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Circadian rhythm changes in healthy aging and mild cognitive impairment

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Abstract

Disruptions in circadian rhythms can occur in healthy aging; however, these changes are more severe and pervasive in individuals with age-related and neurodegenerative diseases, such as dementia. Circadian rhythm alterations are also present in preclinical stages of dementia, e.g., in patients with mild cognitive impairments (MCI), thus providing a unique window of opportunity for early intervention in neurodegenerative disorders. Nonetheless, there is a lack of studies examining the association between relevant changes in circadian rhythms and their relationship with cognitive dysfunctions in MCI individuals. In this review, we examine circadian system alterations occurring in MCI patients compared to healthy aging individuals while also considering their association with MCI neurocognitive alterations. Our main findings are that abnormal circadian changes in rest-activity, core body temperature, melatonin, and cortisol rhythms appear in the MCI stage and that these circadian rhythm disruptions are associated with some of the neurocognitive deficits observed in MCI patients. Also, preliminary evidence indicates that interventions aimed at restoring regular circadian rhythms may prevent or halt the progress of neurodegenerative diseases and mitigate their related cognitive impairments. Future longitudinal studies with repeated follow-up assessments are needed to establish the translational potential of these findings in clinical practice.

Graphical Abstract

This article provides a narrative review of the most relevant findings of circadian rhythm changes/disruptions in four domains, which involve rest-activity rhythm (RAR), core body temperature (CBT), melatonin, and cortisol in patients with mild cognitive impairment (MCI) relative to healthy aging individuals. We also examine the relationships between normal aging and MCI-related changes in circadian rhythms relative to cognitive functions.

Keywords

Circadian rhythm; Mild cognitive impairment; Neurocognitive function; Young adults; older adults

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1. Introduction

With the rapid growth of the world population, it is estimated that between 2010 to 2050, the proportion of adults over 65 years will increase from 8% to 16%.[1] Aging affects virtually all human physiological processes, including circadian rhythms. Although the underlying mechanisms of aging are complex and have yet to be fully understood, an increasing number of studies indicate that changes in circadian rhythms across the lifespan significantly affect age-related modifications in brain physiology and related behaviors.[2-14]

Circadian rhythm changes in the elderly (≥65 years) affect temperature regulation, perception, information processing, as well as general cognitive abilities. Many of these changes are part of the normal aging process, but some can be caused by pathophysiological mechanisms underlying neurodegenerative and neurocognitive disorders.[2] Understanding how to distinguish the above-mentioned processes can provide an opportunity to intervene and improve the quality of life of patients suffering from neurodegenerative disorders, including Alzheimer's disease (AD) and Lewy Body dementia (LBD), since pathological disruptions in circadian rhythms may represent an early sign of these disorders.[4, 15-28] Specifically, circadian rhythm changes that deviate from a healthy aging trajectory are likely to begin when the functional and cognitive decline leading to AD and other major neurodegenerative disorders first occur, thus providing a unique window of opportunity for early interventions aimed at rectifying this abnormal trajectory.

Mild cognitive impairment (MCI) is defined as a greater cognitive decline compared to the average expected decline for an individual's age and education level, which occurs without significant changes in daily routine activities (Figure 1.a).[29, 30] Based on the DSM-5 criteria, MCI is a condition characterized by memory complaints and abnormal memory for the age that does not meet the criteria for dementia, in the context of retained ability to perform activities of daily living independently and preserved general cognitive functioning.[31, 32] MCI has been identified as a high-risk condition for more severe neurological disorders, including AD and LBD, and it is considered a prodromal state of variable duration between normal aging and dementia.[33-37] It is reported that MCI affects up to 42% of people over 60 years of age.[38-40] Within this subgroup, approximately 70% of individuals will develop AD or some other forms of dementia within 5 years.[29, 41] Although it is still unclear whether circadian rhythm changes/disruptions precede the onset neurodegenerative disorders, thus being causally implicated in their development, biological and environmental disruptions to these systems do seem to worsen with the appearance and progression of these disorders.[9] Thus, although prospective, longitudinal studies are needed to establish whether circadian rhythm alterations are risk factor for MCI and dementia.[42-44], comprehensively characterizing these alterations in MCI patients can help identify early disruption in circadian rhythmicity in individuals at higher risk for neurocognitive disorders. However, circadian rhythm dysregulations in MCI individuals have not been thoroughly described.

In this article, we reviewed key findings from the extant literature on circadian rhythm changes in normally aging elderly subjects and MCI patients, including the main established differences in circadian patterns between MCI and control groups. We also investigated the association between circadian rhythm disruptions and altered cognitive function in

MCI relative to age-matched healthy individuals. Finally, we discussed how this body of evidence may inform prognosis and lead to the development of targeted, timely treatment interventions in MCI aimed at preventing worse clinical outcomes and/or progression towards major neurocognitive disorders.

2. Literature search

To infer circadian rhythm changes in healthy aging compared to mild cognitive impairment, we searched the PubMed and Web of Science databases for the "(MCI OR Mild Cognitive Impairment OR Healthy Brain Aging OR Normal Brain Aging) AND (circadian OR diurnal OR actigraph* OR actimet* OR accelerometer) AND (cognitive function)" terms. After removing duplicates, one author (AK) screened titles and abstracts and, where relevant, the full text of the studies to assess their eligibility. Because we wanted to specifically assess circadian rhythmicity in healthy aging and MCI, sleep parameters were not examined, and studies exclusively assessing these parameters were excluded.

3. Circadian rhythm changes in healthy aging and MCI

Based on the findings from our literature search we decided to report on the four main aspects of circadian rhythm changes: rest-activity rhythm (RAR), core body temperature (CBT), cortisol, and melatonin release in healthy aging and MCI: (Table 1, Figure 1).

3.1. Rest activity rhythm (RAR)

Age has a significant effect on the rest-activity rhythm (RAR, also described as the sleep/wake cycle). The shift in preference from eveningness to morningness is consistently associated with age-related circadian rhythm changes.[2-4, 7] Specifically, finding from healthy aging human studies indicate that adults in their 60s and 70s commonly tend to rise from and retire to bed earlier than adults in their 20s and 30s.[2, 3, 45-49] Several studies have also reported that the amplitude of circadian rhythms is progressively blunted in healthy aging.[3, 50, 51] Taken together, weakening amplitude and phase advance in the sleep/wake cycle chronotype appear to be a reliable pattern occurring in healthy aging (Figure 1.b). Compared to healthy, age-matched control groups, MCI patients tend to show a further phase advance in rest-activity, light exposure, and position.[15, 52] Findings also suggest greater wake after sleep onset and increased sleep latency in these patients.[53] Other studies on MCI have highlighted a disruption in circadian rhythm measures, including weakened circadian activity rhythm,[54] significant fragmented and weakened circadian rest-activity/sleep-wake rhythm,[55] a less robust rhythm, lower amplitude, and delayed timing of peak activity based on actigraphy.[56] Patients with MCI have also greater nighttime activity and less activity in the morning compared to aged matched controls (Figure 1.b),[57] although one study found no differences in circadian phase or rest-activity patterns in cognitively intact older adults compared with patients with MCI.[58] Several recent studies have also confirmed that advanced acrophase (representing the rest-activity phase, timing of peak activity) and increased activity fragmentation, as reflected by increased intra-daily variability, are the most consistent alterations in MCI relative to age-matched healthy comparison groups.[23, 35, 59]

