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REVIEW ARTICLE

Running Head: *Chronobiology revisited in psychiatric disorders*

Chronobiology revisited in psychiatric disorders: from a translational perspective

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Abstract

Several lines of evidence support a relationship between circadian disruption in the onset, course, and maintenance of mental disorders. Despite the study of circadian phenotypes promising a decent understanding of the pathophysiologic or etiologic mechanisms of psychiatric entities, several questions still need to be addressed. In this review, we aimed to synthesize the literature investigating chronobiologic theories and their associations with psychiatric entities. We first introduced molecular elements and mechanisms of the circadian system to promote a better understanding of the chronobiologic implications of mental disorders. Then, we comprehensively and systematically reviewed circadian system studies in mood disorders, schizophrenia, and anxiety disorders. Current research has demonstrated that circadian pathologies, including genetic and neurohumoral alterations, represent the neural substrates of the pathophysiology of many psychiatric disorders. However, much more work is needed to identify the causal relationship between circadian physiology abnormalities and mental disorders, and to develop sound pharmacologic interventions.

Keywords: Biological Clocks, Circadian Rhythm Disorders, Psychiatric disorders, melatonin, Hypothalmo-pituitary-adrenal axis

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"*There is a time for many words, and there is also a time for sleep.*"

Homer, 850 BC

Summations

Sleep and circadian biorhythms are major physiologic functions responsible for emotional, cognitive, and somatic responses of the living organism.
Mental disorders are often associated with disruptions in circadian rhythm functions.
Molecular elements and expressions of genes including CLOCK, PER, and CRY, which are directly involved in the circadian system, are reported altered in many psychiatric disorders, particularly in mood disorders.
Glucocorticoid rhythm supported by the hypothalamus–pituitary–adrenal (HPA) axis and melatonergic activity have a crucial role in the regulation of biorhythm, and oscillations of tissue and organ systems including the central nervous system, and both systems have been demonstrated impaired in major mental illnesses including schizophrenia and other psychotic disorders.

Considerations

Despite the review process performed with a detailed searching, selection, and summarization practices, the inadequacy of the studies that establish a causative link between circadian rythm disruptions and mental disorders hinders generalizations on pathophysiologic mechanism.
There is a lack of translational approach to the findings of animal models which might provide clearer understanding of pathophysiologic implications of the circadian system in mental disorder.
Despite studies to date suggesting circadian genotypes and phenotypes as promising subjects for a better understanding of the pathophysiologic mechanisms of psychiatric disorders, a causal relationship between circadian physiology abnormalities and mental disorders has yet to be elucidated.

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1. Introduction

Rhythmicity is a fundamental characteristic of the nature of life. Time as a dynamic and complex phenomenon, playing a pivotal role to sustain rhythmicity for the biologic essentials and needs of living organisms. Chronobiology aims to define basic principles of vital reactions that occur nearly 24 hours per day through circadian rhythms and biologic processes in anything from single cells to human beings. The first scientific awareness of circadian rhythms started with observations of the mimosa plant *(Mimosa pudica)* folding independent of daylight by the French astronomer Jean Jacques d'Ortous de Mairan, in 1729 (Foster and Kreitzman, 2005). In the 1930s, the German biologist Erwin Bünning subsequently noticed that the movement of the bean plant had an intrinsic period that did not change under constant light conditions and inferred that such periodic alterations were arranged with an endogenous clock (Foster and Kreitzman, 2005).

The term 'circadian' was first used by Franz Halberg in 1959. It means 'about a day' and an endogenous day slightly shorter or longer than 24 hours (from the Latin term circa: about and diem: day) depending on constant conditions, preserved from environmental factors (Halberg *et al.*, 2003). Uncovering interactions between molecules and cells within an endogenous day was a major advancement in the discovery of the essential mechanism of circadian rhythm, which was a remarkable scientific milestone in chronobiology. It had been eagerly attempted to explain the further molecular mechanisms of circadian rhythm; however, the oscillation process could not be unraveled until 1971. Konopka and Benzer first determined a gene by observing the differences of circadian period lengths among three mutant flies (Konopka and Benzer, 1971). They demonstrated three mutants, one was arrhythmic, another had a shorter period of 19 h, and the third had a longer period of 28 h; flies with neither the short-period gene nor the long-period gene or the arrhythmic gene would not produce a normal rhythm. They concluded that the same functional gene with a point mutation appeared to be affected in all cases. This work inspired Jeffery C. Hall, Michael Rosbash, and Michael Young, independently. They cloned and rescued the *Drosophila Period* gene, which was recognized as the first clock gene, found in 1984 (Bargiello, Jackson and Young, 1984; Reddy *et al.*, 1984). They defined the transcriptional translational feedback loop (TTFL) model with the analysis of *Per* gene expression and they demonstrated additional genes and proteins in further work. The simple genetic model they postulated revealed the generation of an autonomous

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oscillator, including transcription-translation cycles from interacting positive and negative feedback loops that depend on ribonucleic acid (RNA) and protein levels, which is still used to understand circadian rhythms. Consequently, they were awarded the Nobel Prize in Physiology and Medicine in 2017 for their explanatory findings of molecular mechanisms controlling the circadian rhythm (Huang, 2018).

Despite the fact that the understanding of the neural basis of rhythmicity and central nervous system (CNS) involvement in circadian mechanisms is not long-standing knowledge, the discovery of the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which was later described as the master circadian pacemaker in mammals, is actually not very recent. The SCN was first defined as a cluster of different neurons in the 1880s and was subsequently recognized in a number of mammalian species' brains through comparative studies of the hypothalamus by Crosby and Woodburne (Crosby and Woodburne, 1951; Sollars and Pickard, 2015). However, the discovery of its regulatory function on circadian rhythm occurred nearly 100 years later. The SCN contains a complex neurochemical organization and its functional organization had been revealed with comprehensive experimental studies regarding the function of localization, the neuronal mini-network it contains, and its role in the circadian system. Consequently, the SCN is recognized as a coordinator of biologic processes regulating numerous cellular clocks of the brain and other organ systems.

The findings of considerable studies revealing that a broad range of cell types in the body and brain have biologic clocks raised questions regarding the specific function of circadian rhythm and its contribution to illnesses. Circadian rhyhthms in peripheral organ systems and their impeccable relationship with the SCN and other physiologic and metabolic mechanisms are essential for physical and mental health. Disturbances in the central and peripheral clocks due to shiftwork or a diversity of clock genotypes have been associated with many illnesses including metabolic dysfunctions, obesity, cancer, and mental disorders (Gillette, 2013).

Circadian disruption, a common manifestation of nearly all psychiatric disorders, is not a surprising predisposing factor for mental disorders, because sleep is considered as a cardinal psychological and vital function and requires routine evaluation in every mental state examination. Studies of human circadian rhythm genes revealed that genetic polymorphisms of these genes predisposed to psychiatric disorders (Benedetti *et al.*, 2003; Takao *et al.*, 2007; Lee *et al.*, 2010). Therefore, circadian disturbances seem to be the common thread to all these

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possible underlying mechanisms that contribute to illness onset, maintenance, and even the response to treatment. Special attention ought to be paid toward the physiology and pathology of circadian rhythm to understand the etiology of psychiatric disorders, and to develop appropriate treatment strategies because chronobiology is an essential field of work in mental disorders. Related literature provides information on circadian rhythm disturbances for certain psychiatric diagnoses such as mood and anxiety disorders. However, we are aware of a lack of a comprehensive perspective of molecular and neural substrates to clinical manifestations in psychiatric disorders. Therefore, we aimed to provide a general overview regarding the reciprocal relationship between circadian rhythm and psychiatric disorders in this article.

