REVIEW

# The Circadian System in Alzheimer's Disease: Disturbances, Mechanisms, and Opportunities

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Alzheimer's disease (AD) is a devastating neurodegenerative condition associated with severe cognitive and behavioral impairments. Circadian rhythms are recurring cycles that display periods of approximately 24 hours and are driven by an endogenous circadian timekeeping system centered on the suprachiasmatic nucleus of the hypothalamus. We review the compelling evidence that circadian rhythms are significantly disturbed in AD and that such disturbance is of significant clinical importance in terms of behavioral symptoms. We also detail findings from neuropathological studies of brain areas associated with the circadian system in postmortem studies, the use of animal models of AD in the investigation of circadian processes, and the evidence that chronotherapeutic approaches aimed at bolstering weakened circadian rhythms in AD produce beneficial outcomes. We argue that further investigation in such areas is warranted and highlight areas for future research that might prove fruitful in ultimately providing new treatment options for this most serious and intractable of conditions.

**Key Words:** Alzheimer's disease, chronotherapy, circadian, dementia, SCN, sleep

Disturbances of daily behavioral and sleep patterns are commonly described in neurological and psychiatric disorders (1). In Alzheimer's disease (AD) such behavioral disturbance is a leading reason for institutional care in moderate to severe AD (2). There is considerable evidence that disturbances of sleep-wake cycles are related to alterations in the suprachiasmatic nucleus (SCN), the master circadian pacemaker (3). The SCN is a small nucleus of the anterior hypothalamus located directly dorsal to the optic chiasm (from which it receives direct retinal innervations) that is composed of a neurochemically and functionally heterogenous assembly of neurons (4). Circadian rhythms are generated as an output of the clock gene cycle, produced by a series of interlocking transcriptional feedback/feedforward loops of a panel of clock genes (e.g., *PER1,2, CRY1,2, CLOCK, BMAL1*). Such cycles drive the rhythmic expression of clock-controlled genes, and ultimately such molecular cycles are translated into physiological and behavioral circadian rhythms (3,5). Outside of the SCN there are circadian oscillators throughout the brain and periphery, and the circadian network normally functions as a complex and distributed system that imposes temporal architecture on physiology and behavior (5). There are also circadian rhythms in neurocognitive parameters (6,7) and disruption of circadian rhythms leads to cognitive impairments (8). Circadian dysfunction also impacts negatively on immune, metabolic, and cardiovascular systems (9,10). Such circadian alterations are increasingly being explored with regard to both functional decline during healthy aging and in age-related diseases (11). In this review we examine the evidence with regard to circadian alterations in AD and explore the therapeutic avenues that arise and the opportunities for advancement at the interface between dementia research and chronobiology.

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## Functional Studies of Circadian Disruption in AD

Many studies to date have examined the relationship between aging and circadian function, with decreased amplitude but not period of the rhythm as well as alterations in circadian phase being commonly reported findings (12) (see the glossary of chronobiological terminology in Supplement 1). These alterations in circadian parameters are exacerbated in AD, the most apparent deficit being fragmentation of the sleep-wake cycle leading to increased nocturnal awakenings and increased daytime sleep bouts (13). The use of noninvasive actigraphy (usually via a wrist-worn accelerometer) has been beneficial in monitoring rest/activity cycles in dementia patients since the early 1990s (14,15). Later rest/activity cycles of home-dwelling AD patients were examined over one year, and those with mild dementia displayed rhythms not significantly different from those of control subjects, whereas those with moderate dementia displayed fragmentation of the rhythm and decreased amplitude, although these effects were not correlated with the severity of the dementia (16). Van Someren *et al.* (17) reported that rhythms were most fragmented in institutionalized AD patients and that higher levels of daytime activity predicted more coherent rhythms, whereas lower levels of daytime activity predicted rhythm fragmentation. Changes in circadian parameters are not equivalent across different types of dementias; there are differences in the nature and magnitude of rhythm disturbance in AD, frontotemporal dementia, and diffuse Lewy body disease (18). The overall locomotor changes that occur in AD seem to be related to more specific behavioral changes, for example in meal time, which in turn might be linked to poorer nutritional outcomes (19). Further evidence for the importance of circadian rhythms in AD is provided by the finding that higher daytime activity levels and lower nocturnal activity (i.e., consolidated, nonfragmented sleep/wake cycle organization), is strongly associated with increased wellbeing and functional status (20). Results from a large prospective study indicate that changes in circadian activity patterns (decreased

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rhythm amplitude, phase-delays) are significant predictors of subsequent AD or mild cognitive impairment, suggesting that compromised rhythms might be a preclinical phenomenon (21). Another point of interest is that anti-psychotic medication used in the clinical management of AD might impact on circadian rhythms (22), because these medications might impact on the molecular components of the circadian system (23).

