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Chronobiological Aspects of Mood Disorders

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1. Introduction

Mood disorders, especially those related to depression, are among the most prevalent mental impairments. Therefore, understanding their etiology is important for prevention and improving therapy. Sub-clinical depressive symptoms, which predict the onset of mood and anxiety disorders (Gentil et al., 2007), are correlated with slow information processing, poor memory functioning (Simons et al., 2009) and cardiovascular dysfunction (Taillard et al., 1993; Wassertheil-Smoller et al., 2004).

Depression is a common disorder that affects more than 121 million people worldwide. A recent epidemiological study reported a worldwide prevalence of approximately 10% to 15% (Lepine & Briley, 2011) The prevalence of depression appears to be independent of culture. The prevalence of depression is 8.2% in Canada, 8.7% in the United States, 8.6% in Europe and 10% in Southern Brazil (Mari & Williams, 1986; Patten, 2007), and varies from 3% to 9% in Japan (Lepine & Briley, 2011). According to the World Health Organization, major depressive disorder is among the leading cause of disability among Americans aged 15 to 44 years old (Kessler et al., 2005). This condition is the second leading cause of disabling illness in the world, second only to ischemic heart disease (Sullivan et al., 2000).

One of the primary findings of depression epidemiology is the high female to male sex ratio, especially through the reproductive years. French data from the European Study of the Epidemiology of Mental Disorders (ESEMeD) support these results: Approximately twice as many women suffer from depression as men, and this trend is found all over the world. However, some exceptions were found for specific ages; for example, there was approximate parity between the sexes among 18- to 24-year-olds. The authors of that study suggested that the reduced depression rate in women was the result of increased opportunities for women in education, employment, birth control and other factors associated with rising gender equality (Lepine & Briley, 2011).

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Depressive disorders are more common in individuals with chronic diseases such as obesity, cardiovascular disease, diabetes, asthma, arthritis, and cancer. Unhealthy behaviors (e.g., smoking, physical inactivity, and binge drinking) are also included in these risk factors. All depressive disorder studies emphasize the significance of the condition's associated mortality and morbidity. The risk of suicide in individuals with depression is more than 20 times greater than for the general population (Lepine & Briley, 2011).

Some researchers have shown that the consequences of depression are a risk factor for cardiovascular death. In addition, depressive symptoms are connected with an appreciably higher risk of mortality, including due to cardiovascular death and stroke (Lepine & Briley, 2011). Beyond mortality, the functional impairment and disability associated with depression is also important to note. Depression increases absenteeism and decreases productivity, which results in lowered profits or greater unemployment. Both absenteeism and presenteeism (present but working at a suboptimal level) cause losses of \$36.6 billion per year in the US. The World Health Organization projects that unipolar major depression will be the leading cause of disease burden worldwide by the year 2030 (Lepine & Briley, 2011).

The genetic effects on depression were previously evaluated in a study of 4,639 adult twins from Australia. In this survey, genetic effects accounted for 29% of the variance in seasonality (Madden et al., 1996). The daily modulations of pathological symptoms as well as the relationship between the circadian clock and health have been extensively documented (Foster & Wuff, 2005; Scheer et al., 2009; Ramsey & Bass, 2009; Wulff et al., 2010; Selvi et al., 2010). For example, patients with depressive episodes show variations in daily mood, abnormal patterns in sleep-wake behavior, cortisol secretion, and adrenocorticotrophic hormone (ACTH) levels as well as a daily modulation of other endocrine-metabolic parameters (Soria & Urretavizcaya, 2009). Additionally, clock-gene variants have been associated with abnormal sleep time and mood disorders (Wulff et al., 2010), which indicate that they share pathways. Based on the importance of depressive disorder and the recently contribution of the studies of rhythms, this chapter review the interphase between chronobiology and depressive disorder and point to some clinical evidence.