Searching strategy and selection criteria of reviewed studies

An electronic database search was performed by the authors in the MEDLINE, Embase, PsycInfo, and Scopus databases for relevant articles published between January 1990 and October 2019. We searched reference lists of relevant reviews. Different combinations of the keywords *psychiatric disorder, mental disorder, mood disorder, bipolar disorder, depression, unipolar depression, major depressive disorder, schizophrenia, psychotic disorders, anxiety disorders, circadian rhythms, circadian markers, chronotype, chronobiology, circadian gene, clock gene, melatonin,* and *HPA axis* were polled. Articles published only in English were reviewed. Unpublished studies, case reports, theses, and conference papers were excluded. Several highly cited and regarded comprehensive review articles and meta-analyses are cited due to space considerations. Eligible open-access and institutional-access articles were recruited. The articles were filtered through an inspection of the abstracts in order to select the most suitable articles related to the topic. In addition to database searches, the reference lists of the relevant articles were also evaluated manually for additional publications matching the scope of our review. The authors avoided incorporating duplicated samples of the key papers; however, studies with similar methodology were included when they were of a high-impact nature (Figure 1).

2. Molecular regulation of the circadian rhythm

We believe that it is noteworthy to briefly summarize the molecular underpinnings of circadian science that gave input to the research into neural substrates of rhythmicity.

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Although the aforementioned discovery of the *period* gene was a remarkable finding that identified a genetic determination of the biological clock, it did not mean comprehension of all circadian molecular mechanisms. The circadian rhythm started to be more understandable with the determination of alterations in PER protein and *period* mRNA levels during a day. Hall and Rosbash ascertained that levels of *period* mRNA peaked in the early night, several hours earlier than the peak PER protein abundance (Hardin, Hall and Rosbash, 1990). The TTFL model emerged with the discovery of further circadian rhythm genes found in subsequent studies. According to this model, PER and TIM (a protein encoded by the *timeless* gene) proteins transformed into a heterodimer form in the cytoplasm in order to translocate into the nucleus. TIM protein allows nuclear entry of PER (Gekakis *et al.*, 1995). Besides CLOCK and CYCLE [orthologues of mammalian CLOCK and BMAL-1 (a protein encoded by the *brain muscle ARNT-like protein-1 (Bmal-1) gene)*, respectively] constitute a protein couple that supports the transcription of *period* and *timeless* genes [the equivalent of *period 1-3* and *cryptochrome 1-2(Cry))* in mammalian cells] in the nucleus (Allada *et al.*, 1998; Rutila *et al.*, 1998). When the PER-TIM heterodimer binds to the CLOCK-CYCLE couple, CLOCK-CYCLE segregates from DNA and the transcription of downstream genes related to PER and TIM conclude. In other words, the PER and TIM heterodimer terminate their transcription. However, in the event of a decrement in PER and TIM protein levels, the CLOCK and CYCLE couple activates their transcription once again, and TTFL starts over. All of these biochemical reactions include transcription and translation processes that occur rapidly. However, a near 24-h period needs a delay *period* and *timeless* gene transcriptions. The explanation about the regulation of the needed delay comes from the discovery of the *doubletime* gene, another member of the clock genes (Kloss *et al.*, 1998; Price *et al.*, 1998). The *doubletime* gene's product casein kinase-1 (CSNK-Iε; casein kinase 1 epsilon in mammals) phosphorylates PER for degradation. Thus, activity of the *doubletime* gene reduces the stability and accumulation of PER, thereby promoting a delay between PER-TIM transcription and PER-TIM nuclear function (Lowrey *et al.*, 2000; Huang, 2018). This molecular mechanism occurs both in the SCN and nearly all peripheral cells.

The maestro of chronophysiologic rhythms including body temperature, sleep-wake cycle motor activity, and neuroendocrine functions, is located in the SCN of the hypothalamus. The clock genes in the peripheral cells such as hepatocytes, adipocytes or epidermal and dermal cells have their own rhythmicity; however, cyclic processes in which the SCN is involved

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provide an integrative organization of the physiologic functions and behavioral outputs of the body (Mohawk, Green and Takahashi, 2012; Challet, 2015). The circadian system sustains an endogenous rhythmic activity in spite of environmental cues. Regardless of the presence of light, the neuronal activity in the SCN occurs at a higher frequency during the day compared with the night. The neurons of the SCN tend to be excitable in the day to maintain spontaneous activity through persistent Na^{++} currents, oscillations in chloride pumps, K^{+} channels, and Ca^{++} pools in the morning. Conversely, hyperpolarized neurons are inhibited and keep the silence in the SCN at night (Colwell, 2011). CRY and PER proteins gather in the cytoplasm before translocating into the nucleus where they inhibit CLOCK-BMAL-1 activity during the night. In other words, CRY and PER proteins terminate their own transcription when they inhibit CLOCK-BMAL-1 complex activity. After that, degradation of PER and CRY manages the inhibition of CLOCK-BMAL1 toward the morning, followed by resumed transcription of *period/cryptochrome* and other clock genes (Tsang *et al.*, 2016).

The master clock synchronizes the endogenous rhythm to the external world, mainly in the presence of major environmental input – light (Mrosovsky and Hattar, 2003; Dibner, Schibler and Albrecht, 2010; Pevet and Challet, 2011). A specialized tract, called the retino-hypothalamic tract, which starts from the retinal ganglion cells that include the essential photoreceptor pigment melanopsin, and terminating at the SCN. This tract aids upregulation of clock gene expression and increases neuronal activity in the SCN (Hankins, Peirson and Foster, 2008; Amaral *et al.*, 2018). Nevertheless, functions of the SCN, such as synchronization by the light/dark cycle, do not only depend on this molecular mechanism. Many inputs of the SCN have been determined including melatonin, food intake, blood pressure, and physical activity (Buijs *et al.*, 2014; Asher and Sassone-Corsi, 2015; Sabbar *et al.*, 2017; Pfeffer and Wicht, 2018). In addition, the SCN receives non-photic timing inputs from the raphe nucleus, which means the serotoninergic system plays a substantial role in the regulation of circadian rhythm (Zhang *et al.*, 2016). Furthermore, the SCN serves in the excretion of numerous neurotransmitters that interact with other hypothalamic structures, hence neuropeptidergic signaling maintains circadian rhythm of the SCN. Consequently, the biologic interactions between the brain and body are modulated by the SCN, which is critically involved in the organism's adjustment to the environment through the impact of internal signals, which are mediated by hormonal rhythms, the autonomic nervous system, and external time indicators such as light and food intake (Gillette, 2013).

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Circadian disruption could contribute to a wide range of illnesses including obesity, diabetes mellitus, autoimmune disorders, and particularly mental disorders (Buttgereit *et al.*, 2015; Duval *et al.*, 2017; Rebecca Robillard *et al.*, 2018; Rébecca Robillard *et al.*, 2018; Saetung *et al.*, 2019). Disruption that arises due to a misalignment between inner physiology and the external world or a clock gene polymorphism may facilitate the emergence of diseases, increased disease severity and worsened prognosis, and heightened risk for poor treatment outcomes (Barandas *et al.*, 2015; Charrier *et al.*, 2017). (Table 1)

3. Neurohumoral and hormonal regulation of circadian rhythm

The SCN collects information about the endogenous clocks through nervous projections and peripheral hormones. The SCN's monosynaptic outputs mainly target the pre-autonomic neurons of the paraventricular nucleus (PVN) in the hypothalamus. The SCN is directly involved in the hypothalamic output to the preganglionic parasympathetic regions of the brainstem and to sympathetic preganglionic motor neurons of the spinal cord (Ono *et al.*, 1978; Kalsbeek *et al.*, 2006; Guilding and Piggins, 2007). These projections allow the SCN to command the rhythmic control of hormone release and metabolism of all visceral structures through parasympathetic and sympathetic outputs. It has been determined that the SCN could increase glucose production from the liver through the sympathetic output to the liver with its projections that reach to the PVN (la Fleur *et al.*, 2000). Similarly, the SCN could increase corticosterone secretion in the adrenal or support glucose uptake into the muscle cells via sympathetic activation (la Fleur *et al.*, 2001; Shimazu and Minokoshi, 2017; Buijs *et al.*, 2019). Besides, hormonal signals predominantly controlled by the SCN have a critical role in the regulation of internal synchronization (Challet, 2015). Internal synchronization is supplied by adrenal glucocorticoids, pineal melatonin, adipocyte-derived leptin, pancreatic insulin or stomach ghrelin induced by the SCN. Internal synchronization included many multi-synaptic neuronal pathways that modulate behavior. For example, leptin increases during food intake in rats, ghrelin increases following a fasting period, and adrenaline increases with locomotor activity (Kalsbeek *et al.*, 2001; Shiiya *et al.*, 2002; Buijs *et al.*, 2019).