3.2. Core body temperature (CBT) rhythm

The regulation of core body temperature (CBT) is one of the most critical functions of the nervous system, which is controlled by the thermoregulatory system. Two types of mechanisms, physiologic and behavioral, regulate body temperature. Physiologic effectors are involuntary and mostly autonomic responses that generate or dissipate heat. Brown adipose tissue (BAT) thermogenesis and skeletal muscle shivering are primary physiologic responses to cold exposure, which generate heat, and the constriction of blood vessels via vasoconstriction to prevent heat loss. Warmth exposure triggers a complementary set of autonomic responses, including suppression of thermogenesis and facilitation of heat loss through water evaporation, that can be achieved via sweating and/or vasodilation.[60] Three other physiological aspects that define the CBT variation include the molecules and cells that measure body temperature in the periphery, the neural pathways that communicate this information to the brain, and the central circuits that coordinate the homeostatic response. Behavioral mechanisms are also involved in body temperature control. Thermoregulatory behaviors are motivated, meaning that they are goal-oriented actions that are learned by reinforcement and driven by the expectation of reward. For example, the most basic thermoregulatory behaviors are cold and warm seeking that regulate human behaviors like wearing clothing or using air-conditioning respectively. The engagement of specific thermoregulatory mechanisms is hierarchical, meaning that different effectors become activated at different temperature thresholds and, in turn, affect the shape (e.g., amplitude and duration, etc.) of the CBT rhythm.[60, 63] In young adults (mid-20s), the peak of the core body temperature rhythm is early in the evening, and the minimum core body temperature (i.e., the trough of the rhythm) occurs early in the morning. The period of the rhythm remains stable in older adults (late 60s), when compared with healthy young subjects under carefully controlled lighting conditions.[64-67] However, in older adults (between 60 to 80 years old), the amplitude of this rhythm decreases by about 20-40%, such that the peak and the trough of the core body temperature do not rise as high and fall as low, respectively, as in young adults (Figure 1.c). Furthermore, compared to younger adults in their 20s-30s, a 1-2 hours phase advance in the rhythm has been observed in older adults in their 60s to 80s.[67, 68] MCI patients also show phase advances in temperature rhythms and rest-activity[52] and higher median body temperature and lower peak-to-trough body temperature compared to healthy older adults (Figure 1. c).[69] Review and meta-analysis studies have confirmed these findings in MCI and AD patients, thus suggesting that core body temperature is a potential marker for MCI and major neurocognitive disorders.[15, 70]

3.3. Melatonin rhythm

Melatonin can directly influence the activity of the suprachiasmatic nucleus (SCN), a key regulator of circadian rhythmicity that is considered the “master circadian pacemaker” or “master clock”.[2, 3, 71-76] Melatonin release helps to promote sleep onset, modulating the activity of intrinsically photosensitive retinal ganglion cells that, in turn, provide timekeeping signals to the SCN and regulate core body temperature. [72, 74, 77] However, the complexity of melatonin's actions/function extends to the multiplicity of target cells and signal transduction mechanisms, which are more diverse than originally believed. In mammals, two melatonin-binding GPCRs exist, MT1 and MT2, while in humans, only MT1 has been discovered and MT2 seems to be absent or expressed only at a very low level.

Outside of the SCN, MT1 receptors have been detected in numerous tissues, including the kidney, cerebral arteries, and immune system cells. Moreover, several recent publications have reported melatonin antioxidant actions in numerous tissues that can be activated at physiological melatonin concentrations. Declines in melatonin seem to be, in many cases, the consequence of SCN degeneration, such as tissue destruction in the SCN or in the pineal gland, which leads to reduced melatonin secretion and results in circadian and sleep disturbances. [78] Notably, total melatonin secretion starts decreasing from the third decade of life (Figure 1.d).[71, 72, 74, 79, 80] However, some studies reported that the melatonin rhythm was preserved for healthy older adults, and only the peak amplitude of melatonin was reduced for elderly individuals.[81, 82] This discrepancy (i.e., preserved of the melatonin rhythm in older adults, which however shows a change of the melatonin's peak amplitude in comparison to younger individuals) suggests that the reduction in melatonin is not a strong feature of the aging process. Several articles have explored melatonin activity in MCI.[15, 23, 29, 52-54, 83-92] Nonetheless, only a handful of these studies reported melatonin changes in MCI compared to the healthy age-matched control group. A couple of these studies reported phase advance in melatonin secretion in patients with MCI relative to healthy comparison subjects (Figure 1.d),[52, 53] although the levels of melatonin secreted did not differ [53] or were not compared across groups.[52] One study comparing serum melatonin levels between patients with AD, MCI, and healthy controls found significantly lower levels in AD compared to MCI patients and no differences between the MCI and the control groups.[93] Another study demonstrated that the trough melatonin levels in the peripheral blood were decreased in the MCI group, but it was elevated in the mild and moderate to severe AD groups.[94] Overall, these inconsistent melatonin findings could be caused by differences in study design and demographic/baseline characteristics of subjects in both studies, including age and severity of cognitive impairment.

3.4. Cortisol rhythm

One of the key hormones in human physiology is cortisol, which targets nearly all cells of the body. Cortisol facilitates the transmission of circadian messages from the SCN to the peripheral tissues. For example, as the body perceives stress, adrenal glands release the hormone cortisol into the bloodstream to regulate the body's stress response. The release rhythm of cortisol is under the control of the SCN. [76, 95] Peak of cortisol after waking can play a specific role in synchronizing the body to both the RAR and light-dark cycle. [96] Furthermore, it is reported that the cortisol circadian rhythm transcribes the message of the time of day to the immune system. Cortisol coordination is essential for having good physical and mental well-being, and disruption in this rhythm is correlated with a variety of negative physiological, psychological, and clinical implications. [96] However, the patterns of cortisol rhythm changes during the lifetime and age-related changes in cortisol rhythmicity include phase advance of the peak of cortisol to earlier in the morning and a decrease in peak amplitude due to higher cortisol secretion at night during healthy aging (Figure 1.e). [97-99] Cortisol rhythm disruptions in older individuals may reflect the progression of neurodegeneration, although not all studies support this assumption. [100-103] An association between MCI and cortisol rhythm changes has been reported by several studies,[15, 21, 102-125] some of which compared MCI patients with control groups. [114, 115, 123, 124] For example, a mild elevation of morning cortisol was observed in

cerebrospinal fluids from patients with MCI compared to healthy, age-matched individuals.[114] In contrast, a meta-analysis of five studies showed no difference in blood cortisol levels between MCI patients and cognitively intact individuals.[114] Furthermore, a meta-analysis of ten studies reported no differences in salivary cortisol levels between MCI patients and healthy controls (Figure 1.e), although MCI patients showed a moderate elevation in central cortisol (i.e., CSF) with minimum heterogeneity. [114] Additionally, a cross-sectional study in probable dementia, MCI, and healthy individuals found that lower morning to evening cortisol ratio was associated with cognitive impairment in men, but not women.[126] Another study showed an increased saliva cortisol awakening response in patients with mild cognitive impairment relative to healthy control subjects.[117]

