leftward shift in spectral power. Interestingly, later stages in synucleinopathies often tend to resemble a twilight zone pattern, possibly reflective of evolving synuclein and AD co-pathology or advanced disease severity [76,129,130]. The model also takes a broader approach compared to other models, including elements beyond sleep, such as wakefulness and ultradian patterns (Fig. 2). This allows a more comprehensive explanation of short and long term effects observed through attractor breakdown, both in cognitive performance and pathology (see Sections 4, 5 and 6). Characteristically, breakdown of fronto-hippocampal interplay during sleep-wake or ultradian rhythm breakdown could explain deficient memory consolidation through dysregulation of synaptic plasticity. Attractor breakdown further explains emergent symptoms with disease progression through state dissociation [93], such as visual hallucinations and sundowning. It also explains in a more detailed manner the preferential deposition of amyloid-β in specific nodes of the default mode network, especially the mPFC, and provides a causal temporal link between early tau pathology and subsequent amyloid aggregation in AD. Though many elements remain speculative and require further experimental verification, distinct patterns of attractor breakdown between degenerative dementias also indicate that selective vulnerability involves brainstem and hypothalamic nuclei in addition to subsequent cortical involvement in certain degenerative diseases [1] and should be pursued in future clinicopathologic studies. For example, studies linking unique brain rhythm attractor breakdown between degenerative dementias through encephalographic and actigraphic data, and underlying pathologies as reflected in molecular PET and anatomical pathology can help validate the proposed model. Finally, the model provides a framework for identifying novel therapeutic interventions that can help memory consolidation and potentially even delay pathologic progression through attractor consolidation (Section 6).

8. Concluding remarks

In summary, we outlined how the attenuated range of behavioral-cognitive and neurophysiological fluctuations, the twilight zone, in AD can be explained through breakdown of sleep-wake attractor systems. This approach also allowed for deriving a direct link between early neurofibrillary tangle pathology in AD and subsequent cortical amyloid-β deposition, especially of the mPFC. From a clinical perspective, this hypothesis supports the rigorous evaluation of sleep disorders in otherwise cognitively intact older individuals, and the study of brain rhythm attractor consolidation (e.g., through SWS enhancers) in preventing amyloid-β aggregation in patients with decreased SWS.

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RESEARCH IN CONTEXT

Systematic review: The authors reviewed the literature using traditional sources (e.g., PubMed), conference abstracts and presentations spanning attractor dynamics, sleep-wake and ultradian regulation and their relationship to degenerative dementias, and treatment trials. All relevant citations are appropriately referenced.

Interpretation: This work provides a novel paradigm for approaching brain disease, and neurodegeneration in particular, on the basis of the structural-functional associations between brain architecture and its major function, information processing. The brain rhythm attractor model could help in early diagnosis, understanding disease mechanisms, and treatment selection (see Section 7). In Alzheimer's disease, the model suggests that pathological tau in sleep-regulating brainstem and hypothalamic could contribute to subsequent cortical amyloid-β aggregation.

Future directions: This work lays a foundation for further studies on diagnosis, prognosis and quantification of treatment response in patients with neurodegenerative diseases. For example, prospective studies of cognitively normal individuals, including gene mutation carriers, who have distinct patterns of attractor breakdown will allow earlier diagnosis and better prognosis of neurodegenerative diseases, combining neurophysiological measures with in vivo (e.g., molecular PET) and post-mortem pathologic burden.Similarly, clinical trials can quantify treatment effectiveness using brain rhythm attractor consolidation as a surrogate biomarker of responsiveness.

