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Circadian rhythm disruption and retinal dysfunction: a bidirectional link in Alzheimer's disease?

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Abstract

Dysfunction in circadian rhythms is a common occurrence in patients with Alzheimer's disease. A predominant function of the retina is circadian synchronization, carrying information to the brain through the retinohypothalamic tract, which projects to the suprachiasmatic nucleus. Notably, Alzheimer's disease hallmarks, including amyloid-β, are present in the retinas of Alzheimer's disease patients, followed/associated by structural and functional disturbances. However, the mechanistic link between circadian dysfunction and the pathological changes affecting the retina in Alzheimer's disease is not fully understood, although some studies point to the possibility that retinal dysfunction could be considered an early pathological process that directly modulates the circadian rhythm.

Key Words: Alzheimer's disease; amyloid; circadian rhythm; neurodegeneration; retina

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From the Contents

Introduction

Alzheimer's disease (AD), the most frequent age-related neurodegenerative disorder is characterized by neurocognitive symptoms that progress with age, including progressive loss of memory and, finally, dementia (Ballard et al., 2011; Barnes and Yaffe, 2011; Masters et al., 2015; Scheltens et al., 2016). Although the etiology of AD remains largely unknown, the deposition of amyloid-β (Aβ) and the formation of neurofibrillary tangles of tau protein in the central nervous system (CNS) constitute the main features of the disease. AD is also characterized by the common event of sleep and circadian rhythm disturbance (Holth et al., 2017; Musiek et al., 2018). Currently, it is discussed that these sleep and circadian alterations can be both a consequence and a cause of neurodegeneration, inducing disease onset or exacerbating its progression (Leng et al., 2019).

Circadian rhythms are led by oscillations of circadian clock genes in the suprachiasmatic nucleus (SCN), but also by propagation of light information from the retina. The SCN receives and encodes light information, projecting circadian oscillations and signals to other brain regions. Recent findings have helped to understand and clarify the role of the eye in regulating circadian rhythms, mainly new data on retinal ganglion cells (RGCs) that project to the SCN of the hypothalamus synchronizing circadian rhythms to the light-dark cycle (Kim et al., 2019; Leng et al., 2019; Zhang et al., 2021; Brock et al., 2022). Whether AD-related circadian rhythm abnormalities are an effect of the altered clock gene expression, retinal degeneration, or a mixture of both pathological processes, is still unknown. A deeper understanding of this complex system is essential for the management of AD.

In a transgenic amyloid precursor protein (APP)/PS1 mouse model of AD, we recently described changes in circadian clock gene expression in several brain regions: hypothalamus, cerebral cortex, and hippocampus. In addition, alterations of hypothalamic GABAergic response were observed in APP/PS1 mice, correlating with a decrease in RHT projections in the SCN. Additionally, we detected in the retina of APP/PS1 mice Aβ deposits, loss of melanopsin RGCs (mRGCs), decrease of choline acetyltransferase levels together with functional integrity, leading to retinal degeneration in contrast with age-matched WT mice (Carrero et al., 2023). Considering our findings in addition to other author contributions (Kim et al., 2019; Leng et al., 2019; La Morgia et al., 2021; Zhang et al., 2021; Brock et al., 2022), the theory that AD retinal degeneration plays an important role in affecting circadian rhythm control from early stages of the disease before clinical symptoms appear, gains importance. Then, here we propose to review and discuss the association between brain and retinal Aβ accumulation and the control of circadian rhythm.

Search Strategy

We conducted an exhaustive search within the PubMed database for articles published in English up to 2018 with the terms "Alzheimer's disease", "circadian rhythm", "retinal degeneration", "sleep deprivation", "circadian clock genes", "retinal amyloid", "brain amyloid", among others. We focused on references published within the past 5 years, except for key or landmark studies in the field. The final reference list was made on the basis of relevance to the theme of this Review.