4. Circadian rhythm and gene expression in aging and MCI

In humans, the SCN is the main clock of the circadian system that interacts (i.e., by afferent and efferent connections) with other cerebral and peripheral tissues, which also contain their own autonomous circadian clocks (Figure 2). The interplay and synchronization between SCN inputs and the clocks of other brain and body regions can therefore affect a wide range of functions, including cognition, psychological functions, and behavior. At the molecular level, up to 80% of the mammalian protein-coding genes show circadian rhythmicity in expression levels; a set of clock genes, which regulates the rhythmic expression of the genome also controls these circadian rhythms. The core clock genes include PER1, PER2 and PER3 which encode the period circadian protein homologues, the cryptochromes (i.e., CRY1 and CRY2), as well as CLOCK and ARNTL, also known as BMAL1. These latter genes create a 24-hour synchronized period with a complex, interlocking transcription-translation feedback loop. Other genes and proteins involved in the feedback loop include nuclear receptor subfamily 1 group D members 1 and 2 (NR1D1 and NR1D2), which play an important role in encoding the REV-ERB nuclear receptors, the nuclear receptor ROR-α (RORA), the D site-binding protein (DBP), nuclear receptor ROR-β (RORB), and the nuclear factor interleukin 3-regulated protein (NFIL3).[22] Evidence from major neurodegenerative disorders, including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington Disease (HD), and animal models of such diseases indicate abnormal expression rhythms of these genes, especially BMAL1 and PER2. Specifically, in Alzheimer's disease, complex changes in pattern of BMAL1 mRNA expression was observed.[19, 127] In peripheral tissues and several brain regions of AD patients, BMAL1 mRNA expression remains rhythmic, but the temporal phase relationships among these tissues differ compared with healthy control. It was also reported that in the pineal gland, the rhythms of BMAL1, PER1 and CRY1 mRNA are lost in these patients. Furthermore, circadian distributions during MCI are associated with aberrant cycles of DNA methylation in BMAL1.[19, 127]

5. Circadian rhythm and cognitive functioning in healthy aging and MCI

Numerous studies have investigated the effects of circadian rhythmicity on brain cognitive functioning and performance.[8, 128-133] The relationship between circadian rhythms and cognition was examined using primarily cognitive tasks that require considerable top-down executive control,[132] including attention and working memory. Generally, it was reported

that circadian rhythm can influence cognitive processes in the brain. Cognitive performance tends to fluctuate throughout the day, likely because of the underlying brain regions that play a role in these cognitive functions (e.g., frontal cortex, dorsolateral prefrontal cortex, hippocampus, anterior medial frontal, and posterior cingulate regions), which have a deep relationship with the fluctuation of the circadian rhythm.[132, 134] However, not all cognitive functions are equally affected. For example, worse performances in attention and working memory has been reported in the morning, while better performances were observed in the afternoon.[8, 132] It is also important to point out that cognitive functions are affected by the level of arousal.[132, 136] Age-related decline in working, declarative, spatial, and other forms of memory is well documented.[137-139]. Of note, an in-depth characterization of the effects of circadian rhythms on the different domains of cognition in aging, although important, is beyond the scope of this review that focuses on changes in circadian rhythms in healthy aging and MCI. We do think, however, that it is important to present and discuss how alterations in these four main circadian rhythms affect cognitive function in MCI vs. control by specifying, whenever possible, the cognitive domain affected. Thus, in what follows we discuss findings relative to cognitive dysfunctions and changes in these circadian rhythms in patients with MCI.

5.1. RAR and cognitive functioning

Compared to healthy aging, in MCI patients daytime activity was reported to be negatively correlated with memory deficits,[140] and altered circadian RARs measures have been found to be associated with worse cognitive performance in these patients.[57] Another study suggested that very subtle changes in circadian rhythm are detected in older adults (e.g., amplitude change, mean activity level around which the rhythm oscillates (MESOR), or percentage of variance in activity explained by the 24h cosine wave) that are related to preclinical changes in cognitive performance,[141] while a prospective study confirmed significant changes between delayed acrophase were associated with worse cognition in Hong Kong healthy community-dwelling older adults.[58] Furthermore, a couple of recent studies showed that the reduced amplitude and overall rhythmicity of RAR were associated with adverse cognitive outcomes and that individuals with RAR alterations exhibited a faster cognitive decline during follow-up assessments compared with subjects with intact RAR.[34, 142]

5.2. CBT rhythm and cognitive functioning

Despite a dearth of work examining the association between neurocognitive decline and core body temperature, one study reported that misaligned core body temperature rhythms have a negative impact on the cognitive performance of hospital shift work nurses at the end of their shift.[143] Furthermore, a cognitively healthy control group showed lower median body temperature and higher peak-to-trough amplitude temperature compared to MCI individuals.[69] Overall, these studies demonstrated that higher peak-to-trough body temperature amplitude and lower median body temperature tend to be associated with better cognitive performance.

5.3. Melatonin rhythm and cognitive functioning

Misalignment in melatonin rhythm (i.e., dim light melatonin onset) has shown different effects on cognition in MCI patients and aged-matched control. For example, earlier dim light melatonin onset was associated with poorer memory performance in MCI patients, but not in age matched healthy controls. [53] One study evaluating the trough melatonin levels in early (i.e., MCI stage) and late phases of Alzheimer's reported that melatonin levels in the peripheral blood decreased in MCI, while they increased with AD severity.[53] Review, meta-analysis, and retrospective studies have shown that melatonin administration in patients with MCI but not with AD had positive effects on cognitive status.[87, 125, 144, 145] Other studies showed that melatonin could safely improve some cognitive aspects of sleep, memory, and mood in the elderly following short-term use.[83] Furthermore, positive correlations between MMSE score and melatonin levels suggest a protective effect on cognition, [93] although additional studies are needed to fully elucidate the effects of this hormone levels on cognitive function. However, additional studies with melatonin administration in patients with MCI, or even in patients with preclinical AD, accounting for pre-existing sleep disturbances, are needed.

5.4. Cortisol rhythm and cognitive functioning

Several studies have shown that cortisol plays a critical role in regulating cognition in both healthy aging and MCI individuals.[103, 108, 111, 112, 146] One study reported that visual recognition memory deficits were associated with atypical high evening salivary cortisol levels in healthy subjects,[147] while another study concluded that higher levels of plasma cortisol were associated with worse age-related cognitive changes, but with no age-related brain volume atrophy.[148] Regarding sex covariant differences, it has been reported that high cortisol predicted an impaired performance on episodic memory only in amnestic MCI males.[149] Furthermore, a study examining the association between cortisol levels and visual memory performance in individuals presenting mild MCI or AD compared to healthy control found that higher levels of cortisol were associated with better memory performance in the control group, while higher cortisol levels were correlated with poorer memory performance in MCI patients, but not in the AD group.[112] The effects of the diurnal cycle of cortisol on cognitive function and physical activity in older adults with and without cognitive impairment have been more extensively reported in a recent review: [108] available evidence from this work supports the notion that cognitive improvement is associated with exercise, which could be partially mediated by changes in the diurnal cortisol secretion pattern and/or its related dynamic profile. Other meta-analysis and review studies have suggested that higher morning cortisol accelerates cognitive decline in mild AD or MCI patients, but the results in cognitively healthy adults were inconsistent.[114, 115]

6. Discussion

In this review, we explored four aspects of circadian rhythm disruption: RARs, core body temperature, melatonin, and cortisol rhythms in normal aging and the preclinical/prodromal stage of Alzheimer’s disease (i.e., patients with MCI). Overall, behavioral circadian rhythm disruption parameters (e.g., RAR) have been examined more than biological measures of circadian rhythmicity, such as melatonin or cortisol secretion rhythms and core body

temperature. Circadian rhythm disruption is consistently present in MCI patients and often presented with earlier, more severe disruptions than those typically observed in normal aging.[6, 9, 15, 22, 25] Unlike healthy older adults, who usually have reduced circadian amplitude and advanced circadian phase, patients with MCI tend to have circadian rhythms that are less robust, more fragmented, and severely reduced in amplitude (Figure 1. b, c, d, and e).