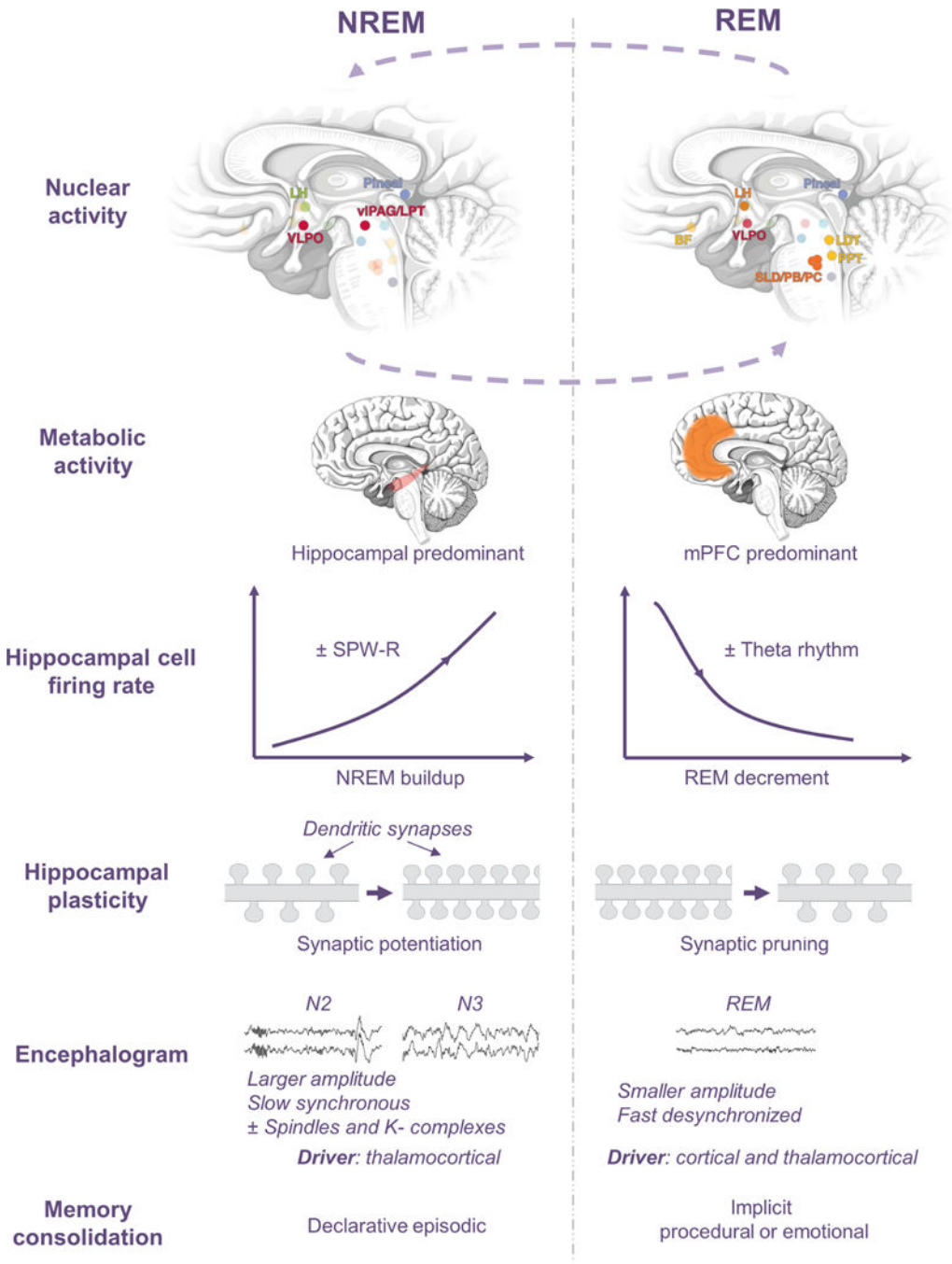

Figure 1. Frontohippocampal interplay between NREM and REM sleep

The GABAergic ventrolateral preoptic nucleus (VLPO) is active during sleep, especially NREM sleep, and inhibits wake promoting and REM promoting nuclear formations. Its sleep-promoting function is supplemented by melatonin, which is secreted from the pineal gland. Orexin producing nuclei of the lateral hypothalamus (LH) show gradually decreasing levels of activity with sleep depth, and their activity further decreases during REM sleep. Melanin concentrating hormone producing neurons of the LH show the opposite pattern and increase their activity during REM sleep. In contrast, acetylcholine producing nuclei (basal