Alzheimer's Disease Pathology

AD, the most common degenerative CNS disease in the elderly, is a progressive and lastly fatal neurodegenerative disorder. According to the Alzheimer's Association, AD accounts for approximately 60–80% of dementia cases (No authors listed, 2022). Faced an increasingly aging society, the number of AD patients and socioeconomic problems will increase severely. The central clinical features are cognitive dysfunction, memory loss, and abnormal behavior changes. The neuropathological hallmarks for AD are extracellular deposition of Aβ peptides, known as amyloid plaques, intracellular neurofibrillary tangles comprised of accumulated hyperphosphorylated tau (pTau) protein in neurons, neuroinflammation, synaptic alterations, and neuronal loss (Guo et al., 2020).

Many theories try to explain the pathogenesis of AD; however, the primary causes and ideal treatments are still undeciphered. Most of the proposed pathogenic mechanisms are based on two fundamental hypotheses: the amyloid cascade hypothesis and the tau hyperphosphorylation hypothesis. One of them, the amyloidogenic pathway, may be involved in the pathogenesis of AD. The Aβ cascade hypothesis has been the most dominant theory explaining the pathogenesis of AD. This hypothesis suggests that the extracellular deposition of Aβ is the initial pathological episode in AD, followed by the intracellular accumulation of abnormal tau proteins in neurofibrillary tangles. These pathological alterations, directly or indirectly, induce synaptic and neuronal dysfunction, and finally, the clinical symptoms of dementia (Hardy and Selkoe, 2002). Currently, the goals of therapeutic strategies based on the Aβ hypothesis are to reduce Aβ formation and

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aggregation and increase Aβ clearance. Based on the amyloid cascade hypothesis, it is believed that the clearance of brain Aβ deposition may treat AD reducing its progression. This hypothesis promoted the development of new anti-Aβ drugs to prevent Aβ aggregation in the brain in the last decades. Although they were able to reduce Aβ deposition (Klein et al., 2019) they did not reach the primary endpoint because they cannot delay the progression of the disease (Honig et al., 2018; Alexander et al., 2021; Knopman et al., 2021). It was highlighted that the pathogenesis of AD is more complex and multifactorial, and the underlying cause of pathological changes in AD is still unknown.

It is time to explore other processes and new pathogenic mechanisms. In AD, neurons undergo genomic destabilization, DNA damage/oxidation, epigenetic alterations, telomere shortening, reductions and alterations in metabolic pathways, and mitochondria dysfunctions (Guo et al., 2020; Song et al., 2021). Glial activation also contributes to AD pathogenesis through oxidative stress, inflammation, and immunomodulation (Zhao et al., 2020; Singh, 2022). AD is clinically heterogeneous, with numerous risk factors that affect its clinical and neuropathologic progression. Most AD patients experience some form of sleep disruption that is highly disruptive to quality of life (Petrovsky et al., 2018). It is hypothesized that sleep disturbances might appear prior to other clinical symptoms and contribute to the preclinical cascade of neuropathological events. Recent efforts have elucidated overlapping mechanisms underlying sleep disturbances and AD pathophysiology, reviewed by Kent et al., 2021. The pre-mild cognitive impairment (MCI) stage is a slow and asymptomatic phase characterized by its duration in time, up to 20 years prior to the first cognitive symptoms and diagnosis of AD. In this pre-clinical stage, besides amyloid and tau hallmarks, disturbances of sleep, vision, hearing, and olfaction occur (**Figure 1**).

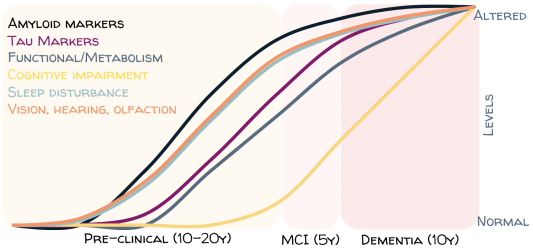

Figure 1 | **Hypothesis of markers and symptoms progression in Alzheimer's disease.**
Created with canva.com. MCI: Mild cognitive impairment; Y: years.