6.1 Intervention strategies on circadian rhythms and their relevance to cognition

Based on aforementioned findings, in what follows we will discuss preliminary but promising treatment interventions aimed at restoring regular circadian rhythms that may prevent or halt the progress of neurodegenerative diseases in MCI individuals as well as mitigate their related cognitive deficits.

Bright light therapy (BLT) has been found to be an efficient method to improve the main parameters of circadian rhythms in mild/moderate cognitive impairment. For example, ninety minutes of BLT (for five days) appeared to achieve a significant improvement in cognitive factors (general cognitive capabilities), circadian rhythms, and general health.[150] BLT is an affordable, effective, fast-acting therapy for age-related disturbances, with many advantages over pharmacological alternatives, and a recent review exploring the connections between circadian sleep disorders, cognition, and neurodegenerative disease showed that intermittent light stimuli improved sleep and cognition in patients with AD and MCI.[151] However, some studies have not confirmed the positive effects of bright light on cognition (e.g., in patients with diagnosed dementia, sleep disruption, and agitated behavior).[15, 152] This discrepancy may be related to differences in BLT parameters, such as exposure duration and intensity of light, which are important for older adults who have reduced circadian system response to light.[15, 22, 150, 153]

Melatonin therapy, used as an add-on treatment, has beneficial effects on MCI and Alzheimer's patients with sleep disorders by improving their sleep quality and their RARs.[154] A recent review study has proposed that melatonin should be prescribed as early as possible and for long periods of time, at a dose between 2 and 10 mg.[154] This review also reported that melatonin may have a beneficial effect on cognitive function in MCI, but showed no effects in moderate to severe Alzheimer's disease.[154] Another study proposing a higher dose of melatonin (i.e., 25 mg) showed that this compound could act as an antioxidant in the MCI stage to reduce progression to dementia.[29] Overall, these studies indicate that melatonin has positive effects in MCI patients[29, 83, 154, 155] while also reporting no significant side effects.[154, 155]

Regular physical activity, which is associated with cortical rhythm, has been proposed as a strategy to mitigate disruptions of circadian rhythms in normal older adults and patients with MCI, which in turn could reduce/halt their cognitive decline.[106, 108, 120, 156-160] Consistent with this assumption, physical activity and exercise has been found to enhance memory formation and memory consolidation in patients with MCI.[160] A review in older adults with and without cognitive impairment reported that exercise could reduce the risk of developing MCI and AD as well as improve cognition in both healthy and cognitively impaired individuals, possibly through the regulation of the diurnal cycle of cortisol.[120]

Another study showed that physical, as well as cognitive activity, had a protective effect on cognitive impairment, even when one or the other was lowly engaged.[158] Furthermore, increasing the overall physical amount by decreasing sedentary helped prevent older adults from developing dementia.[159] Again, the observations that physical activity has protective effects on cognitive decline and cognitive status may differ depending on the goal and type of physical activity intervention in healthy aging, MCI, and AD individuals.[161] In this regard, objective measurements have confirmed that greater levels of physical activity were associated with decreased risk of a future diagnosis of MCI or AD; [157] additionally, findings in MCI patients have shown that, compared with a control condition, exercise interventions successfully increased fitness and resulted in a greater fall in cortisol concentration from peak to midday while also enhancing indices of executive function. [157]

6.2. Limitations of existing research and future directions

Several questions and remaining issues should be addressed before these promising findings may be applied in the clinical practice. For example, we should take into consideration the large between-individual differences (i.e., differing chronotypes) and other non-photic zeitgebers like exercise, food, and caffeine consumption that affect the peripheral clocks and their feedback to the central circadian clock (Figure 2).[15, 162-165] Also, despite underlying pathways, including immune and inflammatory function and alterations of protein homeostasis, have been suggested, the mechanistic connections between the progress of neurodegeneration and altered circadian rhythms is still not fully understood .[15] Currently, most of the evidence linking brain disorders and circadian dysfunction is only correlational; thus, whether and what type of causal relationships may exist between circadian rhythm changes and cognitive decline remain undetermined.[9] Design future research toward an in-depth understanding of the links between circadian disruption and MCI by focusing on the interaction between biological rhythms and cognitive assessments (behavioral aspects) should therefore be undertaken. It would also be important to combine circadian rhythm with neuroimaging assessments, including structural positron emission tomography (PET) and/or magnetic resonance imaging (MRI) scans, to further clarify the contribution of circadian rhythm disruption to functional/anatomical changes in the brain. This work will help establish whether circadian rhythm disruption may represent a biomarker for mild cognitive impairment. Additionally, longitudinal studies with long-term follow-up periods are needed to confirm the effects of circadian rhythm disruption on subsequent cognitive decline and the risk of developing Alzheimer's disease and related dementias in asymptomatic and MCI stages. Relatedly, understanding the relationship and directionality between circadian rhythm alterations and neurodegenerative disorders will help to draw causal inferences and choose suitable therapeutic strategies in the early stage of these disorders. Eventually, it would be important to employ interventions strengthening circadian rhythmicity at the MCI stage and see whether this can help prevent the progression to AD and related major neurodegenerative diseases.

7. Conclusion

In this article, we examined circadian changes for RAR, CBT, melatonin, and cortisol rhythms and their associations with cognitive function in patients with MCI compared to

healthy adults. There is evidence from the reviewed literature that circadian changes are present in the early stage of neurodegenerative diseases. However, future longitudinal studies are needed to further investigate these alterations and to clarify their relationships with cognition, which in turn may lead to novel, early treatment interventions for patients affected by neurocognitive and neurodegenerative disorders.

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Biography

Dr. Ferrarelli earned his MD and Ph.D. in psychiatry at the Catholic University of the Sacred Heart in Rome. At the University of Wisconsin, and while completing his residency at Western Psychiatric Institute and Clinic, he studied the alterations in neuronal circuits contributing to altered sleep architecture in schizophrenia. The primary research interests of his lab focus on the utilization of hd-EEG, MRI, actigraphy, and Transcranial Magnetic Stimulation (TMS) to better understand neurological disorders and to identify potential treatment targets.