Glucocorticoids are produced in the adrenal glands from cholesterol and rhythmically released at ultradian (pulsatile) and circadian (daily) scales. Glucocorticoid release peaks typically prior to the onset of physical activity and depends on the fluctuations of corticotropin

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(adrenocorticotropic hormone, ACTH), a polypeptide secreted from the anterior pituitary under the control of corticotropin-releasing hormone (CRH), during the day. Glucocorticoid levels are regulated by a complex interaction between the adrenal clock and sympathetic outputs from the PVN and SCN (Kalsbeek *et al.*, 2012). Furthermore, the daily variation of glucocorticoids is influenced by stressful life events that activate the hypothalamus–pituitary–adrenal (HPA) axis and the autonomous nervous system. Glucocorticoid rhythm has a crucial role in the regulation of other hormonal rhythms and peripheral oscillations of metabolic gene expressions in the cells of tissues such as liver and white adipose tissue (Kalsbeek *et al.*, 2012).

On the other hand, adrenal glucocorticoids can modulate the synchronization of the master clock to light via serotonergic projections from the raphe nucleus (Van De Kar and Lorens, 1979). Serotonergic neurons release serotonin in the presence of glucocorticoid and locomotor activity. Such neuronal activity ensures transmitting feedback to the SCN in order to sustain the functioning of the clock itself (Malek *et al.*, 2007). In other words, serotonergic projections stimulated by locomotor activity provide a re-synchronization of the SCN (Buijs *et al.*, 2016). Furthermore, brain serotonin synthesis and catabolism have their own circadian rhythm, closely related to the SCN. Neuronal serotonin release in the SCN is provided in the absence of photic stimulation, and serotonin levels increase in the raphe nucleus after the beginning of the dark phase (Pontes *et al.*, 2010). Tryptophan hydroxylase (TpH), the rate-limiting enzyme in the synthesis of serotonin, is one of the regulators of circadian rhythm in the raphe nucleus. It is known that TpH peaks during the dark phase, helping the interaction between the serotoninergic system and the SCN through the increment of serotonin levels (Pontes *et al.*, 2010). Also, serotonergic neurotransmission alterations could cause phase shifts and changes in SCN activity affecting the phosphorylation of CLOCK proteins (Zaki *et al.*, 2018).

Melatonin, a member of the class of acetamides, is another hormone related to biologic rhythm. It is primarily released by the pineal gland, particularly at night. Melatonin release is adjusted by the length of night time and melatonin *per se* regulates the seasonality of energy metabolism and reproduction in photoperiodic species (Pévet, 2003). The nocturnal release of melatonin is induced by the SCN input to the PVN noradrenergic (sympathetic) afferents to the pineal gland (Buijs *et al.*, 2019). Melatonin accumulates sleep both by setting the SCN and inhibiting neural centers such as the locus coeruleus (LC) and raphe nuclei, which mediate arousal through the ventrolateral preoptic nucleus of the hypothalamus (VLPO). It has been

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determined that melatonin receptor agonists increase monoaminergic neuronal activity and contribute to the regulation of dopamine and 5-HT neurotransmission (Chenu, El Mansari and Blier, 2013). In other words, melatonin has a modulatory role on the monoaminergic activity by linking the circadian and monoamine systems. The SCN modulates the release of melatonin mainly through γ-aminobutyric acid (GABA) neurons that project from the SCN to the PVN (Kalsbeek *et al.*, 1999). The daylight in the morning and the bright light in the evening activate the SCN neurons that inhibit the same PVN neurons through GABAergic projections and cease the secretion melatonin (Pevet and Challet, 2011). The daily rhythm of melatonin has remarkable effects on the molecular clockworks of both the brain and body alongside regulating the sleep/wake cycle (Khaldy *et al.*, 2002; Uz *et al.*, 2003). Melatonin receptors (MT1 and MT2) are mainly localized in the CNS but also have been detected beyond the CNS in a wide range of somatic cells (Macchi and Bruce, 2004). This diversity could be interpreted as melatonin having an integrative role in the light-induced circadian rhythms controlled by the SCN in the whole organism.

4. Circadian rhythm and its implications on psychiatric disorders

At the core of any psychiatric disorder is an abnormality in neurotransmitter signaling. It is well known that the disruption of circadian physiology has widespread effects on all aspects of neural and neuroendocrine function, which leads to psychiatric disorders. The aforementioned information regarding neural substrates of biologic rhythm is frequently reported impaired in many mental disorders. Following the comprehensive conceptual framework of neural substrates of chronobiologic processes mentioned above, we will next discuss the reciprocal associations between circadian rhythm disturbances and psychiatric disorders, and draw a clinical picture for common diagnoses (Table 2).

4.1. Mood disorders

In 1681, Robert Burton defined the autumn as the most melancholic season in his best-known classic, The Anatomy of Melancholia (Burton, 1621). Circadian rhythm abnormalities in mood disorders have been pointed towards by the observers of melancholia for sixty years (Richter, 1965; Atkinson, Kripke and Wolf, 1975; Souêtre *et al.*, 1989). A wide range of body functions such as body temperature, blood pressure, pulse rate, and hormones such as plasma cortisol levels, thyroid-stimulating hormone, and melatonin have been found disturbed in patients

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with manic depression and depression compared with people without a mental disorders (Atkinson, Kripke and Wolf, 1975; Souêtre *et al.*, 1989). Moreover, mood and other symptoms of the disorder have been previously reported to show diurnal variation in depression (Hall, Spear and Stirland, 1964). Disordered sleep/wake cycle is considered as another clue for physicians in patients with bipolar disorder (BD) and major depressive disorder (MDD) (Hall, Spear and Stirland, 1964). In addition, it was recognized that disrupted rhythms were re-synchronized after antidepressant or mood-stabilizing treatment (Wehr and Wirz-Justice*, 1982). Another significant feature is that mood episodes recur seasonally and previous studies showed that there could be an association between light and the emergence of mood states (Zung and Green, 1974; Eastwood and Peacocke, 1976; Milstein *et al.*, 1976; Frangos *et al.*, 1980; Berkol *et al.*, 2017). Thus, all of these findings suggested the possibility of circadian rhythm disturbance in mood disorders. Consequently, the earliest mention of seasonality took place in the Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised Version (DSM-III-R), and seasonal pattern was defined as a specifier in the affective disorders section (Spitzer *et al.*, 1990).

Chronotype is another concept associated with mental disorders, particularly with affective disorders, and resembles individual physiologic functions and activities such as sleeping, eating, or hormone release. Chronotype has usually been used to denote sleep habits: morning and evening types. The relationship between chronotypes and several psychiatric disorders has been studied to date and the evening chronotype has been related to a vulnerability to depression and increased alcohol and stimulant drug use (Iasevoli *et al.*, 2016).

Although sleep/wake cycle alteration, which is considered as a consequence of circadian system disruption, had been the best-known contributor to the pathophysiology of mood disorders for years, today, it is well-recognized that circadian rhythm is entangled with a wide range of molecular and cellular processes that are hypothesized to lead to mood disorders (McClung, 2013). Accordingly, below we discuss in detail internal and external factors that may play a role in the emergence of mood disorders through various psychophysiological mechanisms within the circadian rhythm processes.

