The Academic
International Journal of Multidisciplinary Research

An Online Peer Reviewed / Refereed Journal
Volume 2 | Issue 12 | December 2024
ISSN: 2583-973X (Online)
Website: www.theacademic.in

# Disruptions in Circadian Rhythm: Origin of Central Nervous System Disorders

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**ARTICLE DETAILS**

**Research Paper**

**Keywords:**

*Circadian rhythm, Parkinson's disease, Alzheimer's disease, Dementia, Huntington's disease, Multiple Sclerosis, Spinocerebellar Ataxia (SCA)*

**ABSTRACT**

Dysregulation in diurnal oscillation (Circadian rhythm) leads to misalignment between the sleep period and the physical/social 24-h environmental cycle. Delayed sleep phase (typical in adolescents) and advanced sleep phase (frequent in the elderly), situations in which the sleep period is displaced to a later or earlier time, respectively, are the two most prevalent circadian rhythm sleep disorders. However, blind individuals and night-shift/rotating-shift workers are more prone to develop diurnal oscillation sleep disorders. In this article, the circadian rhythm syndromes included in the new International Classification of

Sleep Disorders are reviewed.

**DOI: https://doi.org/10.5281/zenodo.14706701**

## Introduction

It is a widely shared experience that after a night of restful sleep, we often wake up feeling clear-minded and alert. Conversely, if we neglect to get the necessary amount of sleep, our ability to perform daily tasks tends to decline. This phenomenon is not just anecdotal; scientific research supports the notion that both the duration and quality of sleep play crucial roles in maintaining optimal human performance and cognitive function [1]. Individuals who consistently get less than the recommended amount of sleep (i.e., 0-6 hours per night) [2] or suffer from sleep disorders like sleep breathlessness [3] are more likely to experience memory problems and deficits in higher cognitive functions. Animal studies have also yielded similar results [4,5]. Moreover, recent studies have established a connection between sleep deprivation and the development of Alzheimer's disease (AD), which accounts for the majority of dementia cases (50-75%) and other neurological disorders.

Diurnal Oscillations (Circadian rhythms) are nearly full day rhythmic process that occur in virtually every biological function in nervous system of every living person. The suprachiasmatic nucleus (SCN) in the epithalamus is the body's circadian rhythms, modulating neuronal function, core thermal, and endocrine signals. [6].

Nearly there are ten thousand number of nerve cells and thirty-five hundreds of astroglia are present in suprachiasmatic nucleus. Suprachiasmatic nucleus is divided into two area: the " central," and the mediodorsal area referred to as the " peripheral.". The suprachiasmatic nucleus coordinates the activity of biological clocks by exerting neural regulate through both adrenergic and cholinergic pathways, as well as employing fluid-based mechanisms [7,8]. This includes the secretion of neuromodulators [9] [10–14] and the modulation of the stress axis [HPA axis], which regulates the secretion of melatonin from the a drenal cortex [15, 16].

The suprachiasmatic nerves cells are unusual in the human brain because they create cellular communication pathways that perform biological clock cycles of neurotransmission and cell proliferation [10,17]. These cellular signalling pathways are essential for synchronizing suprachiasmatic nucleus activity in the "central" and "peripheral" [18].

Vasoactive intestinal peptide generated by "central" neurons has been shown to operate as a coupling signal, influencing other neuropeptides such as AVP and gastrin-releasing peptide (GRP) [14,19–20]. Vasoactive intestinal peptide deletion was shown to circadian rhythm disruption, and the experimental inclusion of vasoactive intestinal peptide caused phase alterations in biological clock [19]. The suprachiasmatic nucleus governs circadian temporal regulation at the biomolecular level, as evidenced by cycles in suprachiasmatic nucleus impulses with elevated neuronal discharge during light times, regardless of daytime or nighttime activity [21]. Alternatively, vasoactive intestinal peptide-positive nerve cells in the suprachiasmatic nucleus may provide direct signals that promote sleep and tiredness.

This research show that suprachiasmatic nucleus neurons have a broader function than only sustaining full day rhythmic, like controlling important minute elements of the sleep-wake cycle. The peripheral clocks sustain rhythmicity in core thermal, metabolic activity, and endocrine signals [22, 23].

Biological clock is controlled by an autoregulators that includes enhancers for example Brain and Muscle ARNT-1 (BMAL1) and Circadian Clock Protein (CLOCK), and suppressors such as cryptochrome-1/2 and period-1/2/3 [24]. Tissue-specific oscillator follow a diurnal cycle and are impacted on the master oscillator and synchronizers like diet as well as thermal [18, 25, 26]. Those enables biological clock to adapt to the ambient surroundings while sustaining regularity. Examination of twelve tissues' genes encoding proteins revealed that 43% of them exhibit biological clock in transcription. Moreover 1000 identified and new ncRNAs were found to express circadian oscillations [27].

