

Schizophrenia and disruption of circadian rhythms: An overview of genetic, metabolic and clinical signs

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ABSTRACT

A molecular clock in the suprachiasmatic nucleus of the anterior hypothalamus, which is entrained by the dark-light cycle and controls the sleep-wake cycle, regulates circadian rhythms. The risk of developing mental disorders, such as schizophrenia, has long been linked to sleep abnormalities. Additionally, a common aspect of mental disorders is sleep disturbance, which has a direct impact on the intensity of the symptoms and the quality of life of the patient. This relationship can be explained by gene alterations such as CLOCK in schizophrenia which are also important components of the physiological circadian rhythm. The function of dopamine and adenosine in circadian rhythm should also be noted, as these hypotheses are considered to be the most popular theories explaining schizophrenia pathogenesis. Therefore, determining the presence of a causal link between the two can be key to identifying new potential targets in schizophrenia therapy, which can open new avenues for clinical research as well as psychiatric care. We review circadian disruption in schizophrenia at the genetic, metabolic, and clinical levels. We summarize data about clock and clock-controlled genes' alterations, neurotransmitter systems' impairments, and association with chronotype in schizophrenia patients. Our findings demonstrate that in schizophrenia either homeostatic or circadian processes of sleep regulation are disturbed. Also, we found an insufficient number of studies aimed at studying the relationship between known biological phenomena of circadian disorders and clinical signs of schizophrenia.

1. Introduction

Circadian rhythms are about 24-h variations in physiology and behavior that have developed through the course of phylogeny to help organisms anticipate daily environmental changes like the light/dark cycle. The suprachiasmatic nucleus (SCN), located in the anterior region of the hypothalamus, contains a molecular clock that regulates circadian rhythms and is entrained by the dark-light cycle. Circadian locomotor output cycles kaput protein (CLOCK), brain and muscle ARNT-like 1 (BMAL1), period circadian regulators 1 and 2 (PER1 and PER2), and cryptochrome circadian regulators 1 and 2 (CRY1 and CRY2) are some of the core clock genes that make up the molecular clockwork. The transcription-translation feedback loop that controls these genes oscillates every 24 h (Caba et al., 2018; Takahashi, 2017).

Almost every cell in the body contains this fundamental clock machinery (Dibner et al., 2010). A network of cell-autonomous circadian oscillators controls rhythmic outputs owing to the coordination of peripheral clocks by the master circadian pacemaker in the SCN. The principal time cue or “zeitgeber” for the entrainment of the clock to environmental changes is a perception of light input directly from the retina by SCN through the retinohypothalamic tract. The sleep-wake cycle is one of these rhythms governed by the circadian system, but it is also regulated by physiological sleep pressure, which builds up during waking and decreases during sleep (Ashton and Jagannath, 2020; Kandeger et al., 2021). Peripheral clock genes are also entrained by various time cues such as feeding rhythms and daily activity. Altered signaling of time cues may change the rhythms of both peripheral and central clock genes and even result in their uncoupling (Fedchenko et al., 2022).

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About 1 % of the world's population suffers from schizophrenia, a severe psychological condition that is one of the primary contributors to disability. The etiology of schizophrenia is complicated and has been researched for years, although there are still many undiscovered causes. Dopamine is one of the most important neurotransmitters associated with the pathophysiology of schizophrenia (Luvsannyam et al., 2022). It is diverse, characterized by both negative symptoms, including flattened affect, social withdrawal, anhedonia, apathy, and lack of emotions, as well as positive symptoms such as hallucinations, delusions, disorganized speech, and aberrant movements (Ashton and Jagannath, 2020; James et al., 2018). The disease is a severe disorder for many individuals and their families due to its early onset and chronic character. Negative symptoms characterized by loss or deficits in mental functions and cognitive symptoms, such as difficulties with attention, working memory, or executive function, frequently combine to cause disability. Additionally, positive symptoms including suspicion, delusions, and hallucinations might result in relapse (Leposavic et al., 2015; Yevtushok et al., 2021).

In addition to other symptoms, circadian rhythm disruption is a typical feature of the condition and is directly connected to the severity of clinical symptoms and the impact on the patient's quality of life (Cosgrave et al., 2018). However, despite the evident association between schizophrenia and disturbed circadian rhythm, the underlying mechanism is currently not understood yet. In the current review, we summarize the knowledge about genetic, metabolic, and clinical features of circadian disruption in schizophrenia and its relationships.

2. System of circadian rhythm in mental health

Major depressive illness, bipolar disorder, and schizophrenia are all accompanied by circadian disturbances. It is possible that circadian rhythms have a significant impact on several illnesses, albeit the precise nature of that function is yet unclear. The fact that alterations in sleep habits have been shown to alleviate the basic symptoms of these diseases lends credence to this theory. Sleep deprivation, for instance, has been shown to have a (temporary) antidepressant effect on patients (Babson et al., 2010). Furthermore, the length of the day seems to have a role in the development of certain affective illnesses, such as seasonal affective disorder, through modulating emotional states. The master clock in mammals is the SCN, a large nucleus in the hypothalamus. In rats, a lesion to the SCN causes a total breakdown of circadian rhythms (Chiesa et al., 2010). The animals will not follow a routine, instead going to sleep and waking up whenever they like (although still sleeping the same total amount of time each day). The SCN knows whether it is day or night thanks to input from retinal ganglion cells, which help it stay in step with the 24-h day. The visual sense is used, although it is not necessary. Other than light, it is believed that the availability of food, social engagement, and knowledge of the physical surroundings all play an essential part in the SCN's capacity to sustain regular daily cycles. Moreover, it has demonstrated an importance of the social environment in psychorehabilitation of patients with mental disorders (Isakov and Herasymenko, 2022; Yıldız, 2021). But how exactly do the SCN's neurons "maintain time"? As far as can be determined, they are regulated by a negative feedback loop in the cycle of gene expression of CLOCK, BMAL1, PER and CRY. However, it seems that the SCN does not exert direct control over a large number of cells, despite being the hub of circadian rhythms. Instead, it is believed that they use independent timekeeping processes. These cells, known as peripheral oscillators, may respond both to the signals of the SCN and external inputs and are found in a variety of organs (Waddington Lamont et al., 2007). Whether these variants cause, contribute to or are unrelated to the illnesses is yet unknown. But considering how disruptive circadian rhythms can be to everyday life, it seems sensible to look at whether or not they play a role in diseases.

Studies have found a clear link between circadian rhythms and mental health conditions such as anxiety, major depressive disorder,

bipolar disorder, substance use disorders and schizophrenia. Mental health may be affected as a result of circadian system disturbances. On the other hand, substance use can affect circadian rhythms with a negative impact on sleep, regardless of mental pathology (Adan, 2013; Boiko et al., 2021). Although it is yet unclear how disruption of the circadian rhythm relates to the pathophysiology of mental disease, a close examination of experimental studies provides compelling support that circadian rhythm disruptions can alter mood, and their resynchronization in rodents can alleviate symptoms of mood disorders (Walker et al., 2021).