2. Concept of chronobiology

The survival of a species depends upon its ability to adapt to its environment. One of most important adaptations is the ability to anticipate events. This adaptation allows a living being to develop physiological and behavioral responses to predict the changes that occur in nature. The light and dark cycle due to the rotation of the earth is the most reliable and salient of such changes. The ratio of light to dark is dependent upon season and geographic location (i.e., latitude and longitude). Therefore, an internal circadian system able to measure the time or environmental cues is an important response to these natural processes. The endogenous rhythm in the body that is in line with environmental signals (i.e., the circadian system) is such an adaptation (Aschoff *et al.*, 1971).

In normal environmental conditions, the various rhythm functions in the body maintain a stable relationship among these phases. This relationship demonstrates a temporal synchronization that features an internal temporal order (Aschoff, 1960). The term

“biological clock” is used in chronobiology to designate a pacemaker and refers to the entire structure which operation oscillates cyclically over time. Through nervous and humoral pathways, it is able to transmit this oscillation throughout the body as well as impose its rhythm on other structures. The biological clock cannot directly trace most biological rhythms; however, it can trace the first rhythm of a successive chain or cascade of events. The biological clock exerts control at several physiological levels, from gene expression to complex behavior. In constant conditions, the biological clock acts freely with an endogenous period of approximately 24 hours (Aschoff *et al.*, 1971).

Ruppert and Weaver (Reppert *et al.*, 2001) describe the circadian system in mammals as a hierarchy of multiple circadian oscillators dispersed by the organism. The “command center” of this timing system is restrained in the neurons of the suprachiasmatic nuclei (SCN). Most of these neurons may work as “cell clocks” or “circadian oscillators”. The SCN receive photic information through the retinohypothalamic tract, synchronizing for 24 hours; in turn, this information coordinates the actions of oscillators present in other brain areas and “peripheral oscillators” such as the lung, kidney, and liver. These synchronized oscillators regulate the local physiological rhythms that constitute multi-oscillator entities (28). In humans, the circadian rhythms can be synchronized by photic and non-photoc cues (Aschoff, 1960).

Aschoff designated the external events that adjust circadian variables “Zeitgebers” (a German word meaning *Give time*), Halberg and collaborators called them “synchronizers”, and Pittendrigh dubbed them “entrainment agents” (Reinberg *et al.*, 2001). Pittendrigh conducted the first systematic experiment on entrainment in the 1960s. In constant darkness with brief exposures to light pulses at different times throughout the day, Pittendrigh observed that exposure to light promoted phase changes dependent on the time of the stimulus. Later, other experiments found the same effect in humans (Beersma & Dann, 1993).

The SCN are synchronized to outside rhythms by light as well as social and behavioral factors. In humans, the *zeitgebers* associated with social cycles have a special relevance (Aschoff *et al.*, 1971). Daily variations in the intensity of ambient noise; the timing of meals, home and business routines; and social interactions are examples of the rhythms that synchronize zeitgebers in humans (Aschoff *et al.*, 1971).

When these biological rhythms are no longer in phase with external cycles, external desynchronizations occur, such as those observed during the performance of night work or rapid time zone crossing. If the situation persists, external desynchronizations may occur in some people, resulting in a dissociation or desynchronization of the internal phase relationships between biological rhythms.

The ability to predict seasonal changes and other circadian rhythms is based on autonomous regulation of cell transcription and translation via feedback loops of cell clocks, proteins and their bases. The identification of circadian rhythm-based clock genes in *Drosophila melanogaster* and *Neurospora crassa* was a fundamental step in the search for homologues in other animal species. Three clock genes have been found in mammals: 1) CLOCK (*Circadian Locomotor Output Cycle Kaput*) and BMAL1 (Brain and Muscle Arnt-Like; also known as MOP3) are involved in the timing system; 2) Per1 (*Period*), Per2 and Per3 are rhythmically expressed in the SCN (Per1 and Per2 induce the response to pulses of light in the SCN,

whereas Per3 has an oscillatory pattern of expression independent of light) (Ohdo, 2007); and 3) Cry1 (*cryptochrome*) and Cry2 are members of the blue-light receptor family in plants. These genes were first classified as potential candidates for circadian photoreceptors; however, additional analyses showed that these genes have an independent light effect in the circadian system of mammals (Ohdo, 2007).