General activity is not the only parameter that can be used to assess circadian rhythmicity at the gross level in AD. Skin temperature monitoring demonstrates that proximal but not distal skin temperature is raised in the daytime in AD patients compared with elderly control subjects, with no nocturnal difference in either distal or proximal skin temperature (24). Proximal skin temperature was also positively correlated with daytime sleepiness in both AD patients and healthy control subjects. One explanation for these findings is that alterations in proximal skin temperature in AD are functions of altered circadian clock control of autonomic processes involved in the regulation of skin temperature.

A potential consequence of disrupted circadian rhythms in AD is the manifestation of rhythms in behavioral agitation. Patients affected by AD often develop varying disruptive behavioral symptoms, such as agitation and restlessness, verbal outbursts, wandering, physical threats, and aggression (25). "Sundowning" is the term given to the occurrence of the aforementioned symptoms during the late afternoon or early evening (26,27). The prevalence of sundowning in AD is reported as being between 13% and 66% (28–30). The temporal nature of sundowning is suggestive of a circadian origin: nonlinear analyses of actigraphic data in AD show that higher levels of motor regularity, especially during the night, are associated with aggressive behavior in AD patients (31).

Insight into the nature of the circadian disturbances that occur in AD is provided through the analysis of actigraphic activity data for scale invariance of activity fluctuations, which was reduced in AD patients and most reduced in the oldest, most severely demented patients (32). This is of interest, because scale invariance in activity patterns is found in rodents to be dependent on the SCN (33), and so the changes observed in AD might be taken as indicative of changes occurring in the master clock that are then translated into gross patterns of behavior. This finding is in accordance with the findings from neuropathological studies discussed later.

There are some significant issues that limit the interpretation of functional studies of circadian rhythms in AD. First is the nature of the diagnosis commonly used to select study populations, that of dementia of the probable Alzheimer's type, which cannot be confirmed until postmortem examination (itself not routinely carried out). Given that dementia is a symptom of many other diseases of old age and that postmortem examination might not confirm a diagnosis of AD (e.g., 15% of diagnoses are not confirmed at autopsy [34]), it seems likely that the populations examined in the aforementioned studies represent a heterogeneous population representing both AD and non-AD dementias. Another caveat for actigraphy-based studies is the ease with which rhythms might be masked by environmental factors, such as nursing care, occupational therapies, and a host of societal factors for studies in AD patients in the home setting. Such concerns are not just limited to dementia studies and do not negate the usefulness of actigraphy to gain significant insight into circadian rhythm disturbance in AD, but they do highlight that care needs to be taken in the interpretation of results from such studies. Supplement 1 contains information on neuroendocrine changes in AD.

## Postmortem and Neuropathology Studies

Postmortem studies have assessed neuropathological changes within the SCN in both healthy aging and in dementia and neurodegenerative disease (12). Stopa *et al.* (35) evaluated the degenerative changes in the SCN from patients with severe AD and found neuronal loss and tangles, indicating that the SCN is affected by AD, whereas amyloid plaques were only seldom noted in the SCN. Overall SCN volume has been reported to decrease in dementia of the Alzheimer's type (36), and the expression of the neuropeptide vasoactive intestinal polypeptide (VIP) was found to be decreased in the presenile male SCN (37). There is also a loss of rhythmicity of SCN arginine vasopressin (AVP) during aging (38), and in AD this loss of AVP neurons and rhythmicity is accelerated (39,40). Loss of neurotensin-expressing neurons in the SCN of AD patients is also reported along with increased astrocytes (35). Because VIP, AVP, and neurotensin are known to alter SCN neuronal function (41,42), their loss during AD might be of particular functional consequence. Interestingly, there is evidence to suggest that neuropeptide alterations in the SCN occur at early stages of AD and might preface cognitive decline (43). Harper *et al.* (44) also provide evidence that neuropathological progression (as measured by Braak stage) in postmortem AD brains is associated with the severity of circadian abnormalities, suggesting that the circadian rhythm disturbances in AD are directly linked to the central neuropathology of the disease. There is also evidence for neurodegeneration in the SCN in both AD and frontotemporal dementia, as determined by the neuron/glia ratio, and this degeneration correlates to the magnitude of circadian rhythm impairment in core body temperature and activity parameters (45). Loss of SCN neurotensin cells was also associated with dampened activity rhythm amplitude but not with increased fragmentation of the rhythm, although loss of AVP neurons in the dorsomedial SCN was associated with rhythm fragmentation but not dampened amplitude (45). Expression of the MT1 melatonin receptor in the SCN is also markedly decreased in late stage AD (40). Supplement 1 contains an overview of circadian influences on Aβ levels.