Sleep disturbances may be an important pathophysiological component of schizophrenia. It has been reported that circadian disorders in schizophrenia can be observed even in the prodromal phase and can affect therapeutic outcomes (Adan et al., 2023). Difficulties falling asleep, lengthy periods of sleeplessness, worry about sleep, and continuous stress owing to an inability to sleep have all been reported in people with schizophrenia. In many cases, sleep disturbance corresponds with the severity of psychotic and cognitive symptoms, and periods of insomnia frequently precede psychotic symptom exacerbations. Alterations in circadian rhythms have also been recorded, including phase shifting and variations in hormone production. Sleep disturbances exacerbate many of the disease's symptoms and frequently occur before the development of schizophrenia (Pocivavsek and Rowland, 2018).

3. The link between time cues with schizophrenia

One challenging theory about the etiology of schizophrenia proposes that being born at certain times of year increases the risk of developing the disorder (Demler, 2011). This finding inferred that sunlight, specifically ultraviolet radiation (UVR), which is harmful to deoxyribonucleic acid (DNA), especially in an embryo, exerts an epigenetic effect. Several studies have shown that high levels of UVR can have a negative impact on the human lifespan, with evidence suggesting that the maximum intensity of UVR during solar cycles of roughly 11 years may be especially damaging to human cells (Davis et al., 2022; Juckett and Rosenberg, 1993). It has been discovered in several studies (Davies et al., 2003; Karlsson et al., 2019; Torrey et al., 1997) that people with early-onset schizophrenia are more likely to have been born in the winter or spring. However, the frequency of human births varies according to the month of birth, reflecting elements such as the availability of nutrition, sunlight, and other unidentified epigenetic factors. (Rafiepour et al., 2015; Valencia-Vera et al., 2019).

The fetus is exposed to the mother's circadian rhythms during pregnancy, which may help entrain its peripheral clock in the postnatal period (Serón-Ferré et al., 2012). The effect of the season of birth on the preferred sleep-wake cycle was investigated in a study published in 2009. This evidence may support the theory that extended photoperiod exposure leads to a phase delay in human circadian rhythms. The birth season has a statistically significant but quantitatively minor impact on sleep-wake cycles (Natale et al., 2009). Another study looked at the effect of socioeconomic status and season of birth as predictors of deficiency/non-deficiency in schizophrenia patients. The findings revealed a substantial difference in the monthly patterns of deficit/non-deficit schizophrenia. Women who conceived a child in January have an increased proportion of children with non-deficit schizophrenia, which the authors indirectly attribute to the possible viral theory and seasonality of the flu (Gallagher et al., 2007). It is congruent with another study, which found that the relationship between schizophrenia and the season of birth was mediated by its subtype. At the same time, births in the summer are more common among people with deficit schizophrenia (Messias et al., 2004).

Several studies have shown that patients with schizophrenia are often born in late winter and late summer. The similar pattern is seen with the delivery of infants with neural tube abnormalities. In the northern hemisphere, conception rates are highest in May–June and lowest in November–December for both illnesses. Researchers

hypothesize that maternal oxidant stress, which may increase with strong sun radiation exposure, may interfere with both neural tube closure and asymmetry development. The extremes of sunshine in June and December would therefore explain the peaks of seasonal oscillations. Moreover, irrespective of causes, the similarity between the two conception cycles implies that the same periconceptional folate regimens reported to be successful in avoiding neural tube abnormalities may potentially reduce the risk of schizophrenia (Marzullo and Fraser, 2005).

A recent study by G.E. Davis et al. suggests that not a month of birth (MOB) but a month of conception (MOC) is crucial in the development of schizophrenia. Schizophrenics have their peak MOB in November and December when MOC takes place at the spring equinox and UVR sharply rises. With an increase of winter-spring births found in those with schizophrenia, high-constant or fast-growing UVR during this time period activates the embryonic/fetal central nervous system (CNS), which may contribute to the known strong genetic loading of schizophrenia (Davis et al., 2022).

Because pregnant women frequently go through physical, physiological, social, and emotional changes that might impact their usual way of life, pregnancy is considered as prone to chronodisruption. The circadian system and sleep/wake cycles are strongly connected, and the mother's circadian rhythm may be affected by disturbed sleep during pregnancy (Kaur et al., 2020).

Vollmer et al. discovered that adolescents ($n = 2905$) born during the growing photoperiod (Feb–Apr) had a considerably later midpoint of sleep than those born during the falling photoperiod (Aug–Oct). Two chronotype assessments revealed a robust quadratic function across a year cycle. The composite morning scale demonstrates a cosine rhythm linked to rising and declining photoperiods, whose amplitude diminishes with age by looking at each of six consecutive years separately (Vollmer et al., 2012).

Like many other internal and external stimuli of circadian synchronization, food intake is also one of the primary outside factors influencing circadian rhythm adjustment. However, people with schizophrenia were found to have changed eating behaviors which increased the risks for diabetes, obesity, metabolic syndrome, and cardiovascular diseases (Dipasquale et al., 2013; Kandeger et al., 2021; Vancampfort et al., 2016; Yum, 2005). Disturbances in the time of food intake can lead to an altered circadian release of endocrine hormones. For instance, Night Eating Syndrome (NES) is prevalent among schizophrenia patients, with a prevalence of around 10 %. The NES is characterized by frequent eating-related awakenings and evening hyperphagia (Goel et al., 2009). The timing of food intake changes, a marker of NES, is connected to aberrant neuroendocrine patterns. People with NES appear not only to have elevated glucocorticoid levels than the general population but also an altered circadian pattern of release of these hormones into the circulation (Birketvedt, 1999; Vander Wal, 2014). Moreover, lower levels of melatonin were also observed in people with NES (Birketvedt, 1999), therefore, the development of the night feeding syndrome and sleep difficulties are thought to be significantly influenced by the melatonin level, which has been found to be declining.

There is mounting evidence that people with schizophrenia are more likely to experience sleep disruptions of different kinds. Patients spend an average of longer in bed, take longer to fall asleep, wake up later, and experience an average of more interrupted fragmented sleep episodes (Meyer et al., 2020; Wulff et al., 2012). Over consecutive nights, sleep-wake rhythms become increasingly erratic and may be advanced, delayed, or out of synchronization with the 24-h day (Kodaka et al., 2010; Wirz-Justice et al., 2001; Wulff et al., 2012). It is well known that circadian synchronization is reliant on the external input of light–dark cues and the integrity of circadian oscillators in the CNS (Wulff and Joyce, 2011); however, the widespread exposure to light at night has made it difficult to distinguish between day and night. Melatonin release from the pineal gland is subsequently inhibited as a result (Dominoni et al., 2016; Higuchi et al., 2014; Mitsui et al., 2022; Navara and Nelson,

2007).