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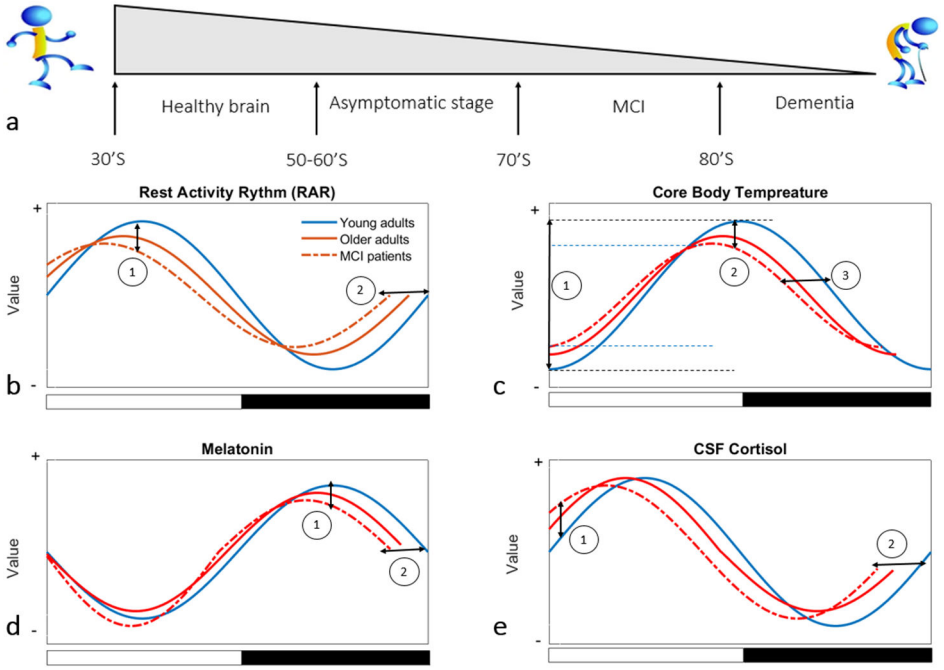

Figure 1.

A general illustration of circadian rhythms in young healthy, older healthy adults and MCI patients: a) presentation of different stages from young, healthy adulthood to dementia, with the gray-shaded triangle reflecting the progressive decrease in life expectancy across the lifespan; b) sketching of rest-activity rhythm in young, elderly, and MCI indicates: (1) a reduction in RAR amplitude in older adults compared to young subjects and of MCI individuals compared to both young and older adults, and (2) a RAR phase advance in older adults compared to young adults and MCI patients compared to other groups; c) sketching of core body temperature (CBT) changes in three groups depicts: (1) a lower peak-to-trough CBT amplitude in MCI compared to young and older healthy adults, (2) a decreased CBT amplitude of rhythm in older adults and MCI compared to young adults, and (3) a strong CBT phase advances in older adults compared to young adults; d) sketching of melatonin rhythm displays: (1) a decrease in melatonin with increasing age and in MCI compared to healthy groups, and (2) a phase advance in melatonin rhythm in older adults and MCI compared to young adults; e) sketching of cortisol rhythm changes in three groups shows: (1) elevation of morning cortisol in MCI patients compared to older and young healthy adults, and (2) phase advance in cortisol rhythm with increasing age. (Note: The X-axis and Y-axis values are on arbitrary units).

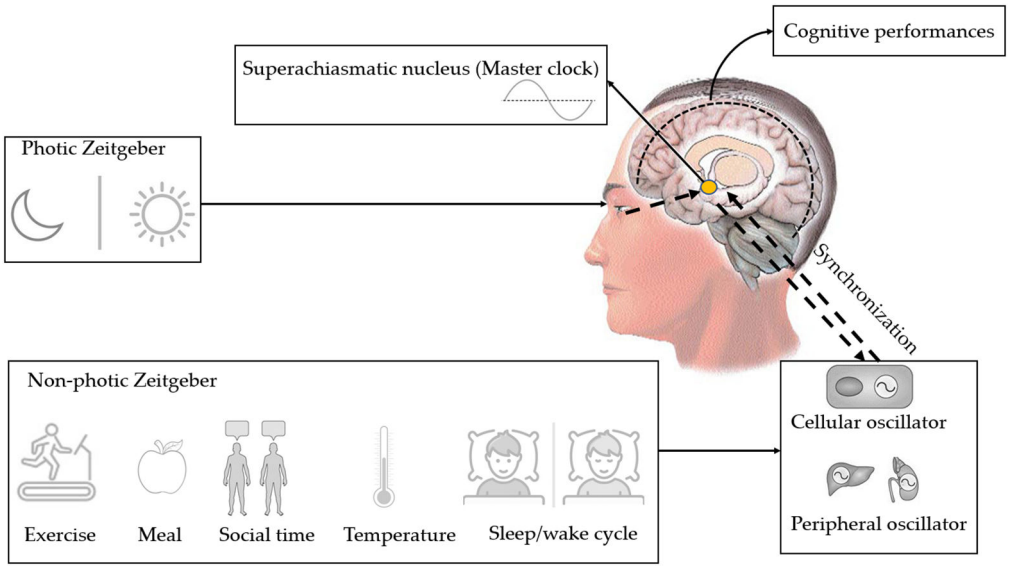

Figure 2.

Organization of human circadian rhythms. The superchiasmatic nucleus (SCN) is the master clock of the circadian rhythms. Photic Zeitgeber and non-photic Zeitgebers synchronize the SCN. All cerebral regions and peripheral tissues have their own internal clocks, where the final synchronization of the rhythms is regulated by SCN via humoral and neural connections.

Table 1.

Studies of circadian rhythm and neurocognitive changes in patients with MCI and healthy adults.

Title	Authors (Year)	Type	Circadian rhythm/ Assessment tool	Diagnosed (Subjects)	Key findings
The Characterization of Biological Rhythms in Mild Cognitive Impairment	Ortiz-Tudela E. et al., (2014)	Original	RAR, CBT, Melatonin, recording wrist skin temperature, motor activity, body position, and the integrated variable TAP (including temperature, activity, and position) for one week.	40 subjects; 21 MCI (74.1 ± 1.5 y) and 19 healthy subjects (71.7 ± 1.4 y)	• MCI patients exhibited a significant phase advance with respect to the healthy group. • Significant advances in the biological clock begin to occur in MCI patients, evidenced by an accelerated aging of the circadian clock, as compared to a healthy population of the same age.
Rest-Activity Pattern and Circadian Phase Alterations Across the Alzheimer's Disease Clinical Spectrum	Hyun W. R. et al., (2021)	Review	RAR, actigraphy	Alzheimer's disease clinical spectrum including MCI	• The most replicated findings were delayed phase and increased activity fragmentation, reflected by increased intra-daily variability.
Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults	Peng L., et al., (2020)	Original	RAR, annual assessments of cognition (with a battery of 21 cognitive performance tests) and motor activities (with actigraphy)	1401 healthy older adults (81·8 [76·3–85·7] y), prospective observational cohort study (followed up for up to 15 years),	• Circadian amplitude, acrophase, and interdaily stability progressively decreased over time, and intradaily variability progressively increased over time. Annual changes in these measures were doubled in magnitude after the diagnosis of mild cognitive impairment, and further doubled after the diagnosis of Alzheimer's dementia. • The longitudinal change of global cognition positively correlated with the longitudinal changes in amplitude and interdaily stability and negatively correlated with the longitudinal change in intradaily variability.
Sleep-Wake Patterns and Cognition of Older Adults with Amnestic Mild Cognitive Impairment (aMCI): A Comparison with Cognitively Healthy Adults and Moderate Alzheimer's Disease (AD) Patients	Wams E. J. et al., (2017)	Review	RAR, Mini-Mental-State-Examination and five computerized tests (CANTABeclipse™), Jupiter Sleep Questionnaire and Pittsburgh Sleep Quality Index, wrist-worn actigraphy	Cognitively healthy adults, amnestic mild cognitive impairment (aMCI) and moderate AD	• Mild cognitive impairment in aMCI individuals was reflected in domains of verbal and visuospatial memory but not attentional capacity or episodic memory. • Moderate AD patients scored significantly lower on all cognitive tests and had lower rest-activity amplitudes and distinctively longer nightly sleep periods that were not associated with sleep disorders, sleep medication or poor sleep efficiency.
A population-based prospective study on rest-activity rhythm and mild cognitive impairment among Hong Kong healthy community-dwelling older adults	Yi Lee P.M., et al., (2021)	Original	RAR, wrist actigraphy, Montreal Cognitive Assessment (MoCA)	174 Hong Kong healthy adults aged ≥65 years (36 males vs. 138 females) (Normal cognition [n=123, 74.9 ± 6.8 y], MCI [n=51, 77.5 ± 7.1 y], Followed up them for 12 months	• There was no association between rest-activity circadian rhythm parameters and MCI or cognitive impairment at baseline. • Baseline survey and follow-up study consistently confirmed that older adults, the majority of which