These clock genes found in other transcription factors such as BMAL1, CLOCK, CRY1 and Cry2. All of these proteins, including Per1, Per2, and Per3 establish oscillation periods of approximately 24 hours. The CLOCK-BMAL1 heterodimer is a linked DNA sequence that stimulates the transcription of genes that regulate behavior and metabolism and maintain physiological states. Moreover, the CLOCK-BMAL1 heterodimer activates the transcription of the PER and CRY genes. The PER-CRY complex is formed in the cytoplasm and translocated to the nucleus where it regulates the transcriptional activity of the CLOCK-BMAL1 heterodimer. A second feedback loop has also been identified that involves Rev-erba and the transcription repression of BMAL1. The expression, transcription suppression, and formation of this gene, as well as the heterodimerization of CLOCK and BMAL1, results in a 24-hour rhythmicity (Mignot & Takahashi, 2007). Moreover, BMAL1 is a transcription factor that controls circadian rhythms and contributes to the control of adipogenesis and the lipid metabolism activity of mature adipocytes. The level of BMAL1 mRNA increases during adipogenesis. BMAL1 is related to the induction and promotion of the activation of many factors involved in 3T3-L1 adipocyte lipogenesis. Maximizing the expression of BMAL1 increases the synthesis activity of lipids involved in the regulation, differentiation and maturation of adipocytes (Ohdo, 2007).

Animal studies have demonstrated that variations in clock genes can cause abnormalities in the regulation of circadian rhythms. Investigations in humans have observed that this system regulates many physiological processes such as temperature, feeding behavior, sleep disorders, hormone secretion, metabolism and drug use, glucose homeostasis, tumor formation and cell cycle progression (Takahashi et al., 2008; Wassertheil-Smoller et al., 2004). One hypothesis that may help to understand the abnormalities in the regulation of circadian rhythms suggests that changes in the length of endogenous period can lead to changes in the phase angle of light synchronization. Circadian phenotypes similar to those found in animals are also seen in humans, which allows scientific research to examine the relationship between changes in clock genes and circadian phenotypes (Harmer et al., 2001).

In 1810, Sprengel observed that depression is typically related to daily circadian rhythmicity such that greater fatigue occurs in the early morning hours versus at night (Lemmer, 2009). This disturbance in the temporal order of the circadian system was associated with genetic vulnerability, gender and age. Mood variations during the day, sleep disorders, and changes in the circadian rhythm of cortisol, ACTH, melatonin and other endocrine and metabolic parameters were observed in patients with depressive episodes (Soria & Urretavizcaya, 2009). Individual chronobiology characteristics and preferences related to allocating activities during the day were also related to mood disorders. Using the Horne and Ostberg Morningness-Eveningness Questionnaire, studies in our laboratory discovered an association between evening-type and depressive symptoms in healthy people (Bernardi et al., 2009; Hidalgo et al., 2009). Bipolar depression was also associated with evening preferences (Giglio et al., 2010).

Bipolar disorder (classically known as manic depression) presents with fluctuations between manic and depressive episodes. The oscillations observed in many patients occur in regular

cycles and can last from several days to several years. This discovery has led some researchers to attribute the origin of the depressive phase of this syndrome to variation in the photoperiod, thus contributing to the explanation that this disease has a natural rhythm. Another example of rhythmic manifestation can be seen in seasonal depression, which Rosenthal (Rosenthal *et al.*, 1984) describes as an infradian circannual rhythmicity disease. Specifically, the symptoms begin in the fall, reach their maximum expression in winter and progressively decrease with the arrival of spring.

Seasonal depression is a circadian rhythm disorder caused by the desynchronization between the light/dark cycle and the human biological clock during seasons with shorter photoperiods (Rosenthal *et al.*, 1984). During these periods, the production of melatonin increases. This increase is related to seasonal depression because photic treatment, which occurs with exposure to light in the morning, inhibits the production of melatonin, thereby reducing the symptoms of depression (Lewy *et al.*, 1987; Wirz-Justice *et al.*, 2005).