Many authors support the role of alterations in the visual (Asanad et al., 2021; Jáñez-García et al., 2021; Snyder et al., 2021; Koronyo et al., 2023) or the olfactory system (Brai et al., 2020) in preclinical stages as reliable biomarkers for early detection and progression of the disease. Bearing in mind these altered mechanisms in the preclinical phases, new horizons for the detection of biomarkers in organic fluids such as saliva or tears, and new therapeutic applications in AD, are presented.

Circadian Clock

The circadian clock is a 24-hour-endogenous biological clock that control physiological and behavioral functions such as cognition, sleep, immune response, or metabolism (**Figure 2**). The circadian clock can be modulated by external clues, being sunlight the most potent factor (Herzog, 2007; Nassan and Videnovic, 2022). Beginning on the retina, the environmental light is transmitted to the SCN, mainly via the RHT. In addition to the photic stimulus and to a lesser extent, there are no photic components, which also have a role in regulating the circadian cycle through the SCN. For example, physical activity, feeding schedules, or temperature are exogenous factors that contribute to regulating circadian rhythms along with light stimuli. Furthermore, there are peripheral clocks distributed in all tissues, synchronized with SCN via neural and/or humoral pathways (Nassan and Videnovic, 2022; **Figure 2**).

Circadian rhythms are generated in highly specialized cells of specific structures that control a complex network of coupled self-sustained clocks in the brain and the peripheral organs. In mammals, the central or master clock of the circadian network is located in the SCN in the anterior hypothalamus and is responsible for coordinating rhythms throughout the body and in different regions of the brain. Specialized neurons of the SCN receive direct synaptic input from the retina, synchronizing activity to the external light-dark cycle. Light input serves to synchronize the core cellular clock machinery in SCN neurons, which keeps 24-hour time and in turn synchronizes cellular clocks throughout the body. The molecular clock is a cellular transcription-translation feedback loop that involves the clock gene product *BMAL1* that interacts with its partner *CLOCK* to drive transcription of their negative feedback repressors, *PER1-3*, and *CRY1-2*, present in nearly all cells of the body. This transcriptional feedback loop maintains 24-hour rhythms in gene expression that are required for behavioral and physiologic rhythmicity at the organismal level (Leng et al., 2019). This circadian system comprised a central clock in the SCN and subsidiary peripheral clocks in neuronal and non-neuronal cells and tissues (Dibner et al., 2010; Nassan and Videnovic, 2022).

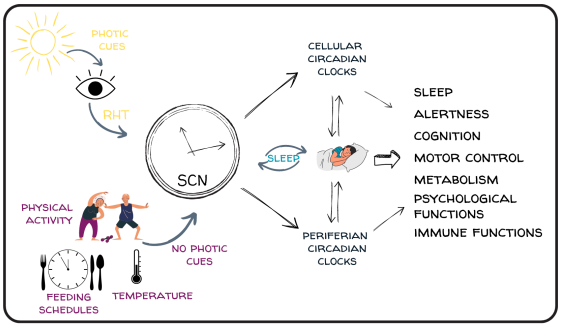

Figure 2 | **Structure and regulation of circadian rhythm.**
Retina-mediated photic information and other exogenous factors transmit signals to the SCN that synchronizes peripheral clocks. All these circadian clocks control physiological and behavioral functions. Created with canva.com. RHT: Retino-hypothalamic tract; SCN: suprachiasmatic nucleus.

New investigations have shown the presence of peripheral clocks in extra-hypothalamic areas of the CNS (Rath et al., 2014; Lim et al., 2017; Fusilier et al., 2021). A distributed network of extra SCN brain regions contains autonomous oscillators, which support circadian function. These secondary oscillators also rely on feedback loops comprising clock genes and proteins. However, the role of the clock pathway in the SCN and extra-SCN regions is thought to be distinct and reflective of the function of each brain region. Therefore, the disruption to the expression of clock genes in specific areas of the brain might contribute to the clinical phenomenology of AD although it cannot address the question as to whether this disruption is a cause or an effect of the neurodegenerative processes.