4.1.1. Major depressive disorder

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As a cardinal element of chronobiologic processes, sleep behavior and its disturbances have received the strongest spotlight regarding research into their undisputed etiologic and prognostic association with mood disorders. The concomitance of sleep disruption and depression had been the main focus of research into the contribution of circadian rhythm disruption to depression development since the 1970s (Wirz-Justice, Pühringer and Hole, 1976; Wirz-Justice *et al.*, 1981; Wehr *et al.*, 1983). The relationship between sleep and mood could easily be observed even in healthy individuals exposed to jet lag or shiftwork (Simon, 2012). The presence of sleep disruption may cause negative effects, irritability, and fatigue. Sleep behavior changes, such as difficulties in initiating/maintaining sleep or early morning awakening have been determined in 90% of patients with MDD (Wulff *et al.*, 2010). Sleep-wake disruptions are among the criteria for the diagnosis of depression, and comorbid parasomnias are associated with poor treatment outcomes, increased suicidality, and greater relapse risk in depression (Iasevoli *et al.*, 2016; Stubbs *et al.*, 2016; Vadnie and McClung, 2017; Vargas *et al.*, 2019). Sleep architecture alterations including shortened latency of the initial rapid eye movement (REM) sleep, prolonged first REM period, increased total REM time, increased REM density and proportion of REM sleep, and decreased non-REM sleep have been demonstrated in depression (Kupfer and Foster, 1972; 'The application of EEG sleep for the differential diagnosis of affective disorders', 1978; Kupfer *et al.*, 1984; Rush *et al.*, 1986; Giles *et al.*, 1987; Monteleone and Maj, 2008; Pillai, Kalmbach and Ciesla, 2011). It should be considered that sleep has multiple regulators related with homeostatic mechanisms along with the circadian rhythm.

Melatonin output and the timing of its release have been found closely associated with other rhythms as mentioned above. Numerous studies have been conducted to show alterations of melatonin release and its phase to determine circadian misalignment in patients with mood disorders (De Berardis *et al.*, 2015). Melatonin secretion peaks a few hours before sleep or at the time of minimal vigilance propensity, and decreases as wakefulness approaches under normal conditions (Reiter, 1993). In contrast, core body temperature reaches the highest degree during the day and has a nocturnal decline related to the melatonin peak (Cagnacci, Elliott and Yen, 1992). This inverse relationship between melatonin and core body temperature is organized by the SCN. To date, the most consistent results suggested lower nocturnal melatonin levels, delayed melatonin secretion onset, and offset in patients with depression (De Berardis *et al.*, 2015). Besides, the length of the interval between melatonin

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secretion and sleep onset has been found related to depression severity (Emens *et al.*, 2009). In addition, elevated nocturnal body temperature and daily mean temperature degrees are observed in patients with depression and these higher values normalized with antidepressant treatment (Iasevoli *et al.*, 2016). However, several studies were unable to explain the causal association between body temperature abnormalities and the melatonin increase in depression (Shafii *et al.*, 1996; Hasler *et al.*, 2010).

There is an irrefutable association between circadian genes and mood regulation. Even though mood disorders are not directly related to clock gene mutations, findings suggest that individual genetic polymorphisms of clock genes may influence the clinical features of the disorder, such as age at disease onset and treatment response (Wirz-Justice, 2006; Kishi *et al.*, 2009). Genetic studies have implicated *clock*, *timeless, cryptochrome-1 (Cry-1), period-2,3 (Per-2,3), Bmal-1,2, neuronal pas domain protein 2 (Npas-2), nuclear receptor subfamily-1, group d, member 1 (Nr1d-1), retinoid-related orphan receptor α (Rora), CSNK-Iε, D site of albumin promoter binding protein (Dbp), acetylserotonin methyltransferase (Asmt), melatonin receptor 1b (Mtnr1-B), arylalkylamine n-acetyltransferase (Aanat)* genes in unipolar depression (Kennaway, 2010; Lavebratt *et al.*, 2010; Soria *et al.*, 2010; Etain *et al.*, 2011; Melhuish Beaupre, Brown and Kennedy, 2018). However, most of these studies have small sample sizes and need to be replicated in larger groups.

Glucocorticoids are adrenal steroid hormones and have multifunctional roles in the body and brain such as metabolism, immunity, arousal, neuronal survival, and neurogenesis (Herbert *et al.*, 2006). Glucocorticoids have their own circadian rhythm and an important role in synchronizing peripheral clocks and the SCN. In addition, they have anti-inflammatory properties and regulate the immune system response (Dumbell, Matveeva and Oster, 2016). Since Carroll defined the resistance of the dexamethasone suppression test in patients with depression in 1968 (Carroll, Martin and Davies, 1968), hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been one of the most consistent findings in mental disorders, particularly in depression (Carroll, Martin and Davies, 1968; McClung, 2013). Hypercortisolemia-flattened HPA axis circadian rhythm and disrupted response of the HPA axis to glucocorticoid feedback are commonly observed in patients with depression (Gold, 2015; Keller *et al.*, 2017). Dehydroepiandrosterone (DHEA), is another adrenal steroid that has a neuroprotective role and modulates corticosteroid-induced cell death. An increased cortisol/DHEA ratio, which assesses the degree of 'functional' hypercortisolemia, is seen in

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adults and adolescents with depression (Goodyer, Herbert and Altham, 1998; Gallagher and Young, 2002; Markopoulou *et al.*, 2009). Glucocorticoid receptor hypofunction has also been found in peripheral tissue cells including mononuclear cells and skin cells (Pariante and Lightman, 2008). Furthermore, findings support that antidepressant treatment repairs the impaired HPA axis dysfunction in depression (Carvalho *et al.*, 2010).

Depression and inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, and asthma have been found coexisting, and such common comorbidities point to the neuroinflammatory background and immune-associated contributions in the etiopathogenesis of depression (Pasco *et al.*, 2010; Raison and Miller, 2011). Studies have also shown that pro-inflammatory cytokines could induce a depression-like symptom cluster including anhedonia, fatigue, increased sleep, and decreased locomotor activity (Postal and Appenzeller, 2015). Inflammatory markers such as interleukin (IL)-1β, IL-2, IL-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and prostaglandin E2 (PGE2) have been reported increased in patients with depression (Felger and Lotrich, 2013). Circadian disruption may be another contributor to increased pro-inflammatory cytokine levels in depression. The arrhythmic clock system interacts with the nuclear factor-kappa B (NF-kB) signaling pathway, which is one of the major regulators of inflammation in the body and activates the inflammatory response (Imeri and Opp, 2009; Narasimamurthy *et al.*, 2012). Besides, sleep disturbances and long sleep duration were found related with the increased cytokines levels and the risk for depression (Irwin, Olmstead and Carroll, 2016). We may interpret the aforementioned findings as the circadian system's involvement in the pathophysiology of MDD being not limited to sleep/wake cycle disruption, it is also related to complex associations between biologic rhythm, environment-gene interactions, HPA axis dysfunction, and immune system alterations.

4.1.2. Bipolar disorder

Sleep disturbances have been the core common characteristic feature in bipolar mood episodes, both mania and depression, since the first definition of Kraepelin (Plante and Winkelman, 2008). In turn, insomnia or hypersomnia and decreased need for sleep are typical for manic and depressive episodes. Studies showed that sleep architecture was characterized by increased REM density and reduced REM latency in bipolar manic episodes (Harvey, 2008b, 2008a). Sleep disturbances are also frequently observed in euthymic patients with BD.

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Increased REM density and the proportion of REM sleep have been shown in remitted patients with BD (Dallaspezia and Benedetti, 2017). Moreover, findings revealed that remitted patients with BD have longer sleep latency and sleep duration and lower sleep efficiency (Rocha, Neves and Corrêa, 2013; Geoffroy *et al.*, 2015). Bipolar depression has similar polysomnographic findings including a tendency for more early awakenings and more fragmented REM sleep periods. However, total REM density was found greater in bipolar depression than in unipolar depression (Dallaspezia and Benedetti, 2017) (See table 2 for detailed information). Although abnormalities of sleep architecture are seen in episodes and inter-episodes, sleep disturbances worsen before relapses. Sleep loss and reduced sleep duration were defined as reliable predictors of hypomania and mania (Dallaspezia and Benedetti, 2017). In addition, hypersomnia in euthymia is found associated with the development of upcoming depressive symptoms (Kaplan *et al.*, 2015). On the other hand, a large amount of euthymic patients describe symptoms that meet the diagnostic criteria for insomnia (Boudebesse *et al.*, 2014; Geoffroy *et al.*, 2015). Sleep-wake disturbances have been found as one of the reasons for a worse course of illness, relapses, increased symptom severity, and poor treatment outcomes (Harvey *et al.*, 2015; Kanady, Soehnera and Harvey, 2015; Ng *et al.*, 2015; Sylvia *et al.*, 2018). These findings may explain the reason for the treatment need in remitted patients with BD (Vadnie and McClung, 2017).