Another area that undergoes neurodegeneration in AD and might be important for circadian rhythm disturbance is the cholinergic basal forebrain. Cells of the nucleus basalis project to the SCN (46), there is cholinergic innervations of the SCN (47), and cholinergic agents act in the SCN to modulate circadian rhythms (48). The question should then be posed as to what effect the loss of cholinergic cells in the basal forebrain in AD might have on circadian function. Lesion of the cholinergic projection to the SCN in rats leads to alterations in the phase-shifting effects of light on circadian rhythms (49), although another study in using lesions of the cholinergic medial septum did not find alterations in circadian parameters (50). Differences between these studies might be due to the neuroanatomical locations of the lesion as well as differences in the behavioral paradigms examined. The study of Wisor *et al.* (51) reports that alterations in non–rapid eye movement sleep in the Tg2576 mouse model of AD might be due to alterations in cholinergic transmission. On balance, it seems reasonable to suggest that further studies examining the role of cholinergic depletion in circadian disturbance in AD (e.g., postmortem analysis of acetylcholine fibers in the SCN) are needed (Figure 1).

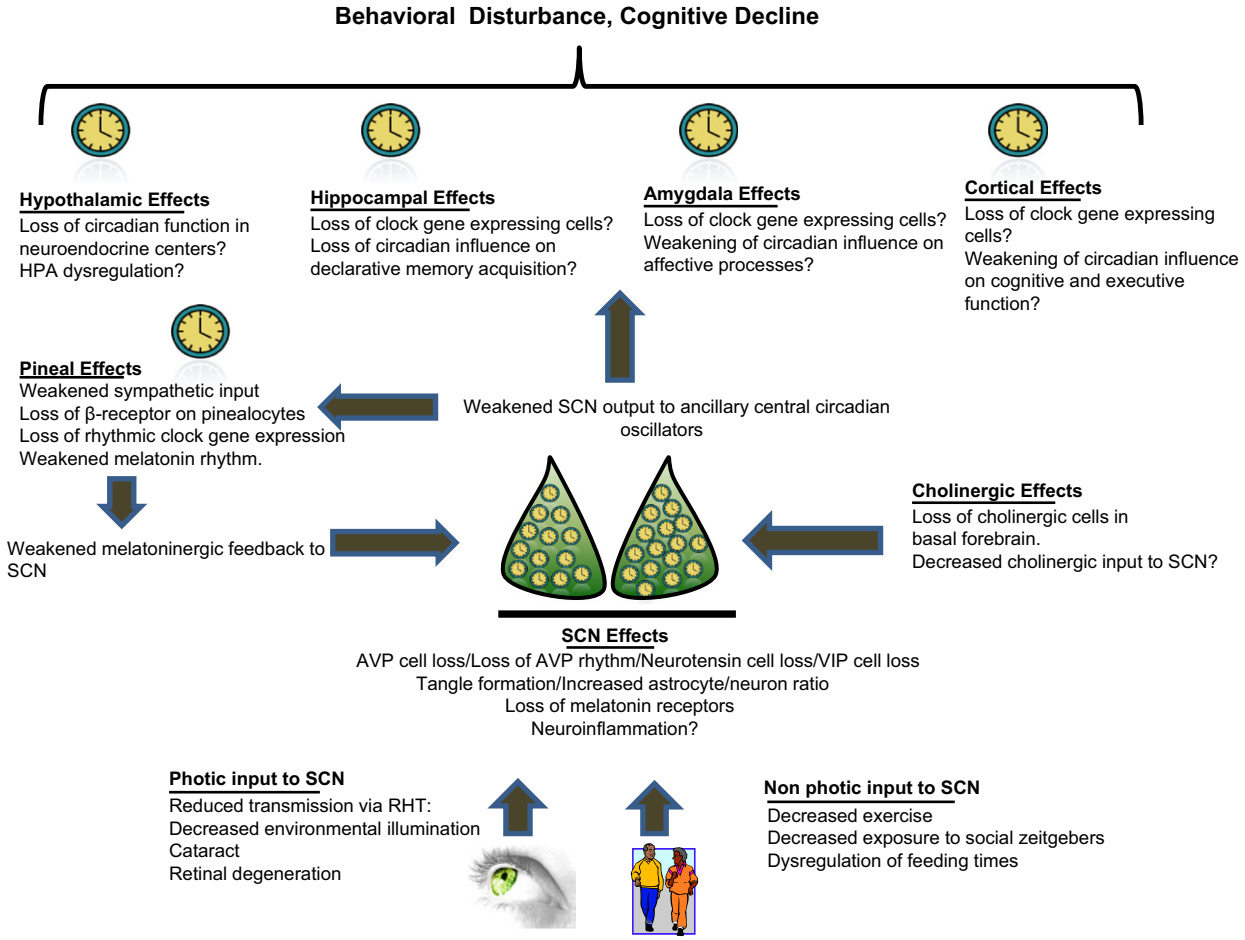


**Figure 1.** Graphic illustrating potential pathways by which circadian rhythms might be disturbed in Alzheimer's disease and how such disturbances might impact on physiological, cognitive, and behavioral changes in Alzheimer's disease. AVP, arginine vasopressin; HPA, hypothalamic-pituitary-adrenal; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; VIP, vasoactive intestinal polypeptide.

## Clock Gene Cycles in AD

Given the key roles played by clock genes in the generation of physiological and behavioral circadian rhythms, it is of particular interest to inquire how clock gene expression cycles are affected in AD and other dementias. Such work is difficult, due to the dependence on postmortem tissue to examine clock gene expression in the SCN and other central sites. Recently, the expression of the clock genes *PER1*, *PER2*, and *BMAL1* was examined in the bed nucleus of the stria terminalis (BNST), the cingulate cortex, and the pineal gland (52). These are core clock genes that serve to regulate the near–24 -hour regulation of clock-controlled gene transcription and ultimately manifest circadian rhythmicity at the physiological level. Both the BNST and the cingulate cortex have previously been shown to express rhythmic clock genes (10,53). Similar peak times for *PER1* and *PER2* in