Circadian Rhythm Dysfunction in Alzheimer's Disease

In the last years, although disruption of circadian rhythm oscillations is common in older adults, this disturbance is more severe in people with neurodegenerative disease. Changes in sleep patterns are common in patients with AD and other dementias. They may wake up often during the night and find it hard to get back to sleep. Sleep fragmentation is an event of repetitive awakenings during sleep, in which the duration between each awakening is shortened, and often indicates a decrease in sleep quality. Enlarged sleep fragmentation due to intermittent nocturnal activation may lead to reduced total sleep time and sleep efficiency (Li et al., 2018). This warning sign is more widespread in MCI and AD patients (Mander et al., 2015; Musiek et al., 2018; Palmer et al., 2018). Besides sleep disturbance, there is growing interest in the association between sleep duration and dementia (Fan et al., 2019; Liang et al., 2019; Kent et al., 2021). Observational studies show both short and long sleep duration to be associated with an increased risk of cognitive decline and dementia (Liang et al., 2019). A recent study showed that short sleep duration in midlife is associated with a higher risk of dementia later in life, independently of sociodemographic, behavioral, cardio-metabolic, and mental health factors (Sabia et al., 2021). It has been suggested that sleep disturbances contribute to cognitive decline and increase the risk of AD by increasing the brain's Aβ burden (Shi et al., 2018; Irwin and Vitiello, 2019). Experimental studies support the detrimental effect of sleep deprivation on cognitive performance and Aβ clearance (Shokri-Kojori et al., 2018). The glymphatic system, responsible for cleaning waste from components from the CNS, is deteriorated in AD patients, decreasing brain homeostasis and the elimination of Aβ deposits (Iliff et al., 2012, 2013; Municio et al., 2023). Additionally, this waste-removal mechanism is partly regulated by circadian rhythms and sleep (Shokri-Kojori et al., 2018).

Although disruption of sleep and circadian rhythm are considered consequences of neurodegenerative diseases, more recently it has been described the presence of sleep disorders long before the onset of AD (Wang and Holtzman, 2020). Additionally, increasing evidences show that sleep and circadian rhythm disruptions may induce neuroinflammation, reduce Aβ clearance efficacy, increase reactive oxygen species levels, and disturb blood-brain-barrier (Musiek and Holtzman, 2016; Cuddapah et al., 2019; Uddin et al., 2020; Navigatore Fonzo et al., 2021). Aβ deposits in sleep-wake regulatory brain regions contribute to sleep deprivation in older adults through severe impact on circadian rhythm regulation (Musiek et al., 2018).

Sleep deprivation also causes increased pTau accumulation. It has been reported that tau levels in the brain interstitial fluid in mice and cerebrospinal fluid in humans are enhanced by sleep deprivation (Holth et al., 2019). In a triple transgenic AD mouse model, sleep restrictions produced a higher accumulation of pTau in the cerebral cortex (Rothman et al., 2013). Another study using the same AD mouse model, reported an increase in pTau insoluble fraction, associated with lower levels of postsynaptic density protein 95 (Di Meco et al., 2014). These results are consistent with the fact that circadian rhythms require synaptic coordination at the molecular and cellular levels for their maintenance. Then, tau-related pathologies may disturb synaptic plasticity leading to circadian rhythm disruption. In agreement

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with this theory, in a mouse model of tauopathy, the expression of the core clock protein such as PER2 and BMAL1 was altered in the SCN of these mice (Stevanovic et al., 2017). On the contrary, the tau protein plays a crucial role in the regulation of circadian rhythm, based on its properties stability and dynamic (Tracy and Gan, 2018), and its loss induces dysregulation of circadian rhythm (Arnes et al., 2019).