The exploration was enlarged to reveal that there are 64 tissue and cerebral areas, across over 80% of genes encoding proteins transcribed using circadian rhythms [28]. Shifts in circadian genes has connected to a number of diseases, including an enhances the risk of diabetes II, insomnia, sleep apnea, narcolepsy, restless legs syndrome and malignancy [29]. It's led to a rise in circadian rhythm interruption in the population due to work nights, sleeplessness, movement across different locations, and attention to blue light devices has in in sequential ailments like Epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and migraine headaches, malignancy, metabolic syndrome, major depressive disorder, bipolar disorder, cyclothymic disorder, and GIT disorders [30–33]. Circadian rhythms interfere with the intestinal flora in interesting ways that help preserve tissue barrier integrity, according to current research. In gut microbiota populations, circadian disturbance was associated with an increase inflammation-promoting in gut microbes, as well as increased gut leakiness [33, 34].

Parallelly, intestinal flora has been demonstrated to alter circadian rhythms via daily compositional and functional oscillations [35, 36]. The ability of diurnal oscillation to affect proximate and comprehensive physiological processes as well as inflammatory responses lends support to the diurnal oscillations and intestinal barrier function association [37-41]. According contribute to the growth observational studies, those who experience frequent body clock disruptions, such as night shifts, have an increased incidence of sleep disorders, which can aggravate existing health difficulties and the of persistent illness in future [42-44].

Significantly, modifications in the intestinal flora possess a significant influence on hematoencephalic barrier through microbiome-gut-brain axis [45–46]. During the diurnal oscillation affects the entire body and controls various critical physiological functions, circadian rhythm control in hematoencephalic barrier (BBB) cells and its impact on hematoencephalic barrier functional modifications. That describe circadian abnormalities in different stress adaptations as well as neuropathic illnesses which linked to hematoencephalic barrier changes. [24, 47].

As the cycle proceeds, Cryptochrome as well as Period deposit and heterologous dimers, preventing the Brain and Muscle ARNT-1/ Circadian Clock Protein, heterologous dimers from initiating RNA synthesis [48]. When Cryptochrome and Period constitutive constitutive RNA synthesis standard fall

below a certain threshold, the Cryptoch+rome/PERIOD complex is focused for proteolytic destruction by E3-ubiquitin ligases, releasing the Brain and Muscle ARNT-1/ Circadian Clock Protein heterodimer complexes and allowing the cycle to resume [49-51]. The mTOR, that is timed to the circadian clock, is one mode of translational control of the circadian TTFL. Indeed, mTOR efficiently transmits in suprachiasmatic nucleus' light synchronization mechanisms, controlling the autonomous clock in circadian oscillators and modulating interconnection between suprachiasmatic nucleus nevers and other related diurnal oscillator [52].

## Parkinson's disease (PD)

PD is over following the 1st popular degenerative brain disease, with an approximate population of 0.3% in overall population, 1.0% in age of age of 60 years, and 3.0% in age of eighty [53].

The latest evidence that attempted to assess the occurrence of PD in America discovered that the average incidence among those aged 45 years was 572 per 100,000 [54]. The development of cytoplasmic structures holding clumps of alpha-synuclein, known as Lewy neurites, and depletion of nerves cells in substantia nigra pars compacta, that produces dopamine in the striatum insufficiency, are disease's neuropathological hallmarks. The etiopathogenesis of the disease is complicated and remains a mystery [53, 55].

Experimentally, pathogenesis dopamine production is influencing several elements, but tyrosine 3-monooxygenase (rate limiting enzyme) play vital role in dopamine production [56].

CLOCK does this by binding to E-box elements found in the promoter regions of monoaminergic mechanism genes, regulating the transcription of tyrosine hydroxylase, dopamine activity transporter, and D1 receptor [57]. Circadian rhythm promotes the monoaminergic mechanism genes by attaching of E box with SLC6A3 (DAT), D1 receptor as well as tyrosine 3-monooxygenase [57]. Clock genes can also control 3,4-dihydroxyphenethylamine function, as demonstrated by the increased activity caused by CLOCK knockdown via RNAi in the ventral tegmental area [58].