control subjects in the active phase were reported, whereas *BMAL1* was shown to peak in the night (52). Interestingly, *PER*s and *BMAL1* displayed significant 24-hour rhythmicity in the brains of AD patients. However, a state of desynchrony in oscillation between cortex, pineal gland, and the BNST in AD patients was found, possibly caused by the degeneration of the SCN cells in AD brains (52). Given the roles of the BNST and cingulate cortex in decision-making and motivated behaviors and the position of the pineal gland as a major output of the SCN, abnormal rhythms in these brain regions or lack of coordination between them might contribute to cognitive and sleep-wake deficits in AD patients. Rhythmic expression of *BMAL1*, *CRY1*, *PER1* in human pineal has been reported, and these rhythms are lost in pineals from both preclinical and clinical AD patients (40). Tseng *et al.* (54) examined expression of *PER1* in peripheral leukocytes during different sleep stages in healthy control subjects, those with mild cognitive impairment, and patients with AD and reported no difference across the groups in terms of *PER1* expression. Although such observations are valuable, their interpretation is hampered by the lack of data on clock gene expression in SCN tissue. There seems to be an opportunity here to use recently developed methods of assaying molecular rhythms in peripheral tissues (55,56) in AD to gain a more systematic insight into circadian rhythm dysfunction than is likely to be afforded by postmortem studies (Supplement 1 contains an overview of clock gene polymorphisms in AD).

## Findings from Animal Models of AD

Given the difficulty in assessing core circadian processes in demented patients (e.g., the unsuitability of forced desynchrony or constant condition protocols needed to assess parameters such as circadian period), attention has been paid to using animal

models of AD to assess circadian alterations. There is no one animal model of AD that recapitulates fully AD (57), and many animal models of AD model the amyloid but not the τ pathology associated with AD. However, such models can provide valuable insight and allow for full behavioral and molecular characterizations from a circadian standpoint. There is the added complexity of the age × background interactions in transgenic animals, and not all studies examining circadian rhythms in animal models of AD have adopted longitudinal approaches sufficient to address this important concern. Furthermore, many studies to date do not undertake a comprehensive circadian analysis, and so only part of the picture is available for many of these AD models.