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Title	Authors (Year)	Type	Circadian rhythm/ Assessment tool	Diagnosed (Subjects)	Key findings
					were females, with delayed acrophase were less likely to have better cognition.
Circadian Activity Rhythms and Risk of Incident Dementia and Mild Cognitive Impairment in Older Women	Tranah G.S., et al., (2011)	Original	RAR, wrist actigraphy for a minimum of three 24-hour periods. Each participant completed a neuropsychological test battery and had clinical cognitive status (dementia, MCI, normal) assessed by an expert panel approximately 5 years later.	1,282 healthy community dwelling women (mean age 83 years)	• After 4.9 years of follow-up, 195 (15%) women had developed dementia and 302 (24%) had developed MCI. • Older, otherwise healthy women with decreased circadian activity rhythm amplitude and robustness, and delayed rhythms had increased odds of developing dementia and MCI.
Associations of actigraphic sleep and circadian rest/ activity rhythms with cognition in the early phase of Alzheimer's disease	Alfini A., et al., (2021)	Original	RAR, standard and novel actigraphic metrics	179 older individuals (72.6 ± 8.4 y) with normal cognition (n = 153, 71.8±8.3 y) and MCI (n = 26, 77.3 ± 7.9 y)	• Individuals with MCI had altered circadian RARs compared to controls, including the novel RAR metric fPC3, reflecting greater nighttime activity and less activity in the morning compared to the mean values. Additionally, these measures were significantly associated with cognitive performance.
Circadian Misalignment and Sleep Disruption in Mild Cognitive Impairment	Naismith S.L., et al., (2014)	Original	RAR, psychiatric, medical, and neuropsychological assessment, followed by overnight polysomnography and dim light melatonin onset assessment, performing episodic memory task	30 patients with MCI and 28 age-matched controls (> 50 y)	• Patients with MCI had advanced timing of their melatonin secretion onset relative to controls, but the levels of melatonin secreted did not differ between groups. • The MCI group also had greater wake after sleep onset and increased rapid eye movement sleep latency. • There were differential associations between dim light melatonin onset and cognition between the two groups, with earlier dim light melatonin onset being associated with poorer memory performance in MCI patients. • Circadian misalignment and sleep disruption were evident in patients with MCI, and was consistent with changes observed in Alzheimer's disease.
Multicenter Study on Sleep and Circadian Alterations as Objective Markers of Mild Cognitive Impairment and Alzheimer's Disease Reveals Sex Differences	Guarnieri B. et al., (2020)	Original	RAR, wearable activity trackers data, actigraphic sleep parameters	158 subjects (86 females and 72 males), 42 AD (64.83±13.36), 28 MCI (80.57 ± 5.71 y), and 88 controls (75.55 ± 7.89 y)	• Wearable activity trackers were utilized to monitor sleep and circadian rhythm parameters in MCI and AD patients as compared to controls, focusing on sex dissimilarities. • Age reduced the dissimilarities for WASO and SE but demonstrated sex differences for amplitude in the overall population.

Title	Authors (Year)	Type	Circadian rhythm/ Assessment tool	Diagnosed (Subjects)	Key findings
					• Sex differences could impact on neurodegeneration and disease trajectory with potential clinical applications.
Association of Circadian Rhythm with Mild Cognitive Impairment Among Pneumoconiosis Workers in Hong Kong: a Cross-sectional Study	Huang B. et al., (2022)	Original	RAR, A wrist actigraphy for 168 hours, a face-to-face questionnaire containing information on sociodemographic, lifestyle behavior, and anthropometric measurements	186 male pneumoconiosis patients and 208 age-matched healthy community men (71.3 ± 7.8 y), Cross sectional	• Weakened circadian activity rhythm among pneumoconiosis workers was positively associated with the prevalence of MCI and composite outcome.
Actigraphic daytime activity is reduced in patients with cognitive impairment and apathy	Kuhlmei A. et al., (2013)	Original	RAR, actigraphy, rating scales for apathy (AES) and depression (Beck Depression Inventory, BDI)	Subjects had a mean ± standard deviation age of 81 ± 7 (Controls [n= 23]: 78 ± 7, subjects with MCI with/ without apathy [n=21] 79 ± 4/86 ± 4, participants with dementia [n=32] without/with apathy 80 ± 2/82 ± 4)	• Daytime activity was negatively correlated with memory deficits. • Cognitive impairment was associated with reduced daytime activity.
Unique Sleep and Circadian Rhythm Dysfunction Neuroinflammatory and Immune Profiles in Alzheimer's Disease with Mild Cognitive Impairment	Pillai J. A., et al., (2021)	Original	RAR, a wrist accelerometer (Motion logger Micro Watch by Ambulatory Monitoring, Inc®)	MCI-AD subjects (69.5 [min=64, max=79] y), Cohort	• Circadian rhythm irregularities were accompanied by altered humoral immune responses detected in both the cerebrospinal fluid and plasma as well as alterations of cerebrospinal fluid biomarkers of neurodegeneration.
Association between circadian rhythms, sleep and cognitive impairment in healthy older adults: an actigraphic study	Cochrane A. et al. (2012)	Original	RAR, a battery of neuropsychological tests and completed sleep diaries and 6 days of actigraphy	26 healthy community-dwelling older adults (intact [n=16], 71.94 ± 2.53 y, declined[n=10], 70.90 ± 1.5 y)	• Minimal differences on the sleep/activity and circadian parameters across the two groups, although there was a significant difference in the acrophase between the declined and intact groups.
The circadian rest-activity pattern predicts cognitive decline among mild-moderate Alzheimer's disease patients	Targa A. D., et al., (2021)	Original	RAR, use of actigraphy for 14 days, cerebrospinal fluid, 12 months of follow-up, neuropsychological evaluation (MMSE)	The cohort included 100 individuals (mean, 76.0 [73.0; 80.0] median [p25; p75]) y) with mild-moderate AD.	• Older age was associated with increased fragmentation of the rest-activity rhythm. • Rest-activity rhythm was also associated with disease-related outcomes. • Increased fragmentation of the rhythm at the baseline was associated with enhanced cognitive decline after one year independent of age, sex, ApoE4 status, educational level, and pharmacological treatment. • The circadian rest-activity rhythm may be a promising target to prevent cognitive decline during aging.
Rest-activity rhythms and cognitive impairment and dementia in older women:	Xiao Q. et al., (2022)	Original	RAR, accelerometry-based rest-activity parameters, telephone Interview for	Cognitively unimpaired women ages 65–79 years at baseline, 193 women	• There were prospective association between weakened rest-activity rhythms (e.g., reduced