From a biological point of view, the temporal character of depression can be observed by changes in the profiles of several circadian rhythms during depression, such as changes in body temperature rhythm and sleep architecture. Some studies have observed changes in the circadian secretion of some hormonal such as cortisol, melatonin, prolactin and growth hormones (Soria & Urretavizcaya, 2009). However, there is no unanimity among these studies. The variety of physiological and clinical phenomena present in mood disorders justifies this lack of agreement. The diversity of experimental findings could be a result of the various types of depression studied and the inclusion of patients with undifferentiated depression who have diagnoses that vary according to the different classification criteria used by the researcher. Other aspects that could influence the results are related to different treatment scheme, disease duration, the duration of changes in the photoperiod and the climate of the study sites, or other differences on the methodology such as design.

3. Circadian rhythms and mood disorders

Biological rhythms can affect mood states; conversely, they may be affected by them and thus contribute to the manifestation of depressive symptoms. Additionally, symptoms may occur at different frequencies: daily, monthly, seasonally or annually. These data imply that there is an association between psychopathology and the pre-existing rhythmic processes in humans. In contrast, early studies in individuals with depression did not find abnormal circadian rhythms (Soria & Urretavizcaya, 2009). As alteration on appetite, motility and memory are important functions that are manifest on depression we describe the relation between this brain capacity and circadian rhythm.

3.1 Feeding and circadian rhythms

Mood disorders are associated with changes in appetite including decreases or increases as well as cravings for carbohydrates. Symptoms of seasonal affective disorder (Sacharczuk *et al.*, 2009) include increased sleep and the need for sleep, increased appetite with carbohydrate craving and weight gain, and decreased energy and increased fatigue (Peiser, 2009). An association between vitamin B12 deficiency and depression has been suggested for older adults. (Kohyama, 2009).

It has been long known that there is a higher frequency of people who are overweight or obese among those with depression compared with the general population. Obesity is associated with several symptoms of major depressive disorder (Zimmerman et al., 2011). In addition to changes in appetite and weight, depression is often associated with endocrine problems such as hypothyroidism and hyperthyroidism, Cushing syndrome, and night eating syndrome (NES), among others. NES is not only associated with depression but also with, anxiety and poor sleep quality (Bernardi, 2009).

The plasma concentrations of metabolic products and the hormones related to energy balance vary according to dynamic conditions. Fasting is the most frequently used approach to study whether a rhythm in glucose metabolism is independent of the (disturbing/masking) effect of feeding because the daily rhythms that depend on feeding should disappear in food-deprived animals (Polakof et al., 2006).

One of the mechanisms by which the processes of some syndromes, such as NES, might be explained includes the desynchronization of temporal order and internal difficulties in synchronizing with environmental cycles, such as delayed eating times. Preliminary studies in humans suggest that polymorphisms or mutations in the CLOCK and BMAL1 genes are associated with obesity and metabolic syndrome (Green et al., 2007; Takahashi et al., 2008). Numerous genes are also involved in the metabolism of fatty acids, cholesterol, and glucose in the liver. These substances are regulated by circadian patterns, which indicate that this clock as a large role in regulating metabolism (Green et al., 2007). Many behaviors, including energy intake, vary in intensity throughout the day. Studies that record daily food intake have shown significant and substantial changes in eating behavior in the natural environment; specifically, there is an increase in food intake and energy consumption (greater than 150%) at night compared with morning. This increase occurs in conjunction with an increase in meal size as the day progresses, producing a modest positive correlation between the time of day and meal size (de Castro, 2004). The volume of the meal as it increases throughout the day can affect the length of the intervals between meals, decreasing the time between them and interfering with satiety. These intervals become shorter as the night progresses for both humans and rats. Clearly, increasing an individual's vulnerability to excessive intake of food during the night reduces satiety (de Castro, 2004). The link between mood disorder and food behavior appears to be connected via hormones that regulate not only feeding but also the neuronal activity in the mesolimbic dopaminergic pathway. In particular, leptin reduces the firing rates of dopaminergic neurons, which indicates that leptin exerts a direct influence on dopamine neurons via leptin receptors (Dibner et al., 2010).