Conversely, monoaminergic impacts circadian genes through ligand-dependent [59]. This is accomplished by increasing RNA synthesis of the CLOCK/BMAL1

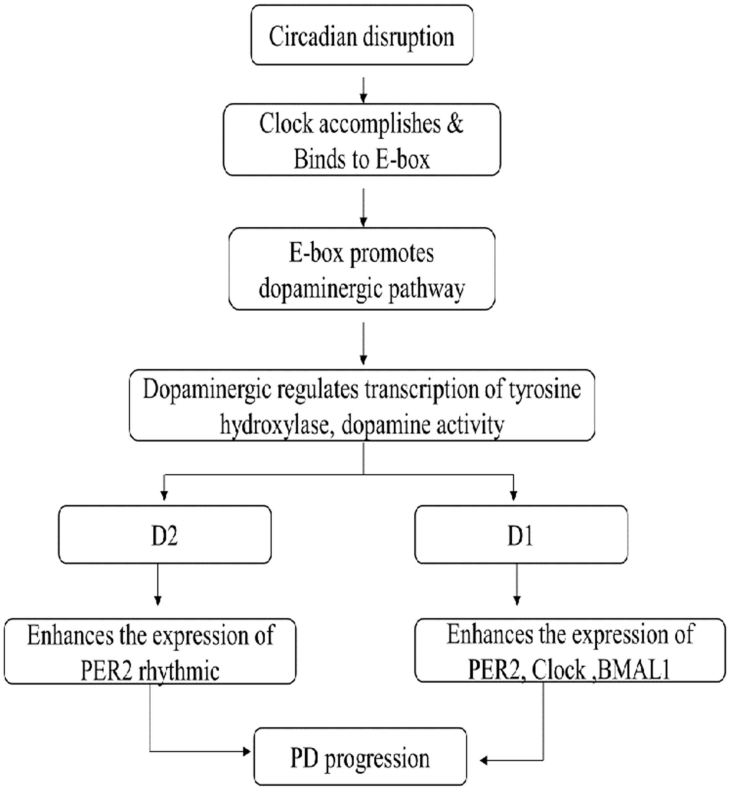


Figure:1

**Fig 1: Represents the pathway of circadian disruption causes PD progression**

heterodimer by activating enhancer element cAMP response element-binding proteins [60]. Impact on CLOCK/BMAL1 heteroduplex are controlled by cAMP activity through transcription factors [60]. Dopamine 2 receptor stimulation can affect Period2" gene activity, with the exception of suprachiasmatic nucleus [61].

Interestingly, Dopamine1 receptor agonists increase the expression of Period1, CLOCK, and BMAL1, but D2 receptor agonists decrease the expression of CLOCK, and BMAL1 [59]. Overall, our data imply that body clock disturbance in Parkinson's disease may be triggered by dysregulation of the connections between the dopaminergic and pathways. A survey discovered disruption of circadian genes in PD patients established the purpose of diurnal abnormalities in PD initiation and progression. For example, BMAL1 mRNA expression in these individuals' peripheral leukocytes was considerably lower in the evening, and BMAL1 levels were found to correspond with motor severity and sleep quality [62].

Furthermore, BMAL1 single-nucleotide polymorphisms (SNPs) were related at risk of tremor dominant subtype, whereas PER1 SNPs were associated with gait problems and postural instability dominant subtype [63].

## Alzheimer’s disease

Alzheimer's disease (AD) is a gradual neurological condition that leads to cause dementia, affecting around 5 crores individuals across the globe [64]. The revelation that beta amyloid (Aβ) plaques may be removed from cerebrum led to the development of several treatments [65]. Regrettably, they did not enhance clinical results. As a result, extra thorough and comprehensive treatment approaches are required to proactively mitigate

deprivation and reestablish mental skills. In lateral phases of disease, of the aggravation of behavioral symptoms toward the end of the day, known as " sunset syndrome," which are linked to AD-prompted phase shifts in typical diurnal oscillations of vigilance [67, 68].

Hematoencephalic barrier changes have been linked to AD pathogenesis as well as therapeutic resistance. The hematoencephalic barrier is thought to govern Aβ equilibrium and contribute to its buildup in nervous system [69]. Impaired hematoencephalic barrier play role as, loss of tight junction integrity, causes decreased Aβ removal, higher circulation Aβ levels, and processing of Aβ precursor proteins [70]. Moreover, peroxidation as well as the excitability of neurohumoral transmissions, which increase the activity of beta(β) as well as gamma(γ) secretases, have been connected to hematoencephalic barrier impairment through the promotion of Aβ generation [71].

RAGE has been demonstrated to transport and accumulate Aβ across the hematoencephalic barrier [72]. Overgrowth of Aβ at neurovascular cells are demonstrated by RAGE which are basic building component hematoencephalic barrier [72, 74]. Aβ has demonstrated circadian rhythmicity for a long time [74].