forebrain [BF], laterodorsal [LDT] and parapontine tegmental [PPT]) have their firing suppressed during NREM sleep and released during wakefulness and REM sleep, associated with fast cortical signal in the encephalogram. Additionally, the glutamatergic sublaterodorsal (SLD), medial parabrachial (PB), and precoeruleus (PC) nuclei promote REM sleep and are in a mutual competitive inhibition with ventrolateral periaqueductal gray (vlPAG) and lateral pontine tegmental (LPT) nuclei which promote NREM sleep. From these bottom-up self-organized nuclear activity patterns, the NREM and REM attractor states emerge, giving rise to specific patterns of metabolism, cortical and hippocampal activity, synaptic plasticity, and memory consolidation. See text for details.
Color coding for most significant neurotransmitters and hormones produced by noted areas: red, GABA; light green, orexin; purple, melatonin; dark yellow, acetylcholine; light orange, melanin concentrating hormone; dark orange, glutamate.

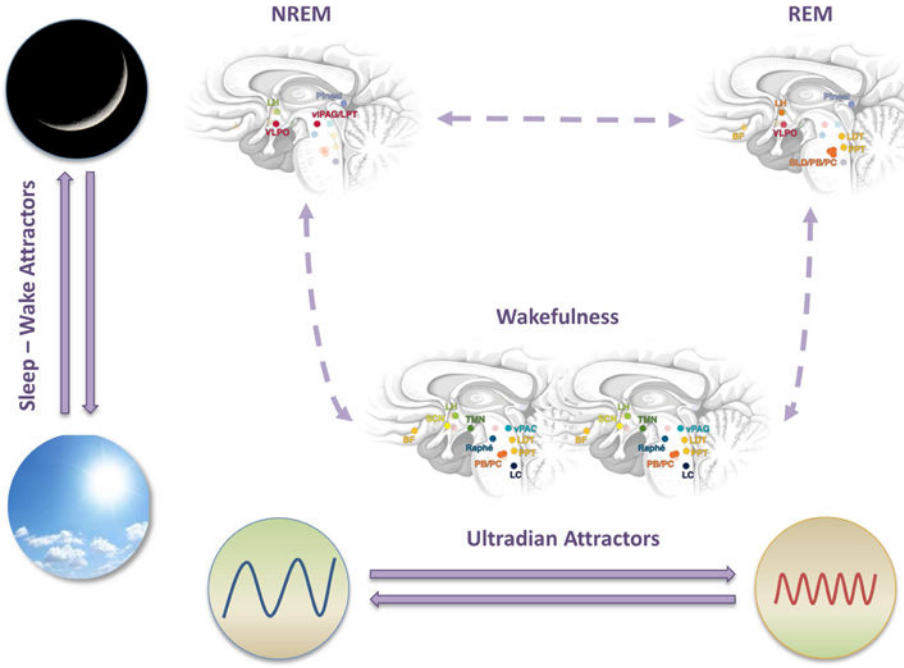

Figure 2. Attractor networks in sleep and wakefulness

The architecture between and within sleep and wakefulness can be described through a simplified model of two attractor systems, sleep-wake attractors and ultradian attractors. Each dimension allows for state separation according to nuclear activity and hormonal levels. Some factors are unique to one dimension (e.g., melatonin in sleep-wake attractors), whereas others contribute to both (e.g., acetylcholine and orexin). These attractor systems allow the brain to enter discrete functional states, each one subserving a specific role, and the recursive interplay between states allow for functional (e.g., memory consolidation) and biological (e.g., tissue homeostasis) processes. Ultradian attractor separation is easier to identify during sleep but more difficult during wakefulness. This can be partly explained by the dominant effects of the wakefulness attractor attenuating ultradian behavioral and encephalographic dynamic patterns and partly by the insufficient knowledge on brainstem and hypothalamic nuclear activity contributions to state generation within wakefulness. See text for details. Abbreviations: basal forebrain (BF), lateral hypothalamus (LH), lateral pontine tegmentum (LPT), laterodorsal tegmental (LDT), locus coeruleus (LC), medial parabrachial nucleus (mPB), parapontine tegmental (PPT), precoeruleus region (PC), tuberomamillary nucleus (TMN), sublaterodorsal nucleus (SLD), suprachiasmatic nucleus (SCN), ventral periaqueductal gray (vPAG), ventrolateral periaqueductal gray (vlPAG), ventrolateral preoptic nucleus (VLPO).