Leptin and ghrelin are hormones that act directly on the timing of food ingestion and regulate appetite. A study that investigated the relationship between leptin levels and ghrelin as well as symptoms of depression, anxiety and stress in women demonstrated a significantly negative relationship between leptin and the severity of depressive symptoms and anxiety but not between leptin and ghrelin (Lawson et al., 2011).

3.2 Activity/rest and circadian rhythm

Studies have shown that amount of physical activity is inversely related to depressive symptoms and weight gain (Kohyama, 2009).

Physical exercise influenced the internal phase relationship of the circadian system: as the minimum temperature rhythm advances phase, mood improved in people after weeks of training in the early morning (Peiser, 2009). Other researchers have found similar results and suggested that treating SAD (Seasonal Affective Disorder) using physical exercise, with or without bright light treatment, can alleviate its symptoms. Physical exercise may work for people with SAD because it can facilitate a circadian phase advance. Nevertheless, neither exercise alone, nor exercise in combination with light therapy, has been reported to positively affect seasonal mood deterioration or its physiological, hormonal, social and psychological symptoms (Peiser, 2009). Numerous recent studies suggest that physical exercise provides an effective and easily accessible treatment for patients who suffer from SAD. Concluding, there is no consensus as to which components of exercise produce beneficial effects on mental health.

Moreover, the activity and rests has been assed by actigraph as a way to improve the diagnose and differentiate among types of depression (See table 1). There were controversial findings on the result, probably related to difference on the samples. Some studies describe depressive patient with higher amplitude than control group and difference on acrophase, other authors describe the opposite (Table 1).

Study	objective	Nº pacientes	Using	Groups	Conclusion
Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients Bipolar Disord. 2008 Mar;10(2):256-65	compared circadian activity rhythms in BPD I patients during ill and recovered states to those of normal controls	36 adults with bipolar disorder during acute mania or mixed states and to 32 healthy controls	wrist-worn, piezoelectric actigraphic monitoring for 72 h	BPD Recovered Controls	abnormalities of circadian motility patterns found in states of acute manic or mixed BPD illness persisted during full and sustained clinical recovery with euthymia, and remained highly significantly different from normal controls
Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/ depression in women treated with breast cancer adjuvant chemotherapy. <u>Support Care Cancer</u> . 2009 Apr 19	examine patterns of circadian activity rhythms and their relationship with fatigue, anxiety/ depression, and demographic/ medical variables in women receiving breast cancer adjuvant therapy treatments (Tx) at three times within a randomized clinical trial (RCT) designed to improve sleep and modify fatigue.	219 women with stage I-IIIa breast cancer who were randomized 2 days prior to starting chemotherapy to a behavioral therapy sleep intervention or healthy eating control group	wrist actigraphy for 7 days at three times: the start (Tx 1), continuation (Tx 3), and recovery (30 days after last Tx) of chemotherapy	Tx 1 Tx 3 30Days	Circadian activity rhythm parameters at three times in both groups were disrupted compared to healthy adults, but similar to values of cancer patients. Significant changes in mesor, amplitude, peak activity, and 24 h autocorrelation values were found over time in both groups
Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. <i>Chronobiol Int</i> . 2007;24(5):921-37	To known if the clinical effects are paralleled by changes in biological rhythms in sleep deprivation (TSD) and light therapy (LT) in bipolar depression and rapid antidepressant effects The action has been hypothesized to involve the enhancement of all of the monoaminergic systems targeted by antidepressant drugs	39 in patients with Type I Bipolar Disorder	Wrist actigraphy	Responders (day 0) No Responders (day 0) Responders (day 7) No Responders (day 7)	Responders showed an increase in daytime activity, phase-advance of the activity-rest rhythm of 57 min compared to the pre-treatment baseline, and reduced nighttime sleep. Non-responders did not show significant changes in the parameters. Phase advance of the activity-rest rhythm is an actimetric correlate of the antidepressant response to TSD and LT in bipolar