In the last five years, new data have reported circadian dysfunction in AD patients focused on the relation with the disease progression. It is postulated that alterations in circadian rhythm may be indicative of neurodegeneration due to Aβ deposition (Kang et al., 2021). Whereas circadian rhythm disturbances have been described in symptomatic AD patients with moderate to severe dementia (Liguori et al., 2014; La Morgia et al., 2016; Weissová et al., 2016; Pillai et al., 2021; Targa et al., 2021), few studies have reported in the pre-symptomatic phase of the disease. One study with preclinical AD patients found disturbances of rest-activity rhythm demonstrating that circadian fragmentation occurs very early in the course of AD pathogenesis and precedes cognitive symptom onset (Musiek et al., 2018). More recently, altered circadian rest/activity rhythms were observed in MCI patients compared to control subjects (Alfini et al., 2021). It was also reported association of disrupted sleep with early brain Aβ accumulation in older cognitively unimpaired adults, demonstrating a circadian rhythm dependence of sleep in preventing Aβ neuropathology (Insel et al., 2021).

To research molecular mechanisms involved in circadian rhythm disturbance and AD, a number of studies have been developed in mice models. A recent study using APP/PS1 transgenic mice showed that chronic sleep deprivation abnormal expression of clock genes in the circadian rhythm-related nuclei, impaired learning and memory, and further exaggerated disease progression in these AD mice (Niu et al., 2022). Senescence-accelerated mouse prone-8 mice also display sleep-wake and rhythm disturbances similarly than AD patients (Beuckmann et al., 2021). Moreover, circadian disruption could promote the development of AD in a mouse model of type 2 diabetes mellitus (Huang et al., 2021). These findings highlight the potential link between the disruption of circadian rhythm and the development of AD.

In our previous study, we show altered circadian clock gene expression in APP/PS1 mice in the hypothalamus, and two extra-hypothalamic brain regions, such as cerebral cortex and hippocampus, although here these alterations were less severe (Carrero et al., 2023). These transgenic mice already showed abnormal expression of clock genes at 6 months of age, increasing at 12 months, consistent with more advanced stages of pathology. Indeed, we proposed a linking between these alterations in the clock pathway with the brain Aβ pathology. Notably, it is known that Aβ could induce degradation and/or abnormal expression of clock genes, including *ARNTL* and *PER2* (Song et al, 2015; Wang et al, 2020). Based on the Aβ accumulation in hypothalamic neurons, we propose a direct association in this brain region between altered expression of circadian clock genes and Aβ accumulation on the control of circadian rhythm (Carrero et al., 2023). Consequently, our results suggest that Aβ-related pathology is related to changes in the expression of circadian clock genes.

However, we cannot rule out that the changes in clock gene expression respond to signals that reach the SCN from the retina through the RHT. Since we found an important deficit of RHT projections connecting in the hypothalamus in APP/PS1 mice, we propose that this reduced input pathway would result in abnormal hypothalamic activity. Supporting this hypothesis, we found dysfunction of the GABAergic pathway in the hypothalamus of these transgenic mice (Carrero et al., 2023). Notably, reduced SCN content of GABA, a neurotransmitter used by light signals to reach the SCN from the retina through RHT (Albers et al., 2017), has been recently associated with dysregulation of the circadian rhythm (Ono et al., 2018; Sonoda et al., 2020). Therefore, retina-related downregulation could be directly associated with altered expression of clock genes and consequently with circadian rhythm disruption.