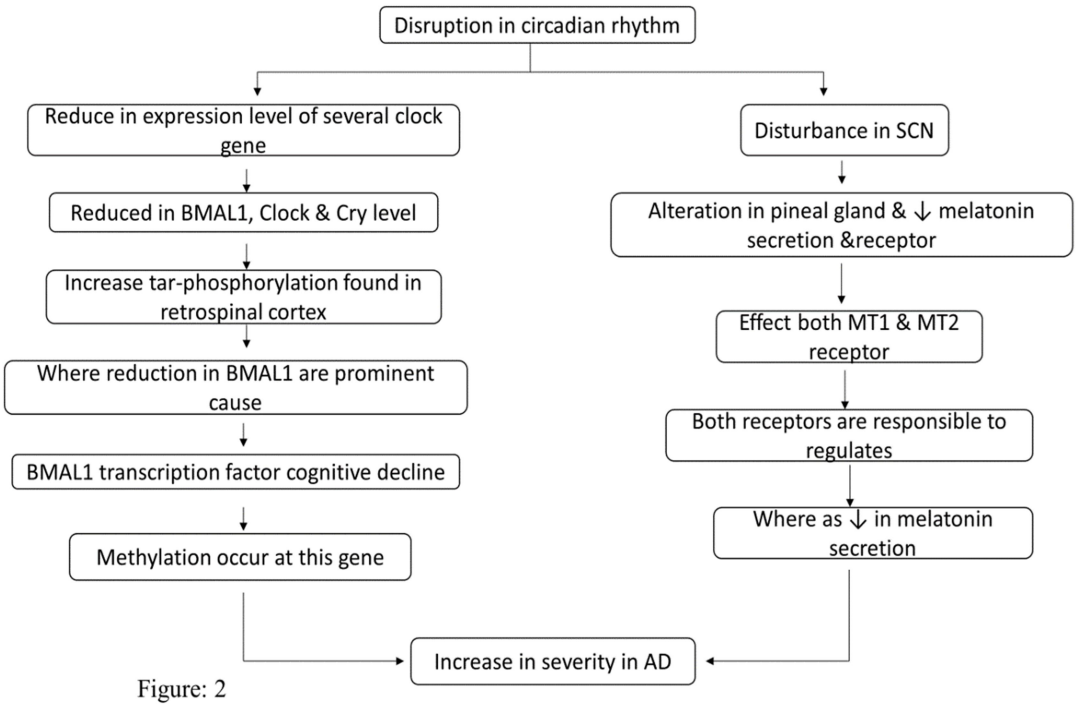


**Fig: 2 Delivers the idea Alzheimer disease caused by circadian rhythm**

Presenilin 2 gene, responsible for regulating amyloid levels, undergoes diurnal oscillations in the SCN which is influenced by the CLOCK/BMAL1 heteromeric complex through both RNA synthesis as well as protein modification processes in tissues outside the central nervous system [75, 76, 77]. In moreover, Aβ removal throughout the hematoencephalic barrier occurs in a diurnal rhythm and increases throughout bedtime [78].

This diurnal pattern is linked to circadian-induced variations in subarachnoid fluid flow in nervous system, which increase waste clearance, as demonstrated in glymphatic clearance pathway [79]. Aβ buildup can disturb the molecular clock, possibly contributing in energy metabolism as well as metabolic circadian oscillations [80].

Amyloid promoted BMAL1 catabolism, resulting in decreased binding to the PER2 promoter [81]. Chronic damage from elevated reactive oxidative species (ROS) and reactive nitrogen species (RNS) inside the nervous system has been linked to Alzheimer initiation and development [82].

Body clock disturbance has been related to increased oxidative stress in neurons, all of which have a role in the early development of Alzheimer's disease [83]. The loss BMAL1 and CLOCK caused defective activation of various redox defence genes as well as increased ROS generation, resulting in persistent oxidative stress and neuronal oxidative damage [84, 85].

Brain and Muscle Arnt-Like 1 removal has been found to accelerate Aβ amyloid formation in circadian oscillation, enhance amyloid and hyperphosphorylated tau proteins deposition in tissue-specific rhythms [86] [87]. Accumulation hyperphosphorylated tau proteins can cause hyperthermia either hypothermia

[88]. Tg4510 mouse model shows modification in molecular and behavioural standard in biological clock [89]. A recent investigation verified the importance of BMAL1 and circadian dysregulation in AD pathogenesis, revealing rhythmic DNA methylation coupled with rhythmic BMAL1 transcription, which was poorly controlled throughout early AD development [90].

## Dementia

Circadian interruption mechanisms in dementia are unknown, numerous aspects are backed by evidence, such as a malfunctioning circadian pacemaker, lowered melatonin production and receptors, zeitgebers, and input to the SCN. Central biological clock situated in the SCN by reducing performance via reduced neurotensin, vasopressin but enhanced GFAP astrocytes [91].