Table 1. Results of actigraphic assessment in psychiatric disorders

3.3 Memory and circadian rhythm

Memory is one of the most important brain functions related not only to survival but also to the notion of time. Borella et al. (2011) examined the effect of testing time on adult

differences in resistance to interference, working memory, processing speed, and vocabulary. Their results showed specifically, older adults tested in the afternoon were more susceptible to interference compared with younger adults. In contrast, processing speed, and vocabulary were not modulated by time of the day (Borella et al., 2011). Using the fractional desynchronization technique to induce internal desynchronization in humans, was observed a period of 21 hours in some performance even when the participant's physiological rhythms are apparently synchronized to the 24-hour day (Folkard et al., 1985)

Memory is linked with mood disorders. The normal function of the circadian clock is disrupted in jetlag. This syndrome is characterized by signs including sleep disorders, concentration impairment, dysphoria, asthenia, irritability and memory alterations (Mahé & Chevalier, 1995)

Memory performances are not constant; rather, they undergo fluctuations with a periodicity that can be analyzed. Infradian, circadian and ultradian rhythms are involved in memory disorders. In addition, the hypothesis that memory impairment is associated with sleep disturbance has been proposed. These rhythms include the light-dark and social cycles, a circadian hypothalamic oscillator that alternates virtually independently of behavior, and a homeostatic oscillator driven primarily by sleep-wake behavior. Both types of internal oscillators contribute to the variation in many aspects of sleep and wakefulness as well as performance parameters including attention and memory. Neither oscillator can independently predict sleep or performance; however, both constructs critically depend on their phase relationship and amplitude. Thus, the amplitude of the observed circadian variation in sleep and performance depends upon the length of time we have been asleep or awake. Paradoxical sleep represents a preferential period in which certain processes (e.g., the activation of the central nervous system) may facilitate the learning process. The relationship between sleep and memory leads to a discussion of the daily course of cerebral activation and its effects on the variation in our capacity to remember (Leconte, 1989)

Also, inter-individual differences in sleep timing, duration, and morning or evening preferences are associated to changes in circadian processes, sleep homeostatic processes, or both. Some of these inter-individual differences in molecular genetic correlates, including polymorphisms in clock genes, are emerging (Dijk & von Schantz, 2005).

Certain structures are involved in the process of retaining information. Izquierdo has demonstrated that memory and mood are correlated with the amygdala and hippocampus as one such structure (Izquierdo et al., 1997). Ma et al. (2007) reported that constant light exposure for 3 weeks disrupted the 24-h cycle of locomotion activity in an open-field test. Compared with control group, experiment group showed shorter escape latencies but impaired hippocampus-dependent spatial memory that did not affect the visual platform learning task in a Morris water maze (MWM) during the initial phase of spatial learning (Ma et al., 2007).

Fujioka et al. examined whether an environment with constant light affected hippocampal neurogenesis in mice. The number of BrdU-labeled cells (proliferating cells) as well as BrdU and Class-III β -tubulin double-labeled cells (newborn neurons) significantly decreased in the granule cell layer of the L/L group compared with that of the L/D group. Also Fujioka found that the exposure to an L/L treatment for 3 weeks impaired spatial learning task performance; These findings demonstrate that constant light conditions impaired hippocampal neurogenesis and cognitive performance (Fujioka et al., 2011).

4. Experimental evidence of desynchronizations in circadian rhythms and mood disorders

Animal studies have demonstrated that variations in clock genes can cause abnormalities in the regulation of circadian rhythms (Bunney & Bunney, 2000). Studies in humans have shown that this system regulates many physiological processes such as temperature control, feeding behavior, sleep disorders, hormone secretion, metabolism, glucose homeostasis, tumor formation, and cell cycle progression (Takahashi et al., 2008).

Recent findings in the fields of molecular biology and genetics regarding the complex machinery that regulates biological clocks support the role of disrupted circadian rhythms in the pathophysiology of depression. Transgenic mice that overexpress the glycogen synthase-kinase-3 β (GSK-3 β) gene, a recently recognized central regulator of circadian rhythms and target of the mood stabilizer lithium (Prickaerts et al., 2006), show some depression-like behavior and an increased startle response reminiscent of mania-like behavior (Nestler & Hyman, 2010). Moreover, mice that carry a CLOCK gene mutation exhibit mania-like behaviors such as a decreased need for sleep and motor hyperactivity, which revert with the chronic administration of lithium. In addition, these behaviors are resolved when a functional CLOCK protein is specifically expressed in the ventral tegmental area of these mutant mice (Monteleone et al., 2011).