One study examined circadian patterns of positive symptoms in schizophrenia, specifically auditory hallucinations are more common at night between 6:00 PM and 9:00 PM. As the plasma concentration of homovanillic acid, a dopamine metabolite, peaks between midnight and 5:00 AM in individuals with schizophrenia, one reason the authors explore is the circadian rhythmicity of dopaminergic activity. Such nocturnal dopaminergic system activation might more frequently result in positive symptoms at night (Koizumi et al., 2019). Psychotic experiences can complicate falling asleep and thus have a negative impact on both sleep quality and quality of life (Afonso et al., 2011).

At the same time, the association between circadian rhythms and negative symptoms in schizophrenia has not been studied. Although such a connection is known in other diseases, for example, it was studied into whether circadian abnormalities were involved in the development of post-stroke apathy (Cosin et al., 2015), and also found that those with Parkinson's disease who had a rapid eye movement (REM) sleep behavior disorder (RBD) had compromised levels of all subdomains of apathy (except emotional reactions) (Shkodina et al., 2022a). The symptoms of schizophrenia may contribute to insufficient exposure to time cues that synchronize circadian rhythms due to a more sedentary lifestyle, which is associated with both deterioration in rhythmic expression and the clinical status of the patient (Mayeli et al., 2023).

4. Clock genes and other genetic alterations related circadian disturbances in schizophrenia

Circadian rhythm disturbances in schizophrenia may be caused by genetic causes. Certain genes have been linked to schizophrenia and circadian rhythm modulation in research. Understanding the disruption of circadian rhythms in schizophrenia requires research into the mechanisms of the molecular clock. Although some studies have demonstrated a limited benefit of non-pharmacological interventions in schizophrenia, chronobiology and circadian medicine approaches in this disease have not yet been explored (Rabinowitz et al., 2019). Between sleep disorders and schizophrenia, a genetic overlap has been defined. The convergence of pathways controlling circadian rhythms and mental disorders has been considered, and an etiological connection between these diseases and sleep disorders has been studied (Boiko et al., 2022; Khanzada et al., 2017).

Many physiological and biochemical processes in mammals are under the molecular genetic control of circadian systems. The fundamental principle of the molecular clock system is based on the interaction of reverse feedback loops of transcription, and protein translation and is represented by a wide range of genes expressed with a 24-h rhythm (Kruchko et al., 2022). Major core clock genes are known to regulate circadian rhythms, which include BMAL1, BMAL2, CLOCK, PER1, PER2, PER3, CRY1, and CRY2 (Shkodina et al., 2022b).

The CRY1 gene, which performs a predominantly regulatory function in the circadian clock, is located in the chromosomal region 12q23–q24.1 and is associated with the 12q24 linkage locus in schizophrenia. The authors suggest that CRY1 interacts with neuroleptics and the dopamine system and is a candidate gene for schizophrenia (Peng et al., 2007).

The CLOCK gene is another crucial component of the molecular clock mechanism in the SCN. It has been determined that schizophrenia is correlated with the single nucleotide polymorphism (SNP) T3111C of the CLOCK gene. The T3111C variant of the CLOCK gene has been linked to daytime sleepiness in 171 individuals with severe psychosis, including schizophrenia, who were receiving clozapine medication (Lattuada et al., 2004). A study of 145 schizophrenic patients in the Japanese population compared to 128 healthy individuals discovered the SNP T3111C of the CLOCK gene, which may be connected with the pathophysiology of schizophrenia (Takao et al., 2007).

The SNP of T3111C of the CLOCK gene and the length polymorphism of the PER3 gene have been linked to the development of schizophrenia.

A survey was done with 148 individuals with schizophrenia and 199 people in the control group. The scientists concluded that the T3111C (rs1801260) polymorphism of the CLOCK gene is connected with schizophrenia and that the length polymorphism of the 18th exon of the PER3 gene is not associated with the development of schizophrenia (Zhang et al., 2011).

Other authors studied patients with schizophrenia in South India and measure the presence of PER3 circadian gene polymorphism. Blood samples were taken from 311 patients with BD-I, 293 patients with schizophrenia, and 346 healthy individuals, to perform DNA genotyping of PER3 by polymerase chain reaction. In patients with schizophrenia, no significant differences were found in the allele frequencies of four- and five-repeat alleles compared to the control group. Thus, it was established that the length polymorphism of the PER3 gene does not affect the pathogenesis of schizophrenia (Karthikeyan et al., 2014).

Another study of the Japanese population examined the relationship between the SIRT1 gene, schizophrenia, and bipolar disorder. SIRT1 interacts with primary circadian genes CLOCK-BMAL1 and promotes PER2 deacetylation and degradation. The SIRT1 gene was investigated in 1158 patients with schizophrenia, 1008 individuals with bipolar disorder, and 2127 control patients using four tagged SNPs (rs12778366, rs2273773, rs4746720, and rs10997875). In allele and genotype analyses, a connection was found between rs4746720 in the Sirtuin 1 gene (SIRT1) and schizophrenia (Kishi et al., 2011). Associations with SNPs in the Timeless Circadian Regulator (TIMELESS) and PER3 genes in an American cohort of patients with schizophrenia and schizoaffective disorder were found using familial and case-control analyzes (Mansour et al., 2006).

The association of CLOCK and Neuronal PAS Domain Protein 2 (NPAS2) genes' polymorphism with restless legs syndrome was investigated in a sample of 190 Korean patients with schizophrenia who were taking antipsychotics. The distribution of haplotypes of the CLOCK gene (rs2412646, rs1801260) differed significantly between schizophrenic patients with and without restless legs syndrome, while the distribution of allelic, genotypic, and haplotype variants of NPAS2 (rs2305160 and rs6725296) did not differ significantly across these groups (Jung et al., 2014). During the study of the glial cells, it was found that their defective clock genes are important in the pathogenesis of schizophrenia. For example, mutations in CLOCK, NPAS2, and/or PER2 decrease glial glutamate uptake by reducing the expression of glutamate/aspartate transporter. In turn, glial glutamate regulates the levels of brain neurotransmitters, including dopamine (Chi-Castañeda and Ortega, 2016, 2017).

The analysis of genome-wide association studies (GWAS) indicated that only the temporal gene BMAL1 has been found as one of the few loci that distinguish bipolar disorder from schizophrenia (von Schantz et al., 2021).

We show the studied association between schizophrenia occurrence and polymorphisms of clock genes in Table 1.

We have not found any study about the relationship between polymorphism of PER1, CRY2, BMAL2, and schizophrenia, despite the fact that they are included in the core of the molecular clock (Stamenkovic et al., 2012).

SNP-based *p*-values for genes encoding molecular clock components in schizophrenia, bipolar disorder, and major depressive disorder were analyzed based on data from the Psychiatric Genomics Consortia association analysis. The authors conclude that there is little evidence for the role of SNP-candidates in clock genes in affective disorders or schizophrenia, supporting the hypothesis that circadian disruption may be a consequence rather than a cause of the disease (von Schantz et al., 2021).