In rats, injection into the SCN of transgenic cells overexpressing β/A4 leads to significant deterioration of the circadian rhythm, in terms of both fragmentation and rhythm period and power (58). In hamsters, injection of β amyloid 25-35 into the SCN resulted in phase-advanced and less consistent diurnal rhythms, effects that were attenuated by melatonin (59). In the amyloid precursor protein (APP)23 mouse model activity levels centered around "dusk" were diminished, although overall activity levels in the active dark phase were increased (60). In a further study on APP23 mice, activity in the second half of the active phase is increased (61), and this might be analogous to sundowning in AD patients, which also occurs in the second half of the active phase. In the APP mouse there are alterations in the temporal organization of anxiety-like symptoms that emerge when compared with age-matched control subjects (62) and again suggest that such changes might be important for understanding circadian influences on sundowning.

The Tg2576 mouse model shows marked lengthening of the free-running period in constant darkness, although under a light/dark cycle activity was confined mostly to the dark period, indicating that—although there might be alterations to the period—these are compensated by normal entrainment mechanisms under a light/dark cycle (51). In a further study of the Tg2576 model, no changes across the lifecourse in period, activity onsets, or offsets were reported, although there were ultradian changes in activity parameters (63). This finding might be consistent with the finding that there was no evidence of amyloid deposits in or nearby the SCN in the Tg2576 mice. In the TgCRND8 model diurnal organization of behavior was altered, with more daytime activity and lessened levels of nocturnal activity, suggesting rhythm fragmentation, and these effects are noted before the appearance of A-β neuropathology (64). Modifications of diurnal patterns of activity in APP knockout animals can be rescued by the secreted β-amyloid precursor protein ectodomain APPsα (65).

The 3xTg mouse model, which displays both A-β and τ pathology, did not display abnormalities in free-running period or photic phase-shifting but did display markedly reduced activity levels after the onset of A-β pathology (66). These mice also displayed changes in the neuropeptidergic content of the SCN (AVP- and VIP-expressing neurons), a situation that echoes findings from postmortem studies of the SCN in AD. Another recent study on the 3xTg model shows exaggerated amplitude and a phase advance of the core body temperature rhythm, and these effects were not dependent on cyclooxygenase and occurred in the absence of neuropathology in the hypothalamus (67). Analysis of the AβPPswe/PSEN1A246E mouse—which carries transgenes for both APP and presenilin-1—shows that, although activity levels are increased, circadian organization of behavior is not increased (68). Likewise, the doubly transgenic model SPPswe/PS1dE9 mouse (up to 7 months of age) does not display marked abnormalities in its circadian organization of behavior, although there is an increase in daytime core body temperature compared with wildtypes (69). The APPxPS1 mouse displays a phase delay of its daytime wakefulness bout, although most parameters of the activity rhythms were not altered (70). Furthermore, old APPxPS1 animals displayed blunted diurnal variation in the SCN expression of *Per2*.

Overall, although studies of individual animal models of AD yield varying results, possibly due to the different natures of these models, some interesting points emerge. One is that there is not necessarily a link between alterations in activity levels and the temporal organization of that behavior. This might be explained if the SCN and by extension SCN output is spared, but neuropathology impacts on cortical and subcortical areas implicated in motor control. There are undoubtedly further opportunities to gain more insight from such animal models, for example by using luciferase-based reporter systems for clock gene expression monitoring in real time in transgenic mouse models of AD as well as the application of electrophysiological examination of SCN neuronal function in AD models.

## Chronotherapeutics in AD

Given that there is considerable evidence of circadian dysfunction in AD, therapeutic approaches that seek to target circadian abnormalities might provide novel avenues of treatment for AD. Such chronotherapeutic interventions might involve environmental (e.g., light therapy), behavioral (e.g., exercise), and/or pharmacological (e.g., melatonin) approaches (71). Satlin *et al.* (14) reported that evening light therapy led to stabilization of rhythms and improved sleep, although morning light therapy also significantly improved sleep (72). Morning light therapy also bolsters circadian rhythms and improves mini mental state examination scores, especially in the early stages of AD (73). Morning light therapy also seems to delay the onset of sundowning by an hour and a half, although the ratings of the agitation are not altered (74). Even in severe dementia morning light therapy might lead to phase advances of circadian rhythms and improve behavioral symptoms (75), and both morning and evening light therapy improves circadian parameters and leads to consolidation of sleep (74). Dowling *et al.* (76) did not report beneficial effects of light therapy on sleep parameters in institutionalized AD patients, but the light therapy did lead to a more stable circadian phase, and it has been suggested that those AD patients with the most severe circadian abnormality are most likely to respond to light therapy (77). Efficacy of light therapy might also be enhanced significantly in combination with melatonin treatment (78). The use of light to simulate dawn and dusk, a more naturalistic light therapy approach, was found not to improve circadian amplitude or stability or cognitive parameters but did advance sleep onset, shorten sleep latency, and consolidate nocturnal sleep episodes (79).