Melatonin activity alteration is also associated with BD due to circadian dysregulations such as changes in the release timing, phase alterations of melatonin secretion, and the sleep-wake cycle (Dallaspezia and Benedetti, 2017). Although findings of melatonin function in patients with BD are inconsistent, circadian system characteristics generally vary depending on the current episode; mania or depression (Iasevoli *et al.*, 2016). Melatonin levels were found higher in the daytime in manic patients than in healthy controls and patients with depressive episode (Nováková *et al.*, 2015). Findings about nocturnal melatonin levels among BD phases are not consistent (Lewy *et al.*, 1979, 1981; Kennedy *et al.*, 1989; Souêtre *et al.*, 1989). It remains unclear as to whether these alterations derive from a primary dysfunction of the circadian rhythm or if they are secondary to sleep disturbances related to the BD episode. However, some studies supported the beneficial effect of exogenous melatonin administration, which provides sleep and mood improvement (Livianos *et al.*, 2012).

Some of the clock genes have been found intimately associated with both the onset of BD and illness course. Studies revealed that circadian gene polymorphisms may increase the

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predisposition to BD and indirectly affect recurrences and symptoms across all BD phases (Geoffroy, 2018). Genetic linkage and gene expression studies implicated the variant genes related to BD as *clock, timeless, Cry-1*, *Npas-2*, *Bmal-1,2*, *Dbp, Nr1d-1*, *Per-2,3*, *Rora*, *Rorb*, *Asmt, Csnk-1ε*, *Csnk-1δ,* and *glycogen synthase kinase-3β (GSK-3β)* (Kripke *et al.*, 2009; McGrath *et al.*, 2009; Etain *et al.*, 2011; McCarthy and Welsh, 2012; Geoffroy *et al.*, 2014; Geoffroy, 2018). It has been demonstrated that *ClockD19*, the mutant gene that occurs with the deletion of exon 19 in the *Clock* gene, produces a dominant negative CLOCK protein capable of DNA binding but deficient in transcriptional activity. This gene induces dopamine synthesis and increased dopaminergic activity, which result in an increase in tyrosine hydroxylase (TH) expression in the ventral tegmental area (VTA) and manic-like behavior in animal models (Abarca *et al.*, 2002; Roybal *et al.*, 2007; Coque *et al.*, 2011). Moreover, *ClockD19*- related higher dopaminergic activity in the VTA normalized after lithium treatment, which suggests increased dopaminergic activity may be the main reason for the manic-like behavior of mice (Roybal *et al.*, 2007). Recently, several lines of evidence have emphasized the importance of the molecular and synaptic mechanisms of monoaminergic systems and circadian gene interactions, which are closely related to molecular alterations associated with the *ClockD19* model in the VTA and nucleus accumbens.(Parekh *et al.*, 2018) On the other hand, lithium, a potent inhibitor of the GSK-3 enzyme, regulates the clock gene *Nr1d-1* and *BMAL-1* through *GSK-3* (Gekakis *et al.*, 1998). Some polymorphisms including *Clockrs3805148*, *Clockrs534654*, *Timelessrs11171856,* and *Timelessrs2291739* are associated with suicidal behavior in BD (Pawlak *et al.*, 2015).

A dysfunctional HPA axis is suggested to play an important role in the pathophysiology of BD, although the mechanism needs to be elucidated. Increased levels of cortisol and ACTH are the most replicated findings in BD (Belvederi Murri *et al.*, 2016; Sigitova *et al.*, 2017). However, CRH levels are not determined to increase in BD.(Belvederi Murri *et al.*, 2016) Depressive symptoms and cognitive deficits are thought to be associated with the higher levels of cortisol, and ACTH and cortisol seem to be related to manic episodes (Sigitova *et al.*, 2017). A meta-analysis suggested that abnormalities of stress-related pathways including increased morning cortisol levels were mainly prominent in manic episodes. Such abnormalities are even observed in remitted patients, which means that the long-term pathology of the HPA axis is related to clinical states of BD and contributes to the stress-vulnerability models of illness development and progression (Girshkin *et al.*, 2014).

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Immune abnormalities have received increased attention due to their possible role in the pathophysiology of BD, as well as MDD. Systematic reviews on cytokine levels in patients with BD revealed that IL-4, IL-6, IL-10, soluble IL-2 receptor, soluble IL-6 receptor, and TNF-α levels were increased in patients compared with healthy controls, whereas IL-2, IL-8, IFN-gamma, and C-C motif ligand were not different from controls (Modabbernia *et al.*, 2013). Moreover, a comparison of cytokine levels in another study determined that proinflammatory cytokines including IL-2, IL-4, IL-6 were higher during manic episodes, and IL-6 levels were higher in depressive state than in healthy controls (Brietzke *et al.*, 2009). It was also demonstrated that mood symptoms had a positive correlation with IL-6 and IL-2 levels (Brietzke *et al.*, 2009). When bipolar depression and unipolar depression were compared, sIL-6R, CRP, sTNF-R1, and monocyte chemoattractant protein-1 (MCP-1) were found at higher levels than in unipolar depression (Bai *et al.*, 2015). In conclusion, sleep disturbances are a reliable indicator of an upcoming mood episode in BD.

4.2. Schizophrenia

Although the relationship between mood disorders and circadian abnormalities has become clearer in recent times, the links between schizophrenia and disrupted circadian rhythms have yet to be elucidated fully. However, sleep and circadian disruption have been known as common and consistent features of schizophrenia and other psychotic disorders since the first definition of Kraepelin in 1883 (Peirson and Foster, 2015). Schizophrenia has been associated with abnormalities in sleep including delayed and advanced sleep onset, altered resting activity patterns, and irregular sleep-wake cycle (Wulff *et al.*, 2012). Research into circadian abnormalities and sleep disruption in schizophrenia has attempted to explain the causal relationship in a reciprocal context. Hyperdopaminergia is a well-known phenomenon in psychosis syndromes and striatal hyperdopaminergic activity may be a result of sleep disruption and circadian abnormalities, and increased dopamine levels may induce sleep disruptions (Howes and Kapur, 2009; Monti *et al.*, 2013; Yates, 2016). There is also supporting evidence showing an association between genetic polymorphisms and circadian disruption, which is consistently confirmed in animal models. For instance, the *Clock T3111C* polymorphism, which is associated with increased dopamine levels in the SCN, has been determined in a population of Japanese patients with schizophrenia (Takao *et al.*, 2007). Furthermore, the blind-drunk mutant mouse, which carries a mutation in the gene encoding

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an exocytotic synaptic protein, synaptosomal-associated protein-25 (Snap-25), exhibits schizophrenia-like symptoms (Fasshauer *et al.*, 1998; Oliver and Davies, 2009). This mouse model of schizophrenia has been shown to display phase advance and fragmentation of the circadian cycle (Oliver *et al.*, 2012). Most consistent findings of the circadian genetics studies have been associations between CLOCK, PERIOD1, PERIOD3, and TIMELESS genes and schizophrenia (Lamont *et al.*, 2010). Circadian rhythm disruption has been reported in approximately 80% of patients with schizophrenia (Cosgrave, Wulff and Gehrman, 2018). Abnormal sleep patterns in schizophrenia have been described in both unmedicated patients and patients currently receiving antipsychotic treatment (Wulff *et al.*, 2010). The major findings in sleep architecture could be aligned, such as long sleep-onset latency, increased intermittent-awakenings, decreased total sleep time, and poor sleep efficiency (Sasidharan *et al.*, 2017). Moreover, reductions in REM latency, REM density, and duration of non-REM Stage 4 are other alterations in micro-sleep architecture (Wulff *et al.*, 2010; Jones and Benca, 2015; Bian *et al.*, 2017; Chan *et al.*, 2017; Kaskie, Gill and Ferrarelli, 2019). Sleep disturbances are also important to predict increased suicide attempts in patients with schizophrenia (Li *et al.*, 2016).