The influence of alterations in the expression of clock genes related to the regulation of circadian rhythms on the probability of relapse after antipsychotic therapy of individuals with schizophrenia compared to healthy controls was examined. The mRNA expression of the clock genes PER1, PER2, PER3 and NPAS2 was evaluated in blood samples obtained

Table 1
Clock and clock-controlled genes' alterations associated with schizophrenia.

Gene	Main findings	Study
BMAL1	rs198235 polymorphism is associated with schizophrenia One of the few loci that distinguish bipolar disorder from schizophrenia	(Mansour et al., 2006) (von Schantz et al., 2021)
CLOCK	Decrease glial glutamate uptake by reducing the expression of glutamate/aspartate transporter in patients with schizophrenia T3111C polymorphism is linked to daytime sleepiness and may be associated with the pathophysiology of schizophrenia T3111C polymorphism is linked to the occurrence of schizophrenia rs2412646 and rs1801260 polymorphisms are associated with restless legs syndrome in patients with schizophrenia Decrease expression in patients with schizophrenia	(Chi-Castañeda and Ortega, 2016) (Takao et al., 2007) (Zhang et al., 2011) (Jung et al., 2014) (Johansson et al., 2016)
CRY1	Interacts with neuroleptics and the dopamine system; a candidate gene for schizophrenia Disruption of the rhythmic and decrease expression in patients with schizophrenia	(Peng et al., 2007) (Johansson et al., 2016)
PER1	Diurnal rhythms in the expression was blunted in patients with schizophrenia Reduction in the expression of mRNA in brains of patients with schizophrenia	(Sun et al., 2016) (Aston et al., 2004)
PER2	Decrease glial glutamate uptake by reducing the expression of GLAST in patients with schizophrenia Delayed phase of expression in patients with schizophrenia Disruption of the rhythmic and decrease expression in patients with schizophrenia	(Chi-Castañeda and Ortega, 2016) (Sun et al., 2016) (Johansson et al., 2016)
PER3	Decrease expression in patients with schizophrenia rs2859387 polymorphism is associated with schizophrenia	(Sun et al., 2016) (Mansour et al., 2006)
TIMELESS	rs774026 polymorphism is associated with schizophrenia	(Mansour et al., 2006)
NPAS2	Decrease glial glutamate uptake by reducing the expression of GLAST in patients with schizophrenia Decrease expression in patients with schizophrenia	(Chi-Castañeda and Ortega, 2016) (Sun et al., 2016)
SIRT1	rs4746720 polymorphism is associated with schizophrenia	(Kishi et al., 2011)
MTRN1	Associated with increased frequency of insomnia in patients with schizophrenia	(Assimakopoulos et al., 2018)
DISC1	Associated with sleep-related behaviors in patients with schizophrenia	(Lee et al., 2021)

at 4-h intervals for 24 h before and after treatment with clozapine for 8 weeks. Disturbances in the daily rhythms of PER2, PER3, and NPAS2 expression were detected in patients with schizophrenia, accompanied by a delayed phase of PER2 expression and a decrease in PER3 and NPAS2 expression (Sun et al., 2016). In a post-mortem study of the brains of 12 individuals with schizophrenia compared to 14 control participants, researchers discovered a reduction in the expression of mRNA of the circadian pacemaker PER1 (Aston et al., 2004).

Recent research has found that people with schizophrenia exhibit a decrease of circadian expression of key clock genes. Analysis of circadian expression of 8 clock genes in cultures of fibroblasts from skin samples from individuals with schizophrenia during 48 h demonstrated a disruption of the rhythmic expression of CRY1 and PER2 compared to healthy controls. A decrease in the expression of CLOCK, PER2 and CRY1 genes was found in the blood samples of patients with schizophrenia who experienced a first episode of psychosis compared to the blood cells of healthy people. These patients were also found to have impaired sleep quality. It has been established that a shift in the expression of clock genes CLOCK, CRY1 and PER2 in patients with

schizophrenia might produce an imbalance in the regulation of circadian rhythms (Johansson et al., 2016).

Polymorphisms in the melatonin receptor 1 gene (MTRN1) have been linked to an increased frequency of insomnia in people with schizophrenia. Schizophrenic patients have an irregular pattern of melatonin production, indicating a disturbance in melatonin's circadian rhythmicity. It supports the hypothesis that circadian misalignment is involved in schizophrenia patients' sleep difficulties and that melatonin plays an important role in regulating neurophysiological activities. Nevertheless, it is unclear if this association is causative or the result of independent processes functioning via a shared but unknown mechanism, such as dopaminergic dysregulation (Assimakopoulos et al., 2018).

Reviewing neuronal changes in schizophrenia that are associated with circadian rhythms, attention should be paid to the gene Disrupted-in-Schizophrenia 1 (DISC1). It is a gene that is linked to the dopaminergic system of the brain and is thought to be a risk factor in the development of schizophrenia. DISC1 gene encodes eponymous scaffold protein. DISC1 is responsible for neuronal proliferation, signaling, intracellular homeostasis (mitochondrial transport in neurons), an outgrowth of the dendrites and the axon, and neurodevelopment. DISC1 has also been associated with sleep-related behaviors. DISC1 expression daily oscillation is regulated by clock genes, namely CLOCK, and BMAL1. At the same time, DISC1 regulates BMAL1 stability (Lee et al., 2021).

In schizophrenia patients, circadian cycles in gene expression in the dorsolateral prefrontal cortex were discovered. When pathways were analyzed, it was shown that top pathways, which are only rhythmic in people with schizophrenia, are connected with mitochondrial function. These rhythms control these and other genes which are associated with schizophrenia pathogenesis (including Brain-derived neurotrophic factor and GABAergic-related transcripts). Genes having circadian patterns in their expression are linked to oxidative phosphorylation and mitochondrial dysfunction in schizophrenia. Expression of these genes reaches a maximum in the morning and decreases in the evening. Should be noted that these pathways are often violated in schizophrenia. At the same time, genes losing rhythmicity in patients with schizophrenia were related to the immune system (for example eicosanoid and neuroinflammation signaling pathway). It was also shown that in schizophrenia, neuroinflammation-related genes increase over the day/night cycle (Seney et al., 2019).

Thus, the well-known link between circadian rhythms and sleep disturbances with schizophrenia has little shreds of evidence explaining the association between clock genes disruption and clinical signs and needs further research for analyzing gaps in the relationships between these conditions.

5. Altered metabolism, sleep homeostatic abnormalities and circadian rhythms in schizophrenia

There is a lot of evidence for the development of severe oxidative stress in different diseases of the central nervous system (Boiko et al., 2022). One of the main reasons for this is the high intensity of oxidative metabolism, as most of the energy needs of the brain are provided by aerobic processes. Currently, there is a sufficient amount of convincing evidence to support the development of redox imbalance in schizophrenia. Nitric oxide (NO) is one of the core elements of the pathogenesis of oxidative stress, an intracellular and intercellular messenger in the brain, and its decreased activity is obviously involved in the pathogenesis of schizophrenia. (Chen et al., 2023).