Other AD-related neuropathological abnormalities are discovered in suprachiasmatic nucleus, including neurofibrillary tangles beta-amyloid plaques [92, 93, 94]. Individuals suffering from Alzheimer has nearly twice lower levels of Pitressin (antidiuretic hormone) as well as enhancer ribonucleic acid [95]. Furthermore, scientific testing has shown that photo-stimulation Cause Period Circadian Regulator 1 protein and 2 protein genetic coding at suprachiasmatic Nucleus [91]. All of these findings suggest that anatomical alterations inside suprachiasmatic Nucleus may contribute to changes in melatonin secretion and its receptors. Melatonin modulates the diurnal oscillation in nervous system levels, via GPCR receptors (melatonin 1 and 2) [91]. Melatonin synthesis diminishes with age, particularly in dementia cases, where the drop commences before the symptoms of AD become apparent [96].

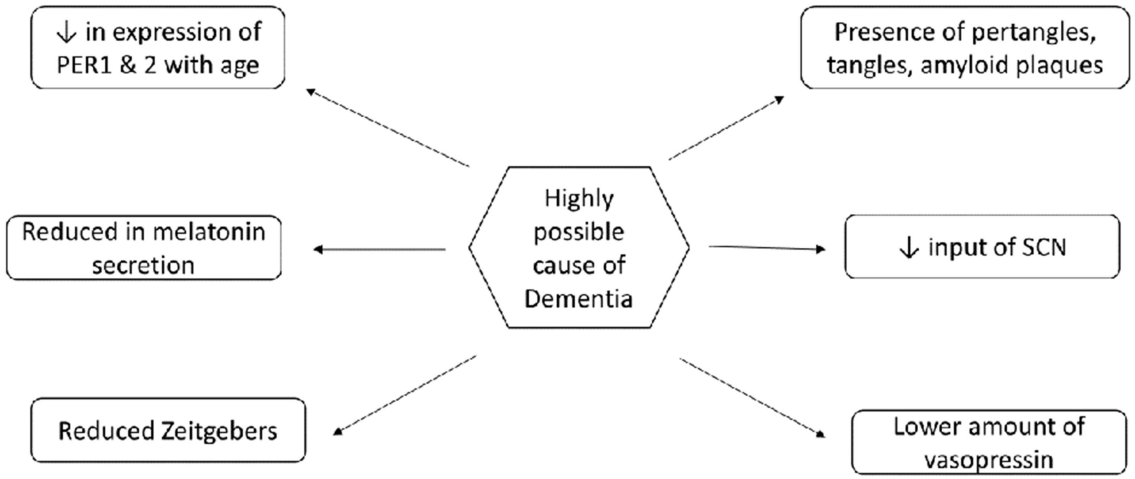


Figure: 3

**Fig 3: Represents the factors cause dementia**

Researchers found lower nighttime melatonin standard in preliminary as well as advanced phases of dementia [91]. The central clock loses sensitivity or becomes dysfunctional due to impaired knowledge processing in the brain mechanisms involved in synchronization [97]. Reduced in response to

suprachiasmatic Nucleus, a risk contributes to diurnal oscillation afflictions, may arise via a variety of processes. First, light influences the SCN via light-related signals channel known as retinal hypothalamus connection. Dementia individuals' Sunlit exposure is limited by reason of numerous nightly awakenings and increased daytime dozing [98, 99].

Second, the power of the lens to transmit light declines with age, and the elderly frequently suffer Lens opacity and macular degeneration [100, 101]. In contrast, evolutionary phase macular disorder has been linked to Alzheimer's disease [102]. Alzheimer's disease is linked to degenerative alterations in photoreceptor layer and visual nerve [103-105], as well as a fivefold increase in glaucoma occurrence compared to controls [106].

All of these factors affect Contribution of diurnal oscillation Fourth, in addition to reduce productivity and capability of the light route, the diminished impact of melatonin on suprachiasmatic Nucleus caused by low amounts of melatonin and melatonin receptors contribute Toward advancement of diurnal oscillation problems. Finally, demented individuals limited holistic health activity may lead to diurnal oscillation problems [107, 108].

## Huntington's disease

HD is the most prevalent single-gene degenerative neurological disease today, with an vertical transmission [109]. Huntington's affects around 10.6-13.7 persons per 100,000 worldwide [110] [111].

The disease often manifests in adults, with gradual course and a mix of motor, cognitive, and behavioural signs [109]. In addition, diurnal and sleep changes are reported at the outset illness, sometimes before clinical symptoms appear [112]. A recent meta-analysis found that Huntington's patients have usual sleep structure abnormalities, Prolonged sleep onset, postponed REM sleep phase, and enhance amount of early sleep phase [113].