Color coding for most significant neurotransmitters and hormones produced by noted areas: red, GABA; light green, orexin; dark green, histamine; purple, melatonin; light yellow, vasoactive intestinal polypeptide and arginine vasopressin; dark yellow, acetylcholine; light orange, melanin concentrating hormone; dark orange, glutamate; light blue, dopamine; blue, serotonin; dark blue, noradrenaline.

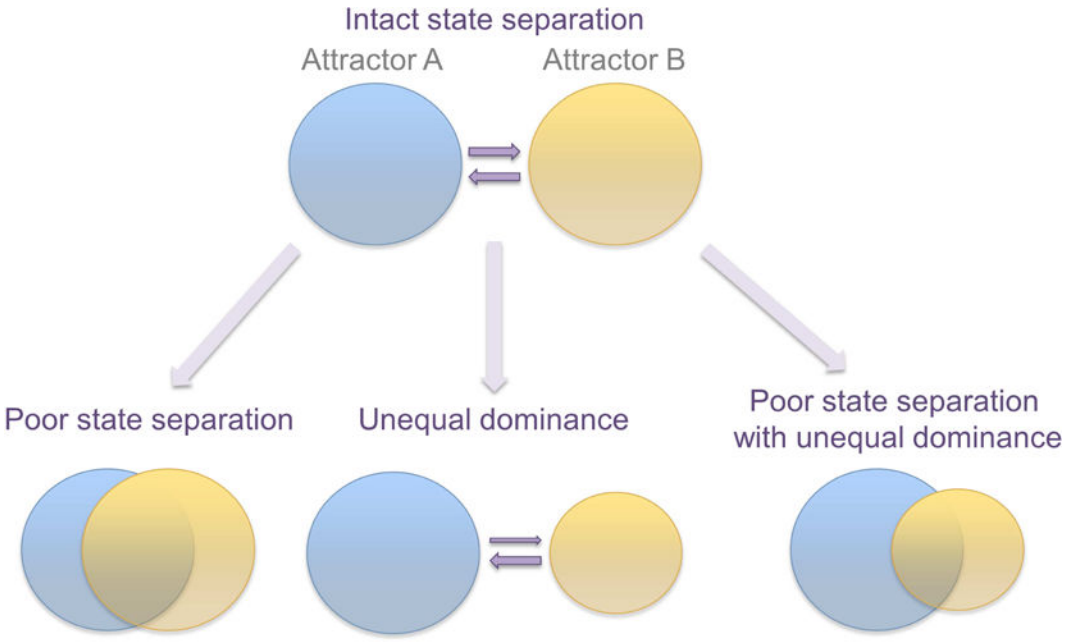

Figure 3. Mechanisms of attractor system breakdown

The attractor system framework allows for an integrated approach in conceptualizing state dependent disruptions and provides three possible mechanistic processes. Each one can be the result of different underlying pathologies, but giving rise to the same functional state-separation pattern, with common downstream effects. First, deficient mutual attractor inhibition leads to poor state separation and coexistence of traits between states. Second, preferential strengthening or weakening of an attractor leads to unequal dominance of the stronger attractor across cycles. Third, a combination of the two mechanisms can lead to a predominant attractor, with traits of the other attractor state surfacing at times. Identifying a specific pattern of attractor system breakdown allows for prediction of downstream effects and possibly specific underlying pathologies.