Several studies have shown elevated NO and NO synthase (NOS) expression levels in the brain and plasma samples of schizophrenic individuals (Baba et al., 2004; Djordjević et al., 2010; Yao et al., 2004). Human genetic and metabolomics studies have identified NOS and several downstream effectors of neuronal NOS as risk factors for schizophrenia (Freudenberg et al., 2015; Reif et al., 2006; Shinkai et al.,

2002; Zhang et al., 2015). These studies also reported disturbed biosynthetic and signaling pathways linked to arginine metabolism (He et al., 2012; Middleton et al., 2002) and decreased expression in genes involved in the regulation of L-ornithine and polyamine metabolism (Liu et al., 2016). According to the enzyme assays, total NOS activity did not change, but arginase activity was significantly greater in the schizophrenia group. Diseased patients showed higher levels of arginase II and reduced endothelial NOS protein, as measured by Western blotting (Liu et al., 2016).

Oxidative stress is also involving in the pathogenesis of different sleep disturbances and may occur as a result of sleep deprivation (Atrooz and Salim, 2020; Vallée et al., 2020). It has been reported that the disturbance of circadian rhythmicity associated with aging may be caused by a reduction in NO production. NO donor administration substantially increased PER clock gene promoter activity. Endothelial NO-synthase activity was significantly decreased during the day in old animals, as were clock gene expression and circadian blood pressure oscillations (Kunieda et al., 2008). Previous research has shown that NO may be also required for photic entrainment of circadian rhythms; general NOS inhibitors reduce phase shifts of free-running behavior, light-induced c-fos expression in the SCN, and phase shifts of neural firing activity in the SCN maintained in vitro (Kriegsfeld et al., 1999). These results indicate potential metabolic crosstalk between pathophysiology of schizophrenia and possible disturbances in circadian system which should be studied more clearly in further research due to the lack of modern evidences in this area.

Oxidative stress and neuroinflammation contribute to the pathogenesis of many mental disorders. Along with this, dysfunction of the glymphatic system can lead to a decrease in clearance and accumulation of reactive oxygen species. The glymphatic system is a system of perivascular spaces that removes waste from the central nervous system and sustains the homeostatic circulation of brain fluids and the lymphatic system in peripheral tissues (Gu et al., 2022).

The last research is trying to find the link between the glymphatic system supported by the water channel protein aquaporin 4 (AQP4) and schizophrenia. This is a system of perivascular fluid pathways for the elimination of waste products from the brain, the activity of which depends on sleep and its quality (Benveniste et al., 2017). While in the Southern Chinese Han population it has been demonstrated an association between the AQP4 gene and schizophrenia occurrence (Wu et al., 2020), in Japanese patients was found no relationships. In addition, it was found that the daily variation of glymphatic circulation depends on the astrocytic activity and polarization of AQP4. In postmortem studies of patients with schizophrenia, it was found that disturbed myelination is related to oligodendrocytes. Their deficits occur due to the disruption in the maturation process regulated by circadian rhythms at different stages (Colwell and Ghiani, 2020; Raabe et al., 2019). The glymphatic system may be a possible link between sleep disorders and schizophrenia. This system is mainly active during sleep, which is regulated by various neurotransmitters.

It is known that sleep is a process that consists of interaction between homeostatic and circadian components and is the result of a multiple neurotransmitter systems (Borbély et al., 2016). As the dopamine hypothesis is the most popular among biochemical hypotheses of schizophrenia etiology and pathogenesis, we paid particular attention to the role of dopamine in circadian rhythm disturbances in this disorder. It should be noted that the relationship between dopamine and the circadian clock is bidirectional (Pritchett et al., 2012).

Dopamine regulates and is regulated by clock genes in the following areas of the brain: retina, striatum, olfactory bulb, midbrain, and hypothalamus. Thus, dopamine is necessary to regulate the correct rhythmicity of these brain areas (Korshunov et al., 2017). The dopaminergic neurons in the ventral tegmental area and dorsal raphe nucleus are the main components in the regulation of sleep/wakefulness states (Ashton and Jagannath, 2020). Overwhelming evidence points to the microbiota-gut-brain axis as a key player in the pathophysiology of

schizophrenia. Zhu et al., determined if certain pathogen-free mice were susceptible to developing schizophrenia-like behavioral impairments after receiving transplants of fecal microbiota from drug-free people with schizophrenia (Zhu et al., 2020). The study's findings showed that antimicrobial-treated mice exhibited aberrant behaviors after receiving a transplant of fecal microbiota from schizophrenia patients, including psychomotor hyperactivity and learning and memory deficits. These animals also had higher levels of baseline extracellular dopamine in the prefrontal cortex and 5-HT in the hippocampus when compared to those given healthy control feces.

The literature describes melatonin's modifying influence on the dopaminergic system of the brain, primarily as an inhibitor of this system. Therefore, melatonin rhythm disturbances, which are present in schizophrenia, change the level of dopamine, affecting the clinical picture of the schizophrenic process (Ashton and Jagannath, 2020; Ciruela et al., 2011). Dopamine receptor expression has a circadian cycle. In addition, enzymes involved in dopamine metabolism also have a circadian rhythm, in particular tyrosine hydroxylase and monoamine oxidase A (Ferris et al., 2014). Also, one of the proofs of the mutually regulating relationship between the dopamine system and circadian rhythms is that sleep deprivation leads to an increase in dopamine levels in the nucleus accumbens (Ashton and Jagannath, 2020).

On the other hand, serotonergic system plays a significant role in the pathogenesis of schizophrenia. Recently 5-HT_{2A} has become one of the most discussed components in this condition. It is supposed to decrease the 5-HT_{2A} expression and can contribute to the prodromal stage of the disease (Hirvonen and Hietala, 2011). Its activity may follow circadian rhythmicity and play role in mental disturbances. For example, selective

agonists of 5-HT_{2A} have demonstrated circadian changes in behavioral response in rats, which might be one of the explanations for the link between serotonin and the circadian system in schizophrenia (Nagayama and Lu, 1996).

Dopamine also interacts with adenosine and glutamate, which regulate sleep and the circadian clock. The adenosine theory of schizophrenia states that its imbalance may provoke hyperdopaminergic or hypoglutamatergic activity in schizophrenia patients (Boison et al., 2012). Adenosine is considered a homeostatic regulator of sleep and its decreasing may be a part of the pathophysiology of schizophrenia, as well as a component of sleep disorders in these individuals. (Lintunen et al., 2021). The generalizing scheme of interaction between neurotransmitters and circadian systems in schizophrenia shows in Fig. 1.

Sleep-oscillatory impairments may be caused by molecular neurotransmission and neural circuitry dysfunctions and are widely known in various mental diseases. Changes in sleep microarchitecture, on the other hand, seem to have more specific features for particular disorders.