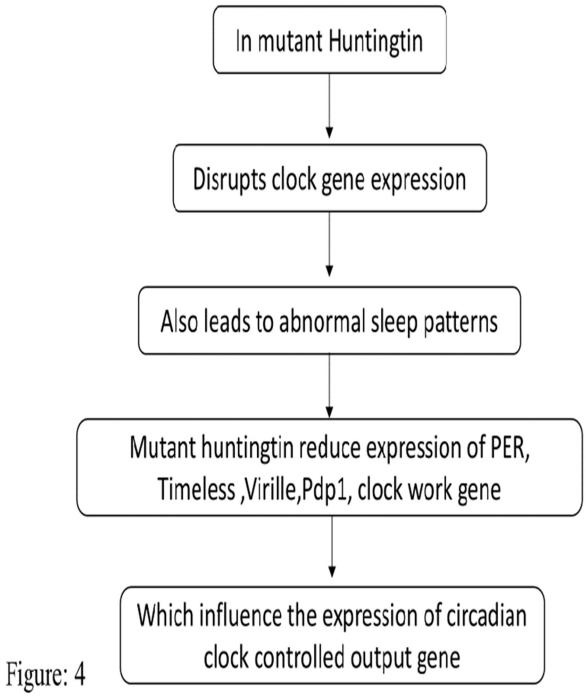


Figure: 4

**Fig: 4 Describe the pathway of huntingtin disease disrupt diurnal oscillation**

A protein involved in Huntington etiopathogenesis concentrate in regions that govern muscle weakness in rapid eye movement decrease in this phase [114] and also leads to reduce in action cardiac rhythm as well as core temperature [115] [116] [117].

Clinical trials found that Huntington patients have reduced diurnal blood pressure fluctuation [118] and aberrant inactive behaviour cycles [119]. latterly, there's been demonstrated those individuals in the early phase Huntington had a considerable loss in hypothalamic gray matter volume, impaired regular sleep effectiveness as well as higher stirrings [120].

A region of hypothalamic nucleus those regulates cortisol and melatonin discharge, which might define alterations pertaining to sleep organization limited research has attempted to estimate the activity patterns of circadian DNA segment in Huntington [121] [122]. Remarkably, alternated huntingtin lowered activity of period, timeless (tim), vrille (vri), par domain protein 1 (Pdp1), and clockwork orange (cwo), all of which are essential diurnal oscillation controllers [121].

It is worth noting that these reported gene changes might be attributed to the accumulation of mutant huntingtin in brain regions such as the hypothalamus [120]. Furthermore, decreased expression of PER, timeless, and vrille is associated with extended nocturnal sleep as well as impact the manifestation of body clock-controlled outcomes of DNA segment that might contribute in sleep pattern [121].

In Drosophila model of Huntington, the manifestation of peroid, timeless, CLOCK, and CRY DNA segments was decreased. N-acetyl-5-methoxytryptamine or melatonin (100 micrograms) or diferuloylmethane (curcumin) (10 micrograms) administered by diet restored the DNA segments activity profile of period and timeless [122]. It is crucial to highlight diferuloylmethane, the primary curcuminoid contained in turmeric, has free radical scavenging and inflammation reduction characteristics that may help prevent or treat neurodegenerative disorders [123][124].

Additional research is required to explain the particular processes behind the link between circadian DNA segments and Huntington etiopathology, as well as to assess the efficacy of melatonin and curcumin as prospective Huntington therapies.

## Multiple Sclerosis

Multiple Sclerosis ranks as the highest prevalent neurological illness among teens (124). It is a diverse, complex, immunologically-driven illness impacted by both nature and nurture variables [125]. The pathologic characteristic is the buildup of plaques in central nervous system [126].

Clinical signs differ by patient, but are often transient periods of neural impairments and remitting recurrent multiple sclerosis. Indefinite brain impairments and physical limitation progression become

more apparent with time [125]. The circadian oscillation is assumed to have an important function in pathogenesis of MS, as shift workers [127]. Individuals who live in nations with daylight saving time [128], which are both circadian disrupting variables, have a increased risk of having multiple sclerosis.

Latest research has demonstrated that in MS patients, circadian oscillation has a deleterious impact on tiredness [129], mood [130], and physical impairment [132].

More recently, researchers have attempted to understand the significance of the circadian cycle in relapsing-remitting multiple sclerosis [133][132][134]. An actigraph revealed that MS patients experience a longer acme of motor performance in early morning as compared to control people [134]. Acme of greater performance can be attributed to increased hypothalamic-pituitary-adrenal axis activity and a higher cortisol response upon awakening, as well as the change in mood observed over the day in these individuals [130].

Recent research suggests that interpretation of circadian genetic material is changed in multiple sclerosis patients [135][136][137]. In genome-wide association studies, changed interpretation is detected in circadian components such as Period Circadian Regulator 3, Reverse-erb alpha [Nuclear receptor subfamily 1, group D, member 1" (NR1D1)], and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Ppargc1α) [137].