Care settings for dementia patients are often dimly illuminated, a factor that might be of consequence when considering the potential beneficial impact of light on strengthening disrupted rhythms. Van Someren *et al.* (80) first reported on the potential therapeutic benefit of increasing incident illumination in care settings. Increasing light exposure of dementia patients does not impact on depression ratings, although there are suggestions that individual cases might benefit (81). Riemersma-van der Lek *et al.* (82) conducted a large randomized control trial increasing illumination levels in care facilities for elderly persons and found

that long-term (approximately 1.5 years) increase in illumination levels slowed the decline in mini mental state examination scores (on average by .9) and lessened depression ratings and functional impairments. Such an approach is being trialled in AD patients, and the results of this study will be very illuminating with regard to the efficacy of a simple environmental intervention in improving cognitive, psychological, and behavioral symptoms of AD (83). A recent study has indicated that lower levels of light exposure in AD patients during the winter might be associated with greater circadian rhythm abnormalities (84), highlighting the putative link between light exposure, seasonal effects, and circadian rhythm disturbances.

The therapeutic use of melatonin has also been examined in AD. Melatonin treatment in the evening is usually used to achieve a phase advance of the circadian rhythm, although morning melatonin might be used to produce a phase delay (85). A double-blind study of melatonin in AD revealed improvements in cognition as well as decreasing nocturnal activity and increased nocturnal sleep (86). A larger, multicenter study trial did not report any beneficial effects of melatonin on actigraphically determined sleep patterns in AD, although it is worthwhile to note that the timing of melatonin treatment in this trial (1 hour before bedtime, and so after the onset of endogenous melatonin synthesis) was specifically selected so as not to elicit phase shifts (87). Another trial examining the effects of melatonin on agitation, sleep, or circadian rhythms in AD failed to find any benefit of melatonin (88). There are many issues left to resolve with respect to the usefulness of melatonin in AD. If it is not effective in improving circadian rhythms and sleep on its own, then does it augment the effects of light therapy (78)? What dose of melatonin is used? And at what time is melatonin treatment administered? Is a long- or short-release formulation used? How well are different melatonin formulations tolerated in AD? Does the antidepressant agomelatine, which is an agonist for the MT1/2 melatonin receptors, have any efficacy in improving rhythms, sleep, or cognitive, behavioral, and/or psychological symptoms in AD? Another general point about light therapy versus pharmacological studies is the difficulty in achieving blinding in studies of light therapy, as opposed to trials with drug treatments. This factor might be important when considering the relative efficacies of light-based treatments versus drug-based treatments. Supplement 1 provides an overview of the roles of activity-based therapies in circadian rhythms in AD (89).

## Conclusions and Perspectives

It is apparent that considerable circadian dysfunction occurs in AD, that such dysfunction seems to preface the clinical onset, and that disease severity seems to correlate with the magnitude of circadian dysfunction. With regard to chronotherapeutics, there are encouraging signs from studies of simple environmental interventions such as increasing the ambient illumination in care facilities, and light therapy also has shown some promise to date. It is important to note that the most marked circadian abnormalities noted in AD are dampened amplitude and rhythm fragmentation rather than circadian misalignment (a more prevalent feature of mood disorders [90]). As such, interventions focusing on strengthening zeitgebers rather than phase-resetting might prove most fruitful. There is a need for large, randomized controlled clinical trials of chronotherapeutics in AD.

With regard to the nature of the circadian disruption that occurs in AD, there is much still to be understood. One aspect that might be of importance is the role of neuroinflammation in AD on SCN and circadian function. Alzheimer's disease, like many other neurodegenerative diseases, is associated with neuroinflammation (91) which can impact on SCN and circadian function (9,92,93). Another area worthy of further investigation is the role that cholinergic cell loss has in circadian rhythm disturbance in AD and whether anti-cholinesterase drugs might impact on such rhythms in AD.

In conclusion, understanding the nature of circadian rhythm disturbance in AD and how such disturbances might be ameliorated for the improvement of patients and caregivers is a topic worthy of considerable future effort.

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