5. Clinical evidence for desynchronizations in circadian rhythms and mood disorders

The concept of internal circadian phase disturbances in individuals with depression can be explained in the previous signs observed during flights across multiple time zones, known as jet lag, and night-shift workers. These transitory symptoms are similar to those observed during depressive episodes. The problem results from the inability of the body's clock to adapt promptly to abrupt changes in zeitgebers during periods when there is a desynchronization between the internal and external rhythms. A temporal loosening in the coordination of these rhythms, which is generated by the environmental and social systems, results in mood variability after the desynchronization period.

One of the first circadian hypotheses of major depressive disorder suggested that patients with depression have a significantly later circadian sleep phase compared with healthy people (Kripke, 1984; Wehr *et al.*, 1979). Several follow-up studies showed that circadian timing is drastically delayed in patients with bipolar disorder (Giglio *et al.*, 2010; Soreca *et al.*, 2009), SAD (Elmore *et al.*, 1993), and major depressive disorder (Drennan *et al.*, 1991; Soria & Urretavizcaya, 2009). SAD is also associated with internal circadian misalignment (Lewy *et al.*, 2006). Although the underlying mechanisms are poorly understood, they are clinically and therapeutically relevant as evidenced by the antidepressant effects of light therapy, sleep deprivation, and rigid sleep schedules (Benedetti *et al.*, 2007; Boivin *et al.*, 1996; Haynes *et al.*, 2005; Lewy *et al.*, 1987; Terman & Terman, 2005; Zeitzer *et al.*, 2000).

In addition, circadian misalignment and sleep disruptions in patients with mood disorders have been linked to abnormal daily patterns of gene expression, hormonal secretion, body temperature, cognitive and behavioral functions (Wulff *et al.*, 2010). An additional indication that circadian misalignment contributes to depressive symptoms is the finding that people who live in urban settings are prone to depressive symptoms (Chelminski *et al.*, 1999;

Giannotti *et al.*, 2002; Hidalgo *et al.*, 2009). The circadian clock in this population is delayed compared to that in rural populations (Roenneberg *et al.*, 2007), which accentuates the discrepancies between social and biological time (Wittmann *et al.*, 2006). This internal desynchronization may be a major factor with regard to mood.

New findings on the desynchronization found in night-shift workers and transmeridian travelers are now evident in an epidemiology study of depression (Levandovski *et al.*, 2011). In this study, late chronotypes exhibited higher levels of depressive symptoms compared with intermediate and early chronotypes. Moreover, jetlag was positively correlated with depressive symptoms: participants with more than 2 h of jetlag showed significantly high levels of depression (Levandovski *et al.*, 2011).

6. Conclusion

Until now, the literature stated that the major environmental signals able to synchronize circadian rhythms in animals and humans are the light/dark cycle and the phototransduction performed by retinal ganglion cells (Hirota & Fukada, 2004). Photoc signals can also synchronize humans, but social signals are the primary determinant (Mistlberger & Skene, 2004). The relationship between social rhythm and circadian rhythm has been known since Aschoff (Aschoff, 1960). Based on his theory, several researchers have developed non-invasive measurement tools that include social rhythms (Monk *et al.*, 1990). Currently, social rhythms are known to be able to interfere with the synchronization of biological rhythms. These rhythms are characterized by regular social zeitgebers whose exposure is defined as an external synchronic agent inserted into a known social context. The study of social rhythms leads to reflect upon the temporal organization of society, thereby revealing the noxious effects of the incompatibility between social demands and biological rhythms in the workplace and how this relationship can affect quality of life. Moreover, it may allow people to think about their career and social organization.

In summary, this study indicated that the misalignment of the circadian and social rhythms is a risk factor for developing depression and there are an amount of epidemiological, clinical and experimental evidence to support a new approach on diagnose and treatment of depressive disorder.

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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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