Melatonin is a versatile neuro-hormone that plays an important role in the pathophysiology of schizophrenia. 5-HT synthesis regulation, sleep-wake cycle, and anti-oxidant effects against neuroinflammation are impaired due to melatonin dysfunction in schizophrenia (Anderson and Maes, 2012; Yates, 2016). It has been shown that melatonin increases endogenous antioxidants by increasing phosphorylated glycogen synthase kinase-3 (GSK-3) levels and provides an anti-inflammatory effect (Olcese *et al.*, 2009; Anderson and Maes, 2012). Galván-Arrieta et al. reported a reduction in axogenesis associated with lower levels of phosphorylated GSK-3 subtype β and less expression of melatonergic receptors in patients with schizophrenia compared with healthy controls. These findings may indicate a melatonin-derived neurodevelopmental deficit at a cellular level (Galván-Arrieta *et al.*, 2017). The absence of melatonin rhythmicity, decreased nocturnal secretion of melatonin, and phase advance in melatonin circadian rhythms have also been described in patients with schizophrenia (Rao *et al.*, 1994; Anderson and Maes, 2012; Yates, 2016). Additionally, pineal calcification in computed tomography has been demonstrated in patients with schizophrenia, and this structural change has been found associated with cortical atrophy (Sandyk and Kay, 1991). Because of its significance in the pathogenesis of schizophrenia, melatonin has become

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a therapeutic target for researchers. It has been shown that melatonin agonists are efficacious agents for schizophrenia-associated sleep disorders and drug-related tardive dyskinesia (Shamir *et al.*, 2001; Gorfine *et al.*, 2006). Moreover, its improving effects on behavioral deficits via reducing brain oxidative stress have been shown in an animal model of schizophrenia (Onaolapo, Aina and Onaolapo, 2017).

The relationship between clock genes and schizophrenia is another undiscovered area for scientists. Few studies have been conducted to show linking circadian clock gene polymorphisms in schizophrenia to date. Takao et al. identified the Clock 311C/T polymorphism, which is associated with higher dopaminergic neurotransmission in the SCN in patients with schizophrenia (Takao *et al.*, 2007). These results were confirmed in another study conducted in a Chinese schizophrenic population (Zhang *et al.*, 2011). *Period-1* mRNA expression in the temporal lobe of post-mortem subjects with schizophrenia was found down-regulated when compared with healthy controls (Aston, Jiang and Sokolov, 2004). In addition, disrupted diurnal rhythms of the *Per-1, Per-2, Per-3, Npas-2* and phase delay in the expression of *Per-2* have been reported in white blood cells of patients with schizophrenia (Sun *et al.*, 2016). More recently, the absence of rhythmic expression of *Cry-1* and *Per-2* was determined in the fibroblasts of patients with schizophrenia compared with cells obtained from healthy controls.(Johansson *et al.*, 2016) Pinacho et al. reported decreased levels of CSNK1ε protein levels in the prefrontal cortex of patients with hschizophrenia (Pinacho *et al.*, 2016). However, due to the small sample sizes of the available studies, the association between schizophrenia and clock genes still needs to be clarified with further studies with larger populations.

The stress-vulnerability model for schizophrenia was first proposed in the 1970s and has been further developed since that time (Zubin and Spring, 1977; Coulon *et al.*, 2016). Thus, the HPA axis has been one of the most attractive research targets to understand the pathophysiology of schizophrenia for decades. Increased cortisol levels have been determined in patients with schizophrenia and even in individuals at high risk for schizophrenia compared with controls (Mittal and Walker, 2011; Carol and Mittal, 2015; Singh *et al.*, 2015). However, mean baseline cortisol level measurements in schizophrenia are not consistent in the literature (Bradley and Dinan, 2010). Nevertheless, blunted cortisol levels in response to stressors are much more consistent findings, regardless of disease stage, chronicity, and treatment condition (Zorn *et al.*, 2017). To conclude, despite it being widely accepted that sleep and circadian disorders have an important role in the etiopathogenesis of schizophrenia, well-designed and

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comprehensive clinical studies are still needed to explicate the genetic and neurobiologic underpinnings.

4.3. Other Psychiatric Disorders

Anxiety disorders are seen as the most frequent type of psychiatric disorders with a lifetime prevalence of 29% in the general population (Remes *et al.*, 2016). Sleep disturbance is a common feature of anxiety disorders and is included in the symptom criteria for several anxiety disorders such as post-traumatic stress disorder and generalized anxiety disorder (Boland and Ross, 2015). The presence of sleep disturbances has been reported as 74% in patients with anxiety disorders (Dallaspezia and Benedetti, 2017). However, MDD as a frequent comorbid condition in anxiety disorders is a confounder in understanding the relationship of sleep disturbances and anxiety disorders. Studies related to generalized anxiety disorder have reported decreased total sleep time, increased sleep-onset latency, and alterations in non-REM sleep architecture, whereas findings of REM sleep and sleep efficiency are inconsistent (Cox and Olatunji, 2016). Patients with panic disorder frequently have both sleep disorder and/or another anxiety disorder because they could have nocturnal panic attacks, which usually occur in Stage-2 or Stage-3 of non-REM sleep, as well as decreased sleep efficiency, total sleep time, and increased sleep onset latency (Cox and Olatunji, 2016; Dallaspezia and Benedetti, 2017). Although sleep disturbances, including REM sleep-related nightmares, have been investigated in post-traumatic stress disorder, conclusions are not consistent (Dallaspezia and Benedetti, 2017). There is no significant difference in sleep architecture in social anxiety disorder (Brown, Black and Uhde, 1994; Mesa, Beidel and Bunnell, 2014). In an animal model, *Cry-1* and *Cry-2* gene protein deficiencies led to behavioral alterations characterized by an abnormally high level of anxiety (De Bundel *et al.*, 2013). Akiyama et al. suggested that *period-1* mRNA levels reduced after anti-anxiety treatment in the mouse cerebellum (Akiyama *et al.*, 1999). *Cry-2* expression was determined reduced in the hippocampus in another animal study (Griesauer *et al.*, 2014). Furthermore, a polymorphism in *BMAL-2rs2306073* has been found associated with social phobia (Sipilä *et al.*, 2010).

Obsessive-compulsive disorder (OCD) is another debilitating disorder that is segregated from the anxiety disorders category in the DSM-5 (*American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5*. 5th edn, 2013). Although sleep disturbances

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have been reported including decreased total sleep time, alterations in REM and non-REM sleep architecture are less clear (Cox and Olatunji, 2016). Certain chronotypes have been found as predictors of OCD symptoms in adults, and circadian rhythm disorders have been found as predictors of treatment outcomes (Cox and Olatunji, 2019). To the best of our knowledge, the role of circadian rhythm disruptions in all anxiety disorders, including OCD, has yet to go beyond showing sleep disturbance; comprehensive research is warranted in the context of chronobiologic mechanisms of anxiety disorder pathology.

(Table 3)

5. Conclusion

The circadian system is responsible for the temporal organization of physiologic functions, and disruptions can have marked functional influences on the living organism. As the role of chronobiologic systems in both physical and mental health have become better understood, research into neurobiologic mechanisms of circadian rhythms has been expanded. Mood, cognition, and behavior have complex relationships with biologic rhythms, and the vast majority of mental disorders are reciprocally associated with impaired circadian biology. Extensive research has shown that impaired circadian mechanisms could lead to psychiatric entities, whereas they may be an outcome of mental disturbances. Impaired HPA axis function and melatonin homeostasis are the most consistent findings in mental disorders. Independent from sleep disorders, the circadian system has a distinct role in homeostatic processes, whose impairment has an impact in emotion regulation, cognition, behavior, and, most importantly, neural plasticity, all of which are often disrupted in psychiatric phenotypes. There is some evidence suggesting that circadian rhythm genes are associated with psychiatric disorders; however, the specificity and causality of these associations have yet to be made clear. In our opinion, we are a long way from establishing a robust causative link between circadian rhythm disruption and phenotypic complexity of psychiatric disorders. A decent translational approach to the findings of animal models would likely result in a clearer understanding of pathophysiologic implications of the circadian system. Further support from continued and integrated investigations of these issues may promote a deeper appreciation of the contribution of circadian disturbances to the pathophysiology of psychiatric illnesses, and will hopefully yield improved therapeutic strategies for their treatment.