Disturbances in sleep architecture and homeostasis in schizophrenia are related to thalamocortical dynamics and oxidative stress in animal models, particularly emphasizing the role of neuroinflammation and disruption of glutamatergic neurotransmission (Czekus et al., 2022). Sleep spindles, the genesis of which includes local thalamocortical loops, comprising GABAergic neurons of the reticular nucleus of the thalamus, thalamocortical glutamatergic neurons of the thalamus, and cortical glutamatergic neurons, are considered possible biomarkers in schizophrenia. Schizophrenia was associated with a decrease in all indices of spindle density and length (Petit et al., 2022). During sleep, patients with schizophrenia had lower delta power, fewer slow-wave episodes,

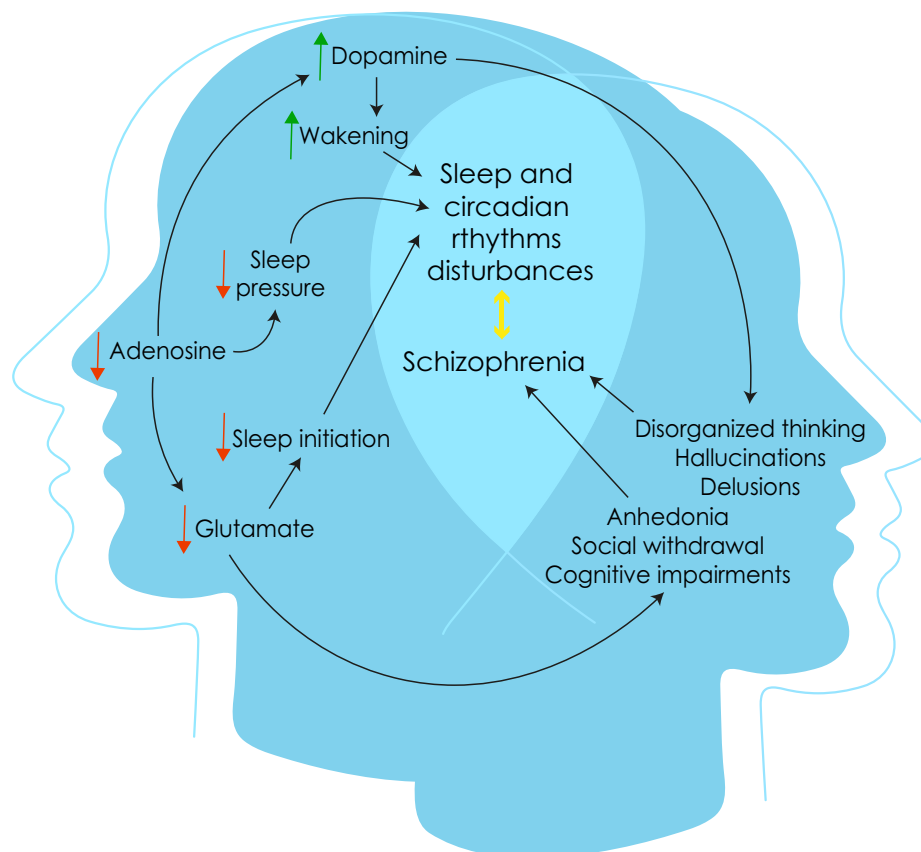


Fig. 1. Neurotransmitters imbalance in sleep disturbances and schizophrenia. An imbalance of adenosine leads to hyperdopaminergic and hypoglutamatergic activation, which are realized in decreasing of sleep pressure due to low adenosine, difficulty in initiating and maintaining sleep due to low glutamate, and promotion of wakefulness due to high dopamine. These processes lead to the disruption of the homeostatic process of the two-factor sleep model. Along with this, an imbalance of neurotransmitters enhances schizophrenia-related symptoms, namely a high dopamine is associated with an amplification of delusions, hallucinations and disorganized thinking, and a low glutamate links with anhedonia, cognitive disorders and social withdrawal.

and lower slow-wave amplitude (D'Agostino et al., 2018). Disorders of circadian rhythms lead to disorders of neurotransmitters and metabolites involved in the regulation of mental functions of the brain, and lead to decreased attention, impaired vigilance, and lack of energy in schizophrenia (Bromundt et al., 2011; Ferrarelli, 2021). Along with this, sleep disorders lead to impaired activity and regulation of the dopaminergic system, which plays a key role in the pathophysiology of schizophrenia, in particular the development of psychotic symptoms (Ashton and Jagannath, 2020; Kaskie et al., 2017).

6. Chronotype, circadian misalignment and clinical sings of schizophrenia

Researchers' attention has recently been directed to the association between circadian chronotype and several mental diseases, including schizophrenia. To yet, no clear association has been shown between the circadian chronotype, the occurrence, and the course of this condition. Among researchers, there are two main approaches to studying this issue. The first one is phenomenological in nature and examines the correlations of chronotype with individual manifestations of schizophrenia (Bauducco et al., 2020; Carruthers et al., 2021; Kilicaslan, 2020). The second one tries to establish general connections between the individual chronotype and schizophrenia as a holistic medical problem (Ahn et al., 2008; Walsh et al., 2022; Zou et al., 2022).

In the paradigm of the first approach, connections between positive and negative schizophrenic symptoms and the patient's chronotype were studied. In one of them, the joint analysis of circadian and cognitive variation in Schizophrenia and Bipolar I Disorder was completed (Thomas et al., 2018). Although the study did not identify any significant correlations between the circadian and cognitive characteristics of patients with schizophrenia, it did find that disturbed circadian rhythms were linked to poorer cognitive test results in these patients (Bromundt et al., 2011). Sleep-wake cycles and circadian activity rhythms are more interrupted in schizophrenia individuals with mainly positive symptoms (Afonso et al., 2011). It was found that patients with schizophrenia had

delayed and/or free-running sleep/wake cycles, took longer to fall asleep, spent a longer time in bed and slept longer than those in the control group (Wulff et al., 2012).

Concerning the second research approach in one of the recent meta-analyses the chronotype of the individuals with schizophrenia was investigated (Linke and Jankowski, 2021). The authors compared people with schizophrenia to healthy people and people with bipolar I disorder. It was shown that eveningness had a moderately higher frequency in subjects suffering from schizophrenia than in controls. The association between chronotype and schizophrenia risk has been demonstrated in two GWAS. A negative correlation between schizophrenia and morning chronotype was demonstrated in 697,828 individuals. The authors found that self-report morningness reduced the risk of schizophrenia (Jones et al., 2019). Another study of 100,420 individuals showed that the tendency towards an evening chronotype is related to greater schizophrenia risk (Lane et al., 2016). The summarized findings of studies on the relationship between chronotype and schizophrenia are presented in Table 2.

Current research suggests that people with schizophrenia possess a typical evening chronotype. Eveningness in schizophrenia looks to be associated with a variety of clinical symptoms, according to the studies. However, the mechanisms that connect circadian characteristics to these manifestations remain unknown. In order to better the rehabilitation and treatment of such individuals, further study is needed to determine the association between chronotype and schizophrenia and its symptoms (Boiko et al., 2017).