Retina Pathology in Alzheimer's Disease

Despite the molecular oscillation in the SCN, the central circadian clock, is first considered to be involved in circadian disturbances in AD, it does not completely explain the alterations of circadian behavior. Importantly, the SCN responds to external environmental cues, such as light/dark cycles, by specific RGCs. The retina is the light-detective tissue in the eye that forms our image and non-image vision. The retina is a heterogeneous tissue made up of a series of stratified cell layers, including photoreceptor cells and glial cells that capture the light signal, transform photon energy into an electrical signal, and transports it to the brain through RGCs as electrical and chemical signals (Wässle, 2004; Palczewski, 2012). Photoreceptors are cells specialized to sense or receive light and convert light energy into neural impulses (Kefalov, 2012). More in detail and upon illumination, photon absorption by visual pigments in the photoreceptors initiates a transduction cascade that results in membrane hyperpolarization, decreasing glutamate in proportion to increases in light intensity (Ebrey and Koutalos, 2001; Arshavsky et al., 2002). Photoreceptors contact by synapse with other retinal cell, including horizontal cells and bipolar cells that relay photoreceptor signals from the outer retina to amacrine cells and RGCs in the inner retina. The dendrites of RGCs receive different combinations of excitatory and inhibitory inputs from bipolar cells and amacrine cells (Masland, 2012). Briefly, the retina is composed of vertical and horizontal pathways: photoreceptors transmit light signals to bipolar cells, which provide excitatory inputs to RGCs. This vertical pathway is modulated by horizontal inhibition from horizontal cells and amacrine cells.

However, the retina does not merely respond to ambient light passively, all of the retinal cells are known to have circadian oscillators, allowing retinal functions. These functions include the regulation of several behavioral and physiological functions, such as circadian rhythm. The role of the retina in regulating circadian rhythm has been clarified with the discovery of these intrinsically photosensitive mRGCs (Berson et al., 2002; Hattar et al., 2002). These mRGCs may receive light information from rods and cones but also in the absence of them, so they were also called intrinsically photosensitive (ip)RGCs (Berson et al., 2002; Hattar et al., 2002; Panda et al., 2002; Lucas et al., 2003). These cells constitute a small subset (4–5%) of RGCs giving rise to the RHT through which they project to the SCN of the hypothalamus synchronizing circadian rhythms to the light-dark cycle (Schmidt et al., 2011). In addition to their projections to the SCN, ipRGCs also project to other rodent brain regions, also involved in the regulation of circadian rhythms and sleep (Schmidt et al., 2011). Severe optic nerve and RGC degeneration with altered electroretinography responses are key manifestations associated with AD pathology (Doustar et al., 2017).

Evidence from histological and imaging examination in patients with MCI and AD reveals that the retina is vastly affected by AD pathology, showing similar alterations than those shown in the brain. Optical coherence tomography measurements have shown that there is a thinning of the retina in AD patients (Hart et al., 2016; Cunha et al., 2017; Doustar et al., 2017). Although several studies reported retinal nerve fiber layer (RNFL) thickness reduction in AD patients (Trebbastoni et al., 2016; Cunha et al., 2017; Jáñez-Escalada et al., 2019), other authors have described no significant differences in RNFL thickness between MCI or AD patients and control groups (Lad et al., 2018; den Haan et al., 2019; van de Kreeke et al., 2019). Aiming to clarify these contradictory findings, mouse models of AD have been used to perform longitudinal studies that assess retinal pathology. Using 3×Tg-AD mice, the thinning of the innermost retinal layers was detected at 4 months of age (Chiquita et al., 2019). Moreover, the thinning observed in the inner retina sub-layers, at early months, seemed to spread to almost every analyzed retinal layer from 8 months onwards (Chiquita et al., 2019).

However, in other mice models of AD, as *App*$^{NL-G-F}$ knock-in mouse, which is characterized by physiological expression of humanized mouse APP in disease-relevant central nervous system regions and cell types, no differences in the overall thickness of the retina layers were identified at any age (Vandenabeele et al., 2021). In double transgenic (APP/PS1) mice, there were also no significant differences in the thicknesses of the retinal nerve fiber layers between transgenic and control mice (Chidlow et al., 2017). In our recent study, we described morphological alterations in the retina of APP/PS1 mice but did not include appreciable changes in the thickness of the layers (Carrero et al., 2023), accordingly with these last reports (Chidlow et al., 2017; Vandenabeele et al., 2021).