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Results from the Women's Health Initiative			Cognitive Status-modified (TICS-m), East Boston Memory Test, Oral Trail Making Test, Verbal Fluency-Animals test, and Digit Span Test	developed MCI (n=120) or probable dementia (n=73) after average of 4.5 years	amplitude and overall rhythmicity) and adverse cognitive outcomes. • Weakened rest-activity rhythms may be predictive markers for cognitive decline, MCI, and dementia among older women.
Disrupted daytime activity and altered sleep-wake patterns may predict transition to mild cognitive impairment or dementia: a critically appraised topic	Covell G.E.S. et al., (2012)	Review	RAR, wrist actigraphy	A prospective cohort study of 1282 cognitively normal women [65 years or older, with a mean age of 83 years]	• Disrupted circadian rhythm measures, including lower amplitude, a less robust rhythm, and delayed timing of peak activity on wrist actigraphy, were predictive of future development of MCI or dementia in cognitively normal women.
Association between circadian disruption and diseases: A narrative review	Hou, Y. et al., (2020)	Review	RAR, Melatonin, CBT, Cortisol	Variety of diseases	• Recent studies have demonstrated that patients with various diseases often showed symptoms of circadian disruption as manifested by the sleep–wake cycle and other biological rhythms. • Circadian disruption resulted in changes to the phase, period, and amplitude of the sleep–wake cycle, melatonin rhythm, and core body temperature. • Several cardiometabolic, psychiatric, and neurodegenerative diseases were closely related to circadian disruption. Several interventions were also discussed, including phototherapy, exogenous melatonin, and exercise.
The clocks that time us'—circadian rhythms in neurodegenerative disorders	Videnovi A. et al., (2014)	Review	RAR, Melatonin, Cortisol, CBT SCN	Neurodegenerative disorders	• Discussed the role of the circadian system in the regulation of the sleep–wake cycle, and outlined the implications of disrupted circadian timekeeping in neurodegenerative diseases.
Association between circadian rhythms and neurodegenerative diseases	Leng Y. et al., (2019)	Review	RAR, Melatonin, Cortisol, CBT SCN	MCI, Alzheimer's disease and related dementias, Parkinson's disease	• Circadian rhythm disruptions were more severe in people with age-related neurodegenerative diseases, including Alzheimer's disease and related dementias, and Parkinson's disease. • The proposed mechanistic link between circadian rhythms and neurodegeneration included alterations of protein homoeostasis and immune and inflammatory function.
Body Temperature Is Associated with Cognitive Performance in Older Adults with and Without Mild Cognitive Impairment: A Cross-sectional Analysis	Eggenberger P. et al., (2021)	Original	CBT, Skin temperatures at the rib cage and the scapula were measured in the laboratory, Neuropsychological tests	80 older adults (74.6 ± 6.0 y), 54 participants were cognitively healthy and 26 participants met the criteria for MCI, Cross-sectional study	• Healthy aging was associated with core body temperatures that were in the lower range of age-related normal values (36.3 ± 0.6°C, oral temperature), while patients with Alzheimer's disease (AD) exhibited core body temperatures above normal values (up to 0.2°C).

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					• Cognitively healthy older adults showed lower median body temperature and higher peak-to-peak body temperature amplitude compared to older adults with MCI. • Both skin and core body temperature measures were proposed as potential early biomarkers of cognitive decline and preclinical symptoms of MCI/AD.
Misaligned core body temperature rhythms impact cognitive performance of hospital shift work nurses	Molzof H. E. et al., (2019)	Original	CBT, Mini-International Neuropsychiatry Interview (MINI), Vital Sense monitoring device	Day shift (n = 14) and night shift (n = 14), 31.2 years (with a range of 22 to 56 years)	• Night-shift nurses exhibited significantly greater sleep fragmentation as well as a greater disparity between their wake-time and time of CBT minimum compared to day-shift nurses. • Night-shift nurses exhibited significantly slower cognitive proficiency at the end of their shifts, even after adjustment for CBT phase.
Increase in Core Body Temperature of Alzheimer's Disease Patients as a Possible Indicator of Chronic Neuroinflammation: A Meta-Analysis	Klegeris A. et al., (2007)	Meta-analysis	CBT	Alzheimer's Disease	• Meta-analysis showed that the mean core body temperature in AD patients was significantly increased by 0.10 ° C when compared to healthy elderly subjects
Trough Melatonin Levels Differ between Early and Late Phases of Alzheimer Disease	Lin C.H. et al., (2021)	Original	Melatonin, Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE), Enzyme-linked immunosorbent assay (ELISA)	270 elder individuals including 73 Healthy controls (66.3 ± 9.0 y), 47 aMCI (66.1 ± 5.0 y), 98 Mild AD (75.2 ± 7.1 y), 52 Moderate to severe AD (82.5 ± 7.0 y), Cohort study	• Melatonin has been considered to have an essential role in the pathophysiology of Alzheimer's disease (AD) for its regulatory function on circadian rhythm and interaction with glutamate for the modulation of learning and memory. • Melatonin levels were decreased in patients with AD. • Trough melatonin levels were decreased in the MCI group but elevated in the mild and moderate to severe AD groups. • Trough melatonin levels were associated with CDR and MMSE in MCI or AD patients significantly. • Trough melatonin levels in the peripheral blood were decreased in MCI and increased with the severity of AD. • Based on these findings, it was concluded that trough melatonin level may be a treatment response biomarker for MCI and AD.

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Title	Authors (Year)	Type	Circadian rhythm/ Assessment tool	Diagnosed (Subjects)	Key findings
Plasma 8-isoPGF2α and serum melatonin levels in patients with minimal cognitive impairment and Alzheimer disease	Sirin F. B. et al., (2015)	Original	Melatonin, serum melatonin levels, Mini-mental state examination (MMSE)	AD group (n = 20, 79.05 ± 8.93 y), MCI group (n = 21, 73.95 ± 7.19 y), and control group (n = 22, 71.59 ± 6.65 y)	• Significant differences were observed in melatonin levels between the MCI and the AD groups. • Both the control and the MCI group mean serum melatonin levels were higher than in the AD group. • Existence of a positive correlation between MMSE score and levels of melatonin showed a protective effect in terms of cognitive status. • Although the plasma 8-isoPGF2α and serum melatonin levels in MCI were not found to be good early diagnostic markers to indicate risk of AD, results were found to support the role of oxidative stress in AD.
Therapeutic application of melatonin in mild cognitive impairment	Cardinali D.P. et al., (2012)	Original	Melatonin, MMSE, cognitive subscale of the Alzheimer's disease Assessment Scale, neuropsychological battery comprising a Mattis´ test, Digit-symbol test, Trail A and B tasks and the Rey´s verbal test	MCI- Melatonin (n= 61, 69.2 ± 9.03 y), MCI-Non-Melatonin (n= 35, 72.0 ± 9.78 y)	• Beck Depression Inventory scores were decreased in melatonin-treated patients. • Retrospective analysis that daily 3 - F given for up to 3 years significantly improved cognitive and emotional performance and daily sleep/wake cycle in MCI patients.
Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study	Furio A.M. et al., (2007)	Original	Melatonin, MMSE, a battery of neuropsychological tests including Mattis' test, Digit-symbol test, Trail A and B tasks and the Rey's verbal test	MCI- Melatonin (n= 25, 72.2 ± 1.02 y), MCI-Non-Melatonin (n= 25, 72.0 ± 0.78 y)	• Patients treated with melatonin showed significantly better performance in Mini Mental State Examination and the cognitive subscale of the Alzheimer's Disease Assessment Scale.
Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment	Jean-Louis G et al., (1998)	Original	Melatonin, Alzheimer's Disease Assessment Scale, Digit Span, Digit Symbol Substitution, Finger Tapping, Mini Mental Status, Self-reported sleep-wake disturbances	10 elderly MCI individuals (68.8 ± 15.8 y)	• Melatonin safely improved some aspects of sleep, memory, and mood in the elderly in short-term use.
Melatonin and cortisol profiles in late midlife and their association with age-related changes in cognition	Waller K.L. et al., (2016)	Original	Melatonin, Cortisol, Saliva samples	24 Cognitively high-functioning men (57.5±0.45 y), 26 cognitively impaired men (57.3±0.45 y)	• Reduced nocturnal melatonin response at 4 am in men with cognitive impairment. • The 24-hour concentration and AUC of melatonin and cortisol were similar in the cognitively high-functioning group and in the cognitively impaired.
Melatonin levels in the Alzheimer's disease continuum: a systematic review	Nous A. et al., (2021)	Review	Melatonin, CSF, blood, saliva and urine melatonin	Alzheimer's disease continuum including MCI	• Disruptions in melatonin levels occurred with age, but also in AD when compared to age-matched controls. Night-time melatonin levels were found