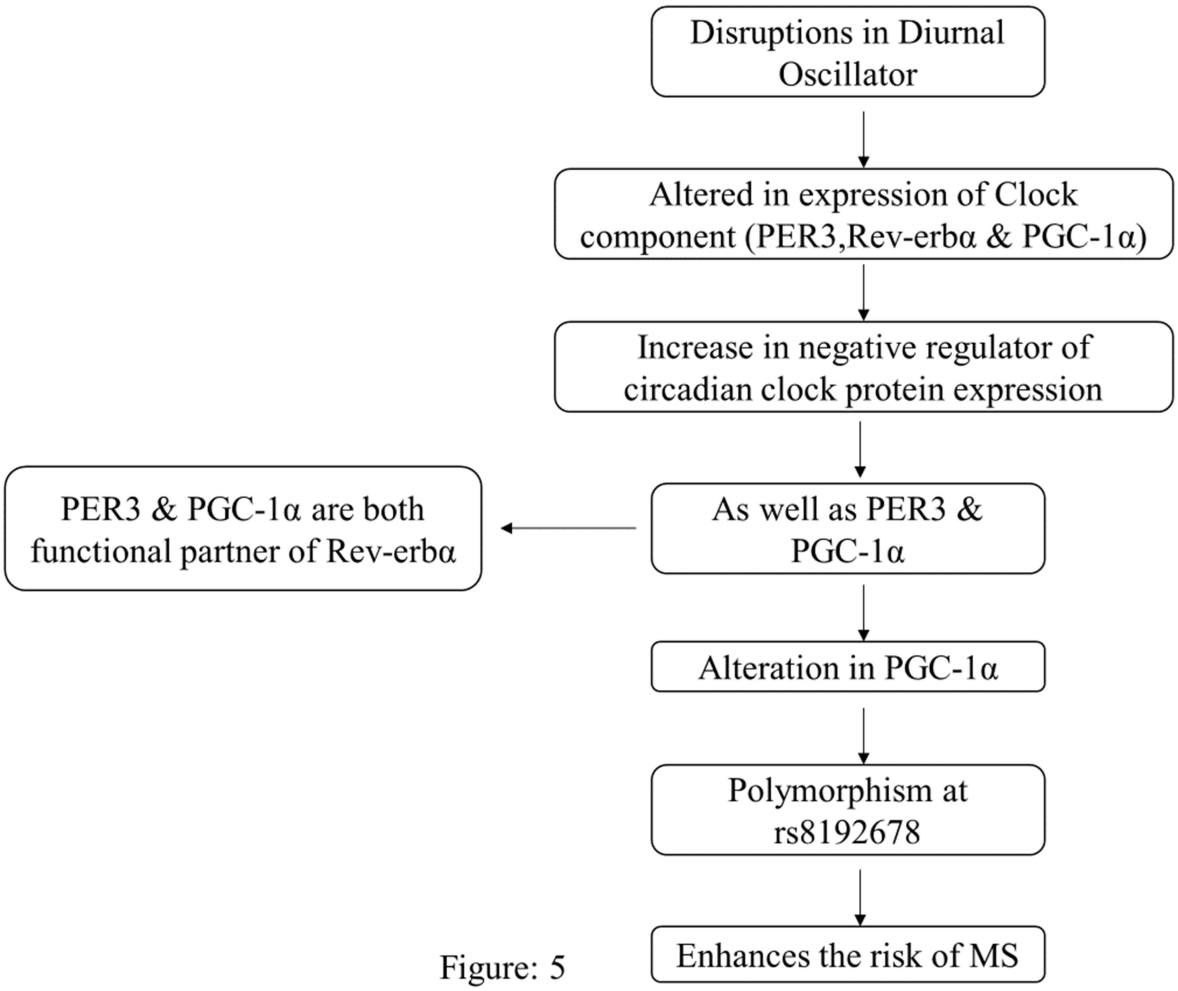


Figure: 5

**Fig: 5 Represents the pathways which leads Multiple Sclerosis caused by circadian disruptions**

Multiple Sclerosis individuals have altered manifestation of Rev-erbα, a negative regulator of diurnal clock protein production, as well as Period Circadian Regulator 3 and PGC-1α, both functional partners of Rev-erbα [137]. PPARGC1A, (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) a transcriptional coactivator, is a crucial component of the circadian oscillator, which generates 24-hour rhythms in animals. The rs8192678 genetic variation increases the chance of getting Multiple Sclerosis [138].

In Caucasian MS patients, genotype distribution differed, with the Brain and Muscle ARNT-1 rs3789327 CC and Circadian Clock Protein rs6811520 CC genetic variants linked with a 40%-67% rise chances of Multiple Sclerosis [136]. Multiple Sclerosis patients exhibit altered expression of clock genes, such as Period Circadian Regulator 3, NR1D1, PPARGC1A, and Brain and Muscle ARNT-like 1. Multiple Sclerosis cases showed elevated expression of NR1D1, Period Circadian Regulator 3 as well as Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, whereas circadian Locomotor Output Cycles Kaput and Brain and Muscle ARNT-like 1 genetic variation are linked to higher chance of causing multiple sclerosis. The rs8192678 PGC-1α genetic variants was linked to an increased chance

of acquiring multiple sclerosis. The disrupted diurnal oscillations in multiple sclerosis may change cellular metabolism pathways, facilitating extended neurodegeneration. Further research is investigating the cellular processes behind the connection between circadian genetic material and Multiple Sclerosis pathology [136].