Many studies have used the detection of retinal neurodegeneration to monitor the progression of AD. For example, thinner RNFL was associated with increased risks for dementia including AD (Mutlu et al., 2018). RNFL consists of axons of the ganglion cells guided to the CNS through the optic nerve. In addition, the thickness of RNFL and the volume of the macular ganglion cell layer were significantly decreased in AD patients (Santangelo et al., 2020). Moreover, a cross-sectional study has validated the association between structural and functional alterations of the retina and neuroimaging biomarkers in preclinical AD patients (Byun et al., 2021). This retinal neural degeneration has also been reported in different AD transgenic mice. RGC degeneration was described in 12-month-old Tg2576 mice compared with age-matched littermates and correlated with synaptic dysfunction mediated by hippocampal dendritic spine loss (Bevan et al., 2020). RGCs are particularly susceptible to AD-related damage because of their intraocular unmyelinated axons, high-energy demand, and complex dendritic trees (Inman and Harun-Or-Rashid, 2017). The loss of these cells may be a consequence of their increased energy demand and number of excitatory glutamatergic synapses (Williams et al., 2010). However, the possible mechanisms involved in the degeneration of cells and the optic nerve involved in the alterations described in AD are not well understood. It has been described that the functioning of retinal cells can be altered by defects into neurotransmitter such as acetylcholine (ACh) (Ngoo et al., 2019). ACh modulates glutamatergic transmission in retinal axons, being essential in the visual signal pathway (Mackey et al., 2012). In our previous study, we described lower retinal levels of ChAT, an enzyme involved in the synthesis of ACh, in APP/PS1 mice (Carrero et al., 2023). Therefore, we propose that ACh-mediated synaptic transmission would be compromised in the RGCs projections leading to reduced inputs that reach the SCN.

Accordingly, with the loss of RGCs projections, we also found a decrease in the mRGCs account in this mouse model of AD, similar than that reported in post-mortem AD retinas (La Morgia et al., 2016). More recently, an increased number of retinal Aβ plaques was reported in AD patients (Koronyo et al., 2017). Soluble Aβ oligomers, which are the main trigger for AD pathophysiology, have been observed in the retinas of AD transgenic mice (Habiba et al., 2020; Habiba et al., 2021; Vandenabeele et al., 2021). Several studies have shown that RGC apoptosis is associated with increased retinal Aβ deposits induced by *in vivo* Aβ administration (Guo et al., 2007; Mohd Lazaldin et al., 2020; Lazaldin et al., 2023). We also found Aβ deposition in the retina of APP/PS1 mice (Carrero et al., 2023). These findings are in agreement with those from a human study that reported Aβ deposits in the retina of AD patients (den Haan et al., 2018).

In addition to retinal Aβ deposition, pTau has also been reported in the retinas of AD patients (Schön et al., 2012; den Haan et al., 2018), and transgenic mouse models of AD (Alexandrov et al., 2011). pTau immunoreactivity was reported in retinal layers, from the ganglion cell layer to the outer nuclear layer (Liu et al., 2009). Particularly, pTau was detected in the somas and axons of RGCs (Yang et al., 2013; Chiasseu et al., 2017). Notably, retinal tau accumulation occurred as an early event, even preceding brain tauophaty and behavioral impairment (Chiasseu et al., 2017). Moreover, using an anti-tau therapy approach, pTau-related retinal pathology was diminished, reinforcing the relevant role of tau modulating retinal degeneration in AD (Latina et al., 2021).

Furthermore, retinal degeneration can be assessed using *in vivo* methods, such as using electroretinography (ERG). ERG assessment is a noninvasive eye exam that provides the bioelectrical activity of RGCs. Some studies indicate retinal dysfunction in mouse models of Aβ deposition using this technical approach (Gupta et al., 2016; Criscuolo et al., 2018; Georgevsky et al., 2019; Lim et al., 2020; McAnany et al., 2021; Frame et al., 2022).