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					to be lower in CSF and blood of AD patients as compared to controls.
Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia	Csernansky J. G. et al., (2006)	Original	Cortisol, plasma cortisol, continuous cortisol, changes in multiple cognitive tests	AD (n=10, 76 ± 4.6 y) MCI (n=23, 74.2 ± 7.5), Healthy control (n= 21, 77.6 ± 9.7 y), Follow up for 4 years	• Identified an association between higher blood cortisol and faster cognitive decline among MCI patients • In contrast, four small cohorts of AD patients showed no association between high blood cortisol and subsequent cognitive decline
Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type	Popp J. et al., (2015)	Original	Cortisol, cerebrospinal fluid cortisol, changes in multiple cognitive tests	MCI-AD (n=102, 67.35 ± 7.92 y), MCI-O (n= 45, 66.22 ± 8.16 y), AD (n= 105, 72.95 ± 7.42 y), Healthy control (n= 37, 64.35 ± 8.08 y)	• Higher baseline CSF cortisol levels were associated with faster clinical worsening and cognitive decline in MCI-AD. • These findings suggested the presence of HPA-axis dysregulation at the MCI stage that may accelerate disease progression and cognitive decline
Lower morning to evening cortisol ratio is associated with cognitive impairment in men but not women: An analysis of 733 older subjects of the cross-sectional KORA-Age study	Johar H et al., (2015)	Original	Cortisol, salivary cortisol level, Cognitive function (determined by telephone interview for cognitive status-modified, TICS-m)	733 study participants (65-90 years old, mean age=74.9), Probable dementia (n= 33, 77.8 ± 6.8 y), MCI (n=101, 77.5 ± 5.6 y), Healthy (n= 599, 74.4 ± 6.1 y), cross-sectional study	• Dysregulated HPA axis reactivity, evidenced by blunted diurnal cortisol responses, was associated with impaired cognitive function in an elderly population.
Increased saliva cortisol awakening response in patients with mild cognitive impairment	Lind K. et al., (2007)	Original	Cortisol, saliva samplings, MMSE	27 patients with MCI (61 ± 6 y) and 15 healthy controls (69 ± 5 y), case-control study	• There was an HPA-axis disturbance, with adequate basal cortisol levels but increased awakening response among patients with MCI.
Exercise, the diurnal cycle of cortisol and cognitive impairment in older adults	Tortosa-Martínez J. et al., (2018)	Review	Cortisol	-	• Physical activity has been shown to attenuate most of stress consequences and risk factors for MCI and AD. • Cognitive benefits attributed to exercise may partially be mediated by changes in the cortisol secretion pattern.
Salivary cortisol day profiles in elderly with mild cognitive impairment	Wolf O.T. et al., (2002)	Original	Cortisol, salivary cortisol levels	MCI (n=16, 70.9±2.0 y), young control group (n= 14, 27.0±2.1 y), and normal elderly group (n=28, 68.6±1.2 y)	• Cortisol level of the MCI group was significantly lower than the level measured in young controls, but did not differ from those of the normal elderly group. • In contrast to the other two groups, within the MCI group mean cortisol levels were inversely related to immediate recall of paragraphs.

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Relationship between cortisol levels and memory performance may be modulated by the presence or absence of cognitive impairment	Souza-Talarico J.N. et al., (2010)	Original	Cortisol, brief Cognitive Screening Battery	Controls (n = 40, 72.2 ± 6.3 y), MCI (n = 31, 74.7 ± 5.8 y), and AD (n=40, 80.1 ± 6.0 y)	• Higher cortisol levels were associated with better memory performance in healthy elderly while higher cortisol levels were correlated with poorer memory performance in MCI subjects
Hair cortisol and cognitive performance in healthy older people	Pulopulos M.M. et al., (2014)	Original	Cortisol, hair and diurnal salivary cortisol levels, Trail-making Test A and B, Digit Span Forward and Backward, word list-RAVLT and Stories subtest of the Rivermead	57 healthy older people (64.75 ± 4.17 y)	• Worse cognitive performance in older people has been associated with hypothalamic pituitary adrenal axis dysregulation (in particular, higher cortisol levels) • Higher ratio of mean levels of diurnal salivary cortisol over HCC were related to worse performance on working memory and short-term verbal memory
Cortisol hypersecretion and the risk of Alzheimer's disease: A systematic review and meta-analysis	Zheng B. et al., (2020)	Review and Meta-analysis	Cortisol, blood samples cortisol, Saliva cortisol, CSF cortisol	Alzheimer's disease continuum including MCI	• People with mild cognitive impairment had higher CSF cortisol than normal controls. • High cortisol was associated with accelerated cognitive decline in people with MCI. • Predictive value of cortisol for cognitive decline in preclinical adults remained unclear.
Plasma cortisol levels, brain volumes and cognition in healthy elderly men	MacLullich A.M. et al., (2005)	Original	Cortisol, plasma cortisol levels, cognitive testing and MRI	97 healthy men aged 65–70 y	• In healthy older men, higher plasma cortisol levels were associated with worse ageing-related overall cognitive change but not with ageing-related brain atrophy.
Sex differences in cortisol and memory following acute social stress in amnestic mild cognitive impairment,	Murphy K.J. et al., (2020)	Original	Cortisol, salivary cortisol, tests of episodic, associative, and spatial working memory with psychosocial stressor (TSST)	age-normal cognition (n= 15, 75.3 ± 8.7 y), amnestic MCI (n=16, 74.6 ± 8.0 y)	• Cortisol moderated the relationship with spatial working memory, whereby higher cortisol was associated with worse performance in age-normal cognition, but better spatial working memory in amnestic MCI.
Intact circadian rhythm despite cortisol hypersecretion in Alzheimer’s disease: A meta-analysis	Saelzler U.G., et al., (2021)	Meta-analysis	Cortisol, cortisol indices like concentration or circadian indices, Mini Mental Status Examination (MMSE)	Alzheimer's disease continuum including MCI	• Observed cortisol hypersecretion in MCI and AD was consistent with the theorized AD-driven deterioration of the hippocampus and subsequent reduction in hypothalamic-pituitary-adrenal axis inhibition.

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