It seems to be a general consideration that patients with mental disorders tend to the evening chronotype. Some studies have shown that patients with clinical psychotic and depressive symptoms are predominantly morning circadian chronotype individuals, while patients with anxiety symptoms are more often evening chronotype individuals (Lemoine et al., 2013). Moreover, eveningness or morningness may be a possible risk factor or indicator of mental health problems in general. But it is the unclear specific role of the chronotype for mental diseases. The circadian rhythm disruption may raise the risk of schizophrenia and

Table 2
Associations between chronotype with schizophrenia and different symptoms in patients with schizophrenia.

Study	Population		Findings		Measurements
	Patients with schizophrenia	Control group	Association with schizophrenia	Association with symptoms in patients with schizophrenia	
(Thomas et al., 2018)	105	87	Patients with schizophrenia were more likely to be evening type	No correlation between chronotype and cognitive variables	Composite Morning Scale; University of Pennsylvania computerized neurocognitive battery
(Kilicaslan, 2020)	50	50	Patients with schizophrenia were more prone to evening-type diurnal after controlling for sociodemographic features	No correlation between chronotype and neurological soft signs	Morningness-Eveningness Questionnaire; Neurological Evaluation Scale
(Mansour et al., 2005)	39	349	Patients with schizophrenia had scores in the evening range regardless of age and were more prone to evening type	N/A	Composite Scale of Morningness
(Hashemzadeh et al., 2023)	75	80 with substance use disorder (SUD)	Patients with schizophrenia and SUD were more evening type than SUD	Evening type in patients with schizophrenia and SUD was associated with the highest rate of polydrug users	Reduced Morningness-Eveningness Questionnaire; Structured Clinical Interview
(Ahn et al., 2008)	113	95	Patients with schizophrenia did not differ from the control groups.	N/A	Composite Scale of Morningness
(Fekih-Romdhane et al., 2021)	54	61		N/A	
(Boiko et al., 2017)	130	0	N/A	Positive correlation between evening type and increased levels of suicidal risk	Morningness-Eveningness Questionnaire; Lyuban-Plotstsa's scale
(Chung et al., 2018)	66	0	N/A	Evening type had a close link with sleep irregularity, social rhythm irregularity, delayed sleep-wake phase disorder	Composite Scale of Morningness; Actigraphy; Sleep diary; ICSD-3 diagnostic criteria
(Balcioglu et al., 2022)	100	0	N/A	Evening type had an association with poorer sleep quality and higher mean blood pressure	Morningness-Eveningness Questionnaire; Pittsburgh Sleep Quality Index; measure of blood pressure

interact with other risk factors (Delorme et al., 2020) and may account for behavioral and neurobiological abnormalities associated with schizophrenia which is shown in Fig. 2.

Circadian rhythm disturbances, manifested by circadian imbalance, difficulty falling asleep, and irregular sleep and wakefulness, often go unidentified in schizophrenia patients. Studies have shown numerous negative effects of irregular sleep, but limited data are available for schizophrenia (Chung et al., 2018). Individuals with schizophrenia frequently experience sleep difficulties in conjunction with persistent negative symptoms and cognitive impairment (Thomas et al., 2018).

Many studies have been conducted to examine the relationship between sleep-wake disorders and schizophrenia (Chung et al., 2020; Girshkin et al., 2016; Martin et al., 2001). Most of them show that patients with more disturbed sleep and less stable circadian rhythms have worse scores on negative schizophrenic symptomatology and cognitive functioning. At the same time, it has been proven that circadian rhythm disturbances in such patients can be the result of a number of reasons. Sleep-wake states are likely to be influenced by lifestyle variables, behavioral factors, mental problems, and drugs. There is evidence suggesting that reducing prepulse inhibition, impaired cognitive function and/or increased propensity for false memories due to sleep disturbances could induce schizophrenia exacerbation (Báthori et al., 2021).

At the same time a link was discovered between alterations in sleep

architecture and clinical state in people with schizophrenia. Lower prefrontal spindle density was linked to worse working memory function. Furthermore, multiple sleep investigations have demonstrated that lower spindle density is related to poor memory consolidation including both procedural and declarative memory in people with schizophrenia. Slow-wave deficiency may appear as the illness progresses and is related to negative and cognitive symptoms in patients with schizophrenia (Ferrarelli, 2021).

In studies of the sleep-wake cycle in patients with schizophrenia, it is difficult to disentangle the medication effects from the consequences of schizophrenia, for example, atypical antipsychotics can improve sleep induction and/or maintenance and increase total sleep time (Afonso et al., 2011). Sleep disturbance is a fairly common clinical phenomenon in patients with psychosis, including schizophrenia. These disorders are currently recognized as expected causal factors in the emergence and persistence of psychotic manifestations, in particular, delusions and hallucinations. Therefore, sleep disruption might be a possible therapeutic target for preventing the onset of psychosis and reducing persistent psychotic symptoms (Waite et al., 2020).