Our recent study proposes that APP/PS1 mice show reduced ERG response, mainly at the inner retinal neurons at younger ages (6 months), but is enhanced at older ages (12 months) (Carrero et al., 2023). These findings agree with a longitudinal *in vivo* study in APP/PS1 mice showing that the function and structure of the inner retina was impaired with age, and started earlier than other alterations as cognitive impairment (Georgevsky et al., 2019). In other AD models such as 5xFAD mice, there are also selective inner retina deficits associated with age (McAnany et al., 2021). In summary, we, and others (Frame et al., 2022) consider that a reduction in ERG amplitude can be indicative of decreased RGC function or loss of RGCs. Notably, electrophysiological evidence of RGC dysfunction in AD patients, as reflected by a diminished ERG response, was provided three decades ago. However, more recently, ERG detected significant RGC dysfunction in pre-symptomatic AD (Asanad et al., 2021). Thus, all these findings suggest that ERG of the retina may be used as a screening tool for the detection of AD (Asanad et al., 2021).

Conclusion

In **Figure 3**, we represent the main summary points of this review. In AD, brain Aβ accumulation could induce altered expression of circadian clock genes, including degradation of clock genes such as *ARNTL* and *PER2*. This data suggests a direct connection of Aβ burden affecting the control of circadian rhythm. Desynchronization of circadian rhythms induces deregulation of sleep that could be the cause of changes in sleep patterns observed in AD patients. Sleep disturbance becomes a detrimental circle lowering Aβ clearance efficacy that contributes to increasing the brain's Aβ burden and neuroinflammation. Thus, these alterations contribute to exacerbating the neurodegeneration process that leads to AD pathology.

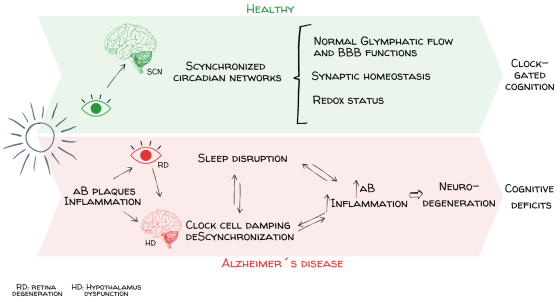

Figure 3 | **Potential relationship between retina dysfunction and circadian rhythms in Alzheimer's disease.**
Created with canva.com. Aβ: Amyloid-beta; HD: hypothalamus dysfunction; RD: retinal degeneration; SCN: suprachiasmatic nucleus.

However, Aβ deposition was also found in the eyes of patients and mouse models of AD, associated with RGC degeneration, including synaptic dysfunction and loss of RGC activity and number. Since RGC projections connect to the SCN, receiving direct synaptic input from the retina that contributes to circadian cycle synchronization, we cannot exclude that the changes in clock gene expression respond to retinal degeneration. Thus, circadian rhythm dysfunction and sleep abnormalities could be direct consequences of these retinal pathologies in AD.

Based on our hypothesis, reducing retinal degeneration and restoring regular circadian rhythms could be used as potential therapeutic strategies for AD, preventing the progress of the disease as well as mitigating their related symptoms. For instance, several clinical studies using long-term light treatment revealed attenuated cognitive decline and depressive symptoms (Riemersma-van der Lek et al., 2008; Figueiro et al., 2019; Zou et al., 2022). Neuroprotective molecules were also tested in the retina, including metformin (Domalpally et al., 2023), or flower extracts with γ-secretase inhibitory activities in the preservation of retinal ganglion cells (Hasegawa et al., 2020). However, the application of these interventions related to retinal circadian rhythm dysfunction in AD is a promising but relatively new field. Many questions remain to be addressed and further studies will be necessary to answer them.

Author contributions: *Conceptualization: CM and EC; investigation: LC, DA, CM, and EC; resources: LC, DA, CM, and EC; writing-original draft preparation: CM and EC; writing-review and editing: CM and EC; funding acquisition: EC. All authors have read and agreed to the published version of the manuscript.*
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Data availability statement: *Not applicable.*
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