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Figure 1. Flowchart of articles selected for the review.

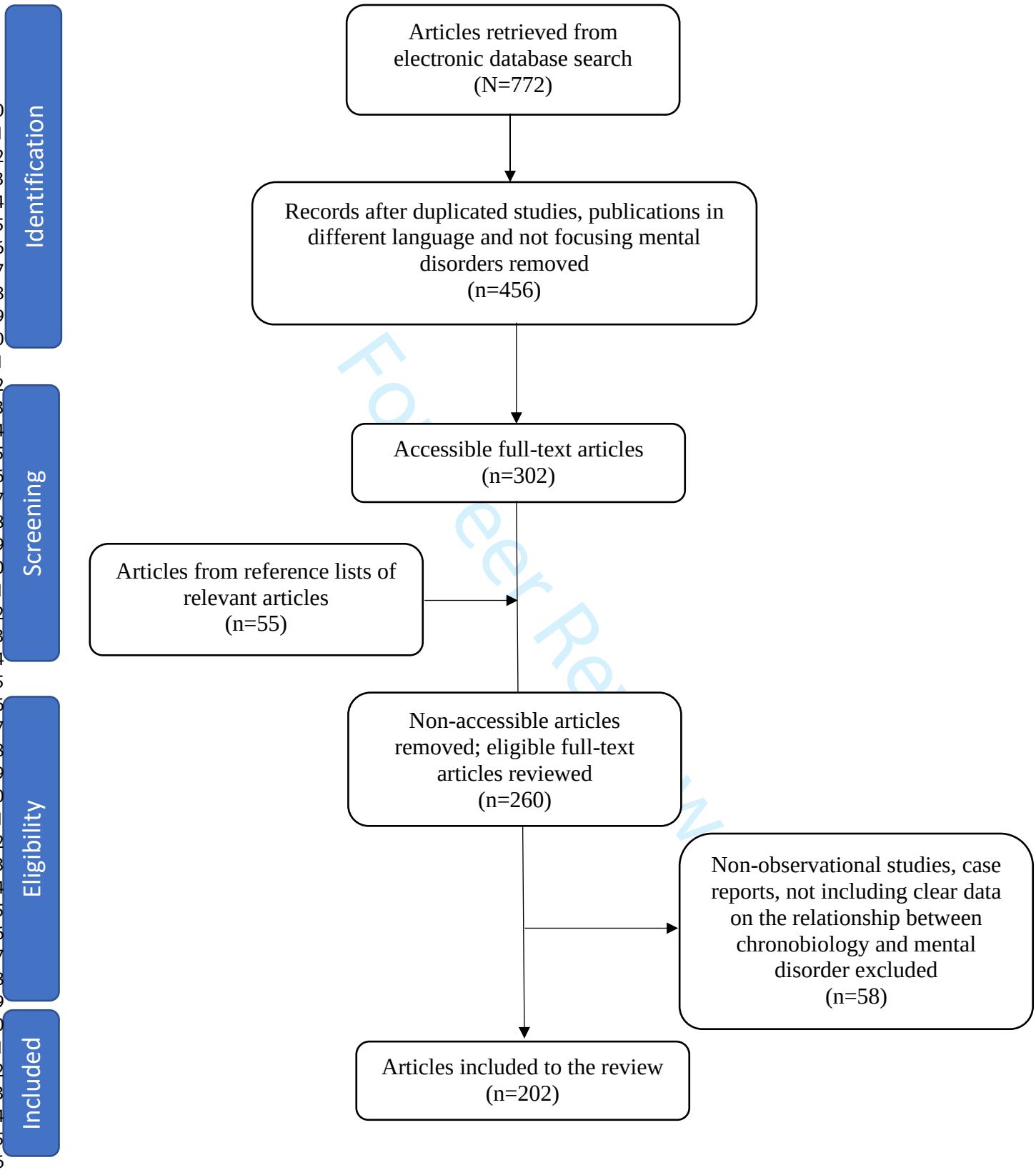

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Table 1. Non-exhaustive list of studied human clock genes, expressed proteins, their main function and associated psychiatric disorders

Gene	Nomenclature and Protein	Protein function	Associated disorder
Clock	Circadian Locomotor Output Cycles Kaput (CLOCK)	Positive regulation of *period* and *timeless* genes through interaction with BMAL-1	MDD(Kishi *et al.*, 2009; Soria *et al.*, 2010; Shi *et al.*, 2016) BD(Shi *et al.*, 2008; Kripke *et al.*, 2009; Lee *et al.*, 2010; Soria *et al.*, 2010; Benedetti *et al.*, 2015; Suzuki *et al.*, 2017) SCH(Takao *et al.*, 2007; Zhang *et al.*, 2011)*
Timeless	Timeless homolog (TIM)	Negative regulation of CLOCK-BMAL-1 activity through interaction with PER and close the circadian feedback loop	MDD(Utge *et al.*, 2010; Dmitrzak-Weglarz *et al.*, 2015) BD(Mansour *et al.*, 2006; Utge *et al.*, 2010; Etain *et al.*, 2014)
Cry-1	Cryptochrome-1 (CRY-1)	Inhibition of CLOCK-BMAL-1	MDD(Soria *et al.*, 2010; Hua *et al.*, 2014) BD(Soria *et al.*, 2010) SCH(Johansson *et al.*, 2016) ANX(De Bundel *et al.*, 2013)
Cry-2	Cryptochrome-2 (CRY-2)	Inhibition of CLOCK-BMAL-1	ANX(De Bundel *et al.*, 2013; Griesauer *et al.*, 2014)
Per-1	Period homolog 1 (PER-1)	Negative regulation of CLOCK-BMAL-1 activity through interaction with CRY and close the circadian feedback loop	BD(Kripke *et al.*, 2009) SCH(Aston, Jiang and Sokolov, 2004; Sun *et al.*, 2016) ANX(Akiyama *et al.*, 1999)
Per-2	Period homolog 2 (PER-2)	Negative regulation of CLOCK-BMAL-1 activity through interaction with CRY and close the circadian feedback loop	MDD(Partonen *et al.*, 2007; Lavebratt *et al.*, 2010; Soria *et al.*, 2010) BD(Kripke *et al.*, 2009) SCH(Liu *et al.*, 2015; Johansson *et al.*, 2016; Sun *et al.*, 2016)
Per-3	Period homolog 3 (PER-3)	Seems not to have a critical role circadian rhythm. Contribute to determination of diurnal preference	MDD(Artioli *et al.*, 2007; Soria *et al.*, 2010; Maglione *et al.*, 2015; Shi *et al.*, 2016) BD(Mansour *et al.*, 2006; Nievergelt *et al.*, 2006; Benedetti *et al.*, 2008; Dallaspezia *et al.*, 2011; Karthikeyan *et al.*, 2014; Brasil Rocha *et al.*, 2017) SCH(Sun *et al.*, 2016)
Bmal-1 (or ARNTL-1)	Brain muscle ARNT like protein-1 (Aryl Hydrocarbon Receptor Nuclear Translocator like 1) (BMAL-1/ARNTL-1)	Positive regulation of *period* and *timeless* genes through interaction with CLOCK	MDD(Partonen *et al.*, 2007; Soria *et al.*, 2010; Utge *et al.*, 2010) BD(Nievergelt *et al.*, 2006; Soria *et al.*, 2010; Bengesser *et al.*, 2018)
Bmal-2	Brain muscle ARNT like protein-2	Probably has a role in activation of CLOCK and CLOCK-controlled genes	ANX(Sipilä *et al.*, 2010)
Npas-2	Neuronal PAS domain protein- 2 (NPAS-2)	Intrinsic enhancer for pre-mRNA splicing	MDD(Partonen *et al.*, 2007; Soria *et al.*, 2010; Shi *et al.*, 2016) BD