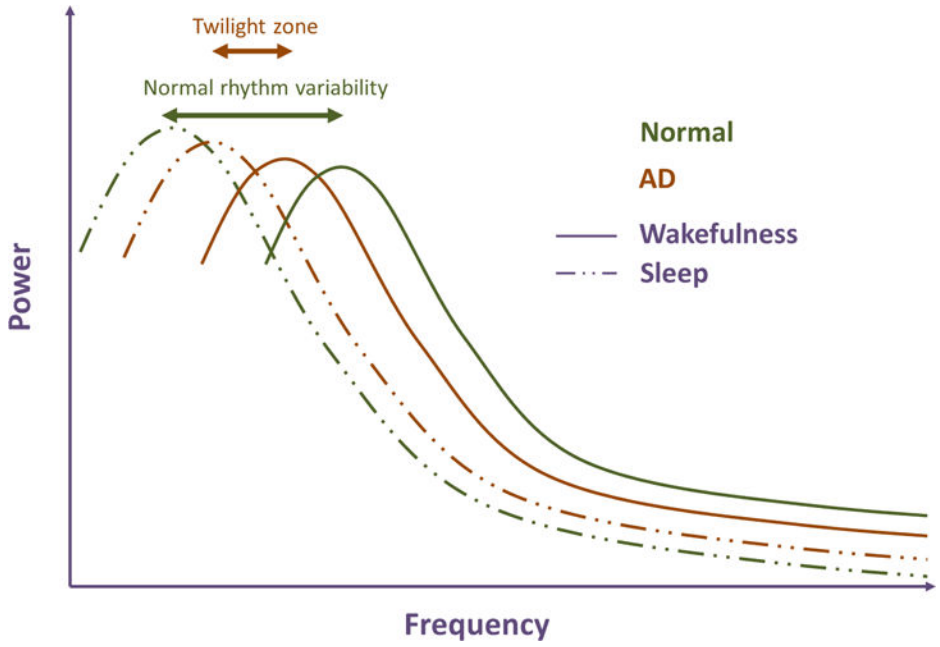

Figure 4. The twilight zone of attenuated rhythm fluctuations with Alzheimer's disease progression

Spectral density plot representing attenuated rhythm fluctuations in AD. As early as precognitive stages of AD pathology, there is gradual attenuation of rhythms in AD, with patients being unable to reach extremes of wakefulness or sleep. Behaviorally, they are less alert during daytime and more prone to awakenings with lighter sleep at night. Encephalographically, these behaviors are respectively expressed as a cumulative higher power in low frequencies with lower power in high frequencies during wakefulness (leftward shift), and an inverse pattern during sleep (rightward shift). The outcome is that of a constantly working cortex in the background even during sleep, and an inability to mount higher vigilance patterns during wakefulness.

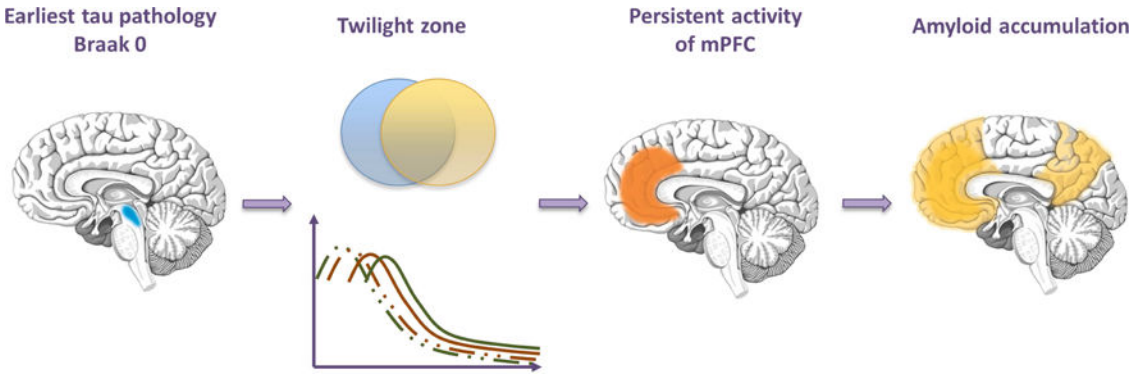

Figure 5. Proposed causal association between early brainstem tau pathology and subsequent cortical amyloid-β deposition

Attractor network breakdown in AD as a result of hypothalamic (e.g., VLPO) and isodendritic core neurofibrillary tangle pathology (e.g., locus coeruleus n., raphe n.) and related tau dysfunction leads to persistent cortical activity, especially of the mPFC, which in turn leads to amyloid-β deposition in the mPFC and subsequently other areas of the default mode network, prior to amyloid-β deposition across the entire brain.