## Spinocerebellar Ataxia (SCA)

SCA is a neurological disorder marked by gradual retinoid as well as cerebellar degeneration [139]. The primary illness path ways comprise toxic ribonucleic acid enhance performance, mitochondrial malfunction, muscle trauma, self-eating, gene expression disruption of regulation [140].

The degree of Spinocerebellar ataxia signs fluctuates consistent with to their over forty variety, the most prevalent of which is increasing ataxia, dysarthria [139]. In addition to these distinctive motor symptoms, Spinocerebellar ataxia individuals manifest to considerable decrease sleep density in rapid eye movement [141, 142], indicating that the diurnal oscillation might contribute in SCA pathophysiology [143].

Alternative investigations have linked adapted diurnal oscillations along Spinocerebellar ataxia [144][145][146][147][148][149].

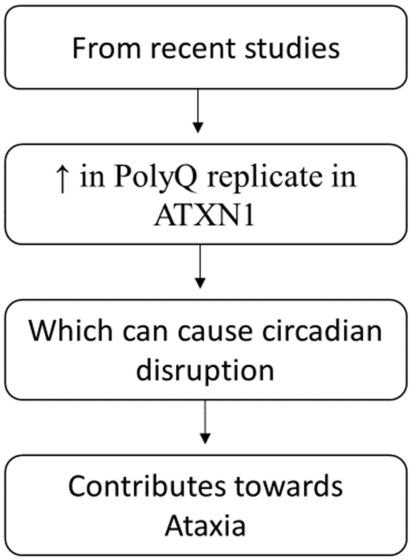


Figure:6

**Fig: 6 Represents pathway caused Spinocerebellar Ataxia (SCA)**

Type 3 Spinocerebellar ataxia transgenic mice exhibit higher disintegration in both rest as well as awake stages, bigger oscillation of β-waves during REM and non-REM sleep, represent the shared sleep-related etiological mechanisms may support the Spinocerebellar Ataxia Type 3 traits of mice [148]. Notwithstanding of changes in sleep architecture and blood pressure oscillations While the sun is up, the expression standard of Period 1" gene and Period 2" gene, those are essential diurnal oscillations controllers [150].

Nonetheless, CLOCK Protein as well as Brain and Muscle ARNT-like 1 demonstration standard are shown to be low in skin fibrous cells in type 17 Spinocerebellar ataxia patients [145]. Moreover, Latest studies [144] found in increase of polyQ replicas in ATXN1, Genetic code associated to Spinocerebellar ataxia 1, disrupts circadian rhythms in Drosophila, perhaps contributing to illness pathogenesis. The discrepancies in gene expression discovered by the research might be attributed to SCA's varied group of subtypes based on the locus or causal gene. Future research on disrupted diurnal oscillations in

Spinocerebellar ataxia Must concentrate on understanding the core processes and creating novel treatment techniques. More study is needed to discover the particular genetic material and processes that alter diurnal oscillations in distinct Spinocerebellar ataxia subtypes. Researches might also investigate the possibilities of employing time-dependent therapy, a therapy technique that involves timing drug delivery according to an individual's circadian cycle in order to enhance symptom control in Spinocerebellar ataxia patients. Finally, the potential application of gene therapy to restore correct diurnal oscillations in Spinocerebellar ataxia patients is a promising area for further investigation [144].

## Conclusion

Sleep and circadian rhythm abnormalities have been related to many mental and neurodegenerative illnesses across the lifetime. While most preclinical investigation is generalizable, exploring potential causative links between altered circadian rhythms and other brain illnesses, aiming to find molecular pathways. Most of the pathway are linked through clock, BMAL, PER1, 2 and 3, tim, cwo, pdp1, Rev-erbα. In case Parkinson disease literature proves that there is reduction in standard Clock, BMAL, PER1 and PER2. In Hun tington disease there are fall in expression of PER, tim, Vri, pdp1, cwo, clock. On other hand marked rise in level of Rev-erbα, PER3, PGC1α, BMAL1, Clock in case of multiple sclerosis. Recent studies reveal that there are fall in expression of BMAL1, Clock, Cry in Alzheimer and dementia.

This review suggests that diurnal oscillation dysregulation may have a role in the etiology of neurodegenerative disorders, highlighting the need for more investigation.

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