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			(Kripke *et al.*, 2009; Soria *et al.*, 2010) SCH(Sun *et al.*, 2016)
*Nr1d-1 (*or *Rev-erb-α*)	Nuclear receptor subfamily-1, group d, member 1 (or orphan nuclear receptor REV-ERB-α) (NR1D1/REV-ERB-α)	Works as nuclear hormone receptors. Compete with RORA for binding to the BMAL-1 promoter and repress the BMAL-1	MDD(Soria *et al.*, 2010; Utge *et al.*, 2010; Byrne *et al.*, 2014) BD(Kishi *et al.*, 2008; Kripke *et al.*, 2009; Severino *et al.*, 2009)
Rora	Retinoid-related orphan receptor a (RORA)	Works as nuclear hormone receptors. Compete with NR1D1 for binding to the BMAL-1 promoter and activate the BMAL-1	MDD(Lavebratt *et al.*, 2010; Utge *et al.*, 2010; Maglione *et al.*, 2015) BD(Etain *et al.*, 2014; Lai *et al.*, 2015; Geoffroy *et al.*, 2016)
Rorb	Retinoid-related orphan receptor b (RORB)	Works as nuclear hormone receptors. Compete with NR1D1 for binding to the BMAL-1 promoter and activate the BMAL-1	BD(McGrath *et al.*, 2009; Lai *et al.*, 2015)
Dbp	D site of albumın promoter bındıng protein	Being regulated by CLOCK-BMAL-1 and CRY-1. Supports the rhythmic transcription of downstream genes	MDD(Soria *et al.*, 2010) BD(Shi *et al.*, 2008)
Asmt	Acetylserotonin methyltransferase	The last enzyme of the melatonin synthesis pathway	MDD(Gałecki *et al.*, 2010; Talarowska *et al.*, 2014) BD(Etain *et al.*, 2012; Geoffroy *et al.*, 2014)
Mtnr1-B	Melatonin receptor 1b	G protein coupled melatonin reseptor	MDD(Gałecka *et al.*, 2011)
Aanat	Arylalkylamine N-acetyltransferase	The first enzyme of the melatonin synthesis pathway	MDD (Soria *et al.*, 2010)
Csnk-1ε	Casein kinase 1 epsilon (CSNK1ε)	Phosphorylates of PER, CRY and BMAL, increases their degradation	MDD(Utge *et al.*, 2010) BD(Shi *et al.*, 2008; Matsunaga *et al.*, 2012; Lee *et al.*, 2018) SCH (Matsunaga *et al.*, 2012; Pinacho *et al.*, 2016)
Csnk-1δ	Casein kinase 1 delta (CSNK1δ)	Phosphorylates of PER, CRY and BMAL, increases their degradation Regulation circadian period length	BD(Kripke *et al.*, 2009; Matsunaga *et al.*, 2012) SCH(Matsunaga *et al.*, 2012)
GSK-3β	Glycogen synthase kinase-3β (GSK-3β)	Regulation circadian period length	BD(Szczepankiewicz *et al.*, 2006; Kaladchibachi *et al.*, 2007)

Note: MDD: Major depressive disorder, BD: Bipolar disorder, SCH: Schizophrenia, ANX: Anxiety disorders *CLOCK T3111C polymorphism,

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Table 2. Main alterations of sleep architecture in psychiatric disorders

Disorder	Major alterations
MDD	Shortened latency of the initial REM sleep, prolonged first REM period, increased total REM time, increased REM density, and proportion of REM sleep, decreased non-REM sleep (Kupfer and Foster, 1972; Kupfer, 1976; Rush *et al.*, 1986; Giles *et al.*, 1987; Pillai, Kalmbach and Ciesla, 2011)
BD	*Euthymia*; Increased REM density and proportion of REM sleep, longer sleep onset latency and sleep duration, lower sleep efficiency (Sitaram *et al.*, 1982; Millar, Espie and Scott, 2004; Rocha, Neves and Corrêa, 2013; Geoffroy *et al.*, 2015) *Mania;* Shortened REM sleep latency, increased REM activity and REM density, reduced total sleep time (Hudson *et al.*, 1988, 1992; Linkowski and Mendlewicz, 1993) *Depression*; More fragmented REM sleep periods, shortened REM sleep latency (Gillin *et al.*, 1979; Lauer, Wiegand and Krieg, 1992) longer sleep onset latency, increased proportion of REM sleep, trend toward higher percentage of awakenings in bipolar depression than in unipolar depression (Giles, Rush and Roffwarg, 1986; Jernajczyk, 1986; Fossion *et al.*, 1998)
SCH	*Comparison to healthy control*; Redused total sleep time, longer sleep onset latency, lower sleep efficiency and REM latency, increased REM density, decreased total REM time, decreased non-REM stage-3 and stage-4 (Chan *et al.*, 2017) *Medication naive patients*; reduced total sleep time, lower sleep efficiency, increased REM latency, decreased stage-4 of non-REM sleep, increased stage-1 of non-REM (Bian *et al.*, 2017) Duration of illness has no effect on polysomnography parameters (Chan *et al.*, 2017)
ANX	*Generalized anxiety disorder;* reduced total sleep time, longer sleep onset latency, alterations in non-REM sleep architecture, inconsistent findings for REM sleep architecture and sleep efficiency (Cox and Olatunji, 2016) *Panic disorder;* decreased sleep efficiency and total sleep time, longer sleep onset latency, REM and non-REM sleep architecture findings are less clear (Cox and Olatunji, 2016) *Post-traumatic stress disorder;* reduced total sleep time, longer sleep onset latency, variations in REM sleep
OCD	Reduced total sleep time, increased wake after sleep onset, inconsistent findings for REM and non-REM sleep architectures (Cox and Olatunji, 2016)

Note: MDD: Major depressive disorder, BD: Bipolar disorder, SCH: Schizophrenia, ANX: Anxiety disorders, OCD: Obsessive-compulsive disorder

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Tab 3. Summary of consistent findings on the alterations of two major neurohumoral systems regulating circadian ryhthm in psychiatric disorders

DIAGNOSIS	NEUROHUMORAL SYSTEM	
	HPA Axis	Melatonergic System
MDD	Elevated baseline cortisol levels, disruption in dexamethasone suppression test results (Carroll, Martin and Davies, 1968; Nelson and Davis, 1997; Belanoff *et al.*, 2001; Keller *et al.*, 2006, 2017; Gold, 2014) increased cortisol/ DHEA ratio (Goodyer, Herbert and Altham, 1998; Gallagher and Young, 2002; Markopoulou *et al.*, 2009)	Lower nocturnal melatonin levels, delayed melatonin secretion onset and offset (Wetterberg, 1979; Beck-Friis *et al.*, 1984; Nair, Hariharasubramanian and Pilapil, 1984; Claustrat *et al.*, 1984; Beck-Friis *et al.*, 1985; Wehr *et al.*, 1985; Brown *et al.*, 1985; Frazer *et al.*, 1986; Parry and Newton, 2001; Fountoulakis *et al.*, 2001; Paparrigopoulos, 2002; Tuunainen *et al.*, 2002; Crasson *et al.*, 2004; Emens *et al.*, 2009; Rahman *et al.*, 2010; Buckley and Schatzberg, 2010; Khaleghipour *et al.*, 2012)
BD	Increased cortisol and ACTH levels in manic phase Findings about HPA axis abnormalities are seen both depressive and euthymic phase, it is preferred to evaluate them as state and trait markers due to clinical variations (Belvederi Murri *et al.*, 2016)	Higher melatonin levels in manic phase in the daytime (Nováková *et al.*, 2015) Findings about nocturnal melatonin levels among BD phases are inconsistent (Lewy *et al.*, 1979, 1981; Souêtre *et al.*, 1989; Kennedy *et al.*, 1996)
SCH	Baseline cortisol levels are inconsistent Blunted cortisol stress response (Zorn *et al.*, 2017)	Lower nocturnal melatonin levels, (Monteleone *et al.*, 1992, 1997) phase advance in melatonin rhythm,(Rao *et al.*, 1994) the absence of melatonin rhythmicity (Bersani *et al.*, 2003)

Note: MDD: Major depressive disorder, BD: Bipolar disorder, SCH: Schizophrenia

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