7. Conclusions and future perspectives

Circadian rhythms have evolved throughout phylogeny to allow

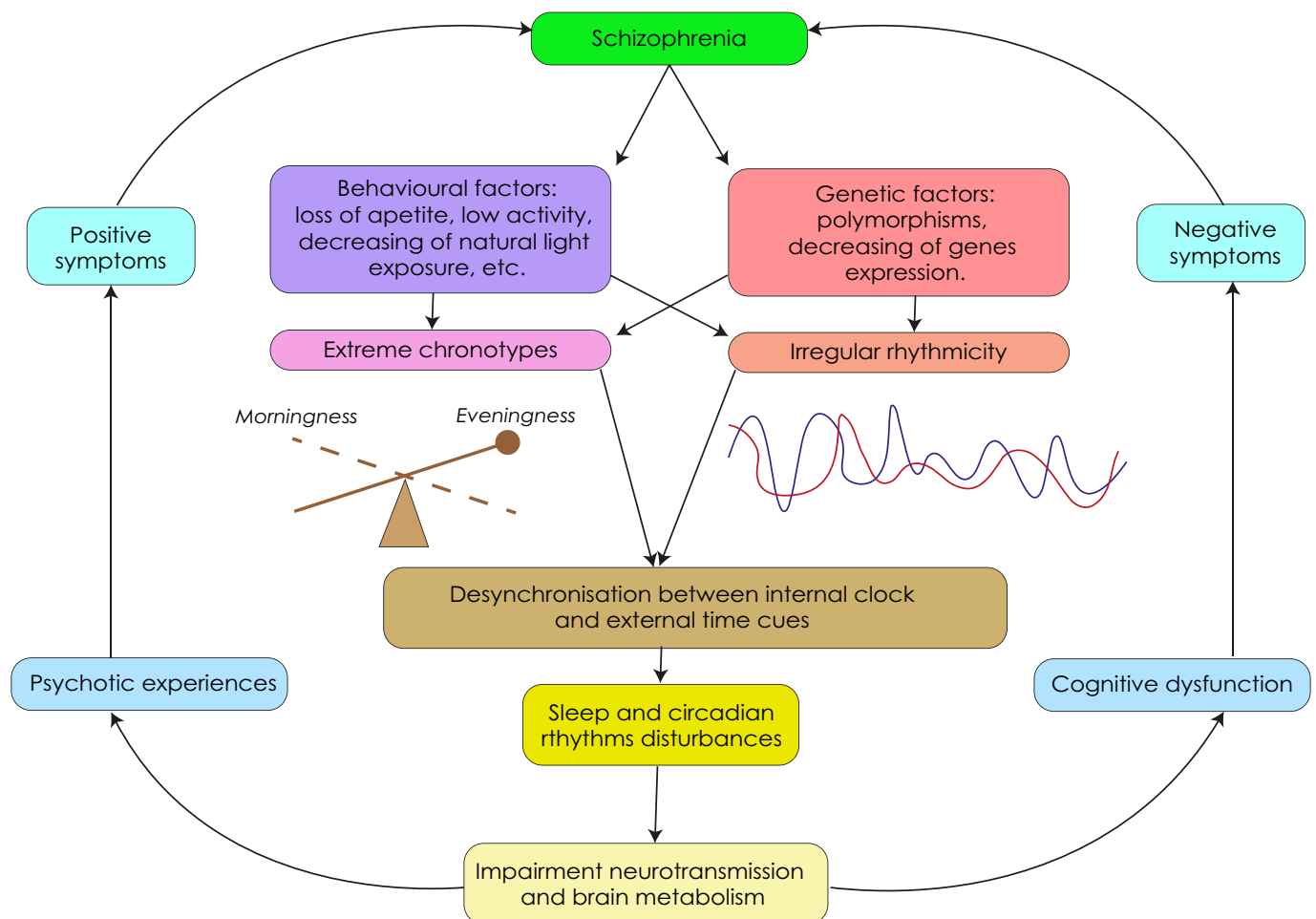


Fig. 2. Disruption of the circadian drive of sleep regulation in schizophrenia. Schizophrenia is associated with genetic alterations in the central circadian oscillator and clock-controlled genes, which can disturb the regularity of the circadian rhythm. Among the behavioral features of schizophrenia, it is worth noting a decrease in appetite, which is associated with one of the keys “zeitgebers”, and changes in motor activity, which leads to a decrease or increase in the time spent under light exposure and, as a result, to the development of extreme chronotypes. These indicators lead to a disruption of the synchronization between the internal molecular clock and external stimuli, which, in schizophrenia, presents as circadian rhythm disturbances. Sleep abnormalities, on the other hand, may also exacerbate schizophrenic symptoms, circadian rhythm irregularities or shifts, and associated behavioral changes through impairments in neurotransmitter systems and brain metabolism.

organisms to predict daily environmental changes, such as the light/dark cycle. Additionally, important to consider is its role in sleep regulation. Sleep disturbances are a common feature of several psychiatric pathologies such as schizophrenia. These disorders and their association with sleep disturbances can emerge as a potential therapeutic target and warrant further investigation. We demonstrated that in schizophrenia either homeostatic or circadian processes of sleep regulation are disturbed. Patients with schizophrenia show a higher prevalence of circadian rhythm disturbances in comparison to the general population.

In conclusion, the potential link between being born at certain times of the year and increased risk of developing schizophrenia has been extensively studied. Studies have suggested that exposure to high levels of UVR at certain times, as well as disruptions of circadian rhythms due to factors such as season of birth, socioeconomic status, and sleep disturbances during pregnancy, may be a risk factor. However, recent research has indicated that the month of conception, rather than the month of birth, may be more critical in the development of schizophrenia. Moreover, changes in eating behavior and meal timing can lead to changes in the circadian release of endocrine hormones.

Genetic factors may also play a role in the circadian rhythm disturbances observed in schizophrenia. *BMAL1*, *CLOCK*, *PER1*, *PER2*, *PER3*, *CRY1*, *TIMELESS*, *NPAS2*, *SIRT1*, *MTRN1* and *DISC1* have been associated with circadian disruption in schizophrenia. Specific SNPs have been identified in the *BMAL1*, *CLOCK*, *PER3*, *TIMELESS*, *NPAS2*, *SIRT1* and *MTRN1* genes related to the schizophrenia. However, the *PER3* gene length polymorphism does not appear to be linked to schizophrenia. In schizophrenia patients also disrupted rhythmicity and/or expression of *CLOCK*, *CRY1*, *PER1*, *PER2*, *NPAS2* and *DISC1*.

Studies have also explored the potential relationship between sleep disorders and schizophrenia. The glymphatic system maintained by the AQP4, the dopaminergic system of the brain, oxidative stress and the microbiota-gut-brain axis are thought to be involved in the pathophysiology of schizophrenia. Furthermore, the modifying effect of melatonin on the dopaminergic system can impact the clinical presentation of schizophrenia. Neurotransmitters imbalance have a crucial role in dysregulating of sleep wake cycle in schizophrenia and may affect its symptoms.

Ongoing research is investigating the relationship between circadian chronotype and schizophrenia. Although some studies have demonstrated a higher eveningness among individuals with schizophrenia, no clear link has been established between chronotype and the onset or progression of the disease. Sleep disturbances are common in schizophrenia, and disruption of circadian rhythms may contribute to various symptoms.

In this review, we address the current knowledge gaps surrounding the underlying factors responsible for circadian rhythm disturbances in schizophrenia. We found an insufficient number of studies aimed at studying the relationship between known biological phenomena of circadian disorders and clinical signs of schizophrenia. This can be recognized as a relevant yet interesting focus of clinical research. Despite the significant amount of research investigating the pathogenesis and clinical characteristics of these disturbances, little is known about the social, environmental, or genetic predictors of these conditions. Furthermore, the potential long-term consequences of circadian rhythm disturbances on the cognitive and physical health outcomes of patients with schizophrenia remain inadequately understood. To bridge this gap, future studies should focus on investigating the potential long-term consequences of these disturbances in individuals with schizophrenia and identifying strategies to mitigate adverse health outcomes. Additionally, while there is some evidence to suggest that disturbed sleep and circadian rhythms may precede the onset of schizophrenia and exacerbate some symptoms, there is a limited understanding of the causal relationship. Therefore, further research is needed to evaluate the impact of drug treatment and non-pharmacological interventions in the management of circadian rhythm disorders in individuals with schizophrenia.

CRedit authorship contribution statement

Conceptualisation, writing - review and editing, visualization: Dmytro I. Boiko; writing - writing the original draft: Hitesh Chopra, Muhammad Bilal, Pavlo V. Kydon, Larysa O. Herasymenko, Vadym O. Rud, Lesia A. Bodnar, Ganna Yu. Vasylyeva, Rustam I. Isakov, Liliia V. Zhyvotovska, Aashna Mehta; Writing - critical revision, review and editing, supervision - Andrii M. Skrypnikov.

Declaration of competing interest

None.

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