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Circadian Clocks as Modulators of Metabolic Comorbidity in Psychiatric Disorders

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Abstract

Psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder are often accompanied by metabolic dysfunction symptoms, including obesity and diabetes. Since the circadian system controls important brain systems that regulate affective, cognitive, and metabolic functions, and neuropsychiatric and metabolic diseases are often correlated with disturbances of circadian rhythms, we hypothesize that dysregulation of circadian clocks plays a central role in metabolic comorbidity in psychiatric disorders. In this review paper, we highlight the role of circadian clocks in glucocorticoid, dopamine, and orexin/melanin-concentrating hormone systems, and describe how a dysfunction of these clocks may contribute to the simultaneous development of psychiatric and metabolic symptoms.

Introduction

Our environment is characterized by daily recurring changes caused by the cyclic rotation of the earth. In order to optimally adjust their behavior, metabolism, and physiology to such predictable regular environmental changes, most living beings evolved internal timekeeping systems, so called circadian clocks. In mammals, a complex network of molecular clocks regulates circadian rhythms of behavior (e.g. sleep/wake cycles, mood regulation or food intake), metabolism (e.g. fat and glucose metabolism or energy expenditure), and physiology (e.g. stress response, hormone secretion or blood pressure). Circadian rhythm disturbances have been linked to individual psychiatric and metabolic disorders, and polymorphisms in clock genes have been associated with increased incidence of obesity in mood disorders [1, 2], but circadian aspects of such disorders have not been considered previously in an integrated manner. Since circadian clocks regulate brain functions that control mood, cognitive and metabolic processes, disturbed circadian rhythms may contribute to the frequent psychiatric and metabolic comorbidity in many patients. The aim of this review is to summarize the connections between disturbed circadian clocks, psychiatric disorders, and metabolic diseases. We focus on three fundamental systems, the stress axis, the motivation and reward system, and the orexin/melanin concentrating hormone (ORX/MCH) neuronal network. All three systems are closely intertwined with the circadian clock and, when disturbed, contribute to the development of psychiatric as well as metabolic disorders. Treating and preventing disturbances of circadian clocks in patients suffering psychiatric and metabolic symptoms may be a central element for therapies targeting both disorders concurrently.

General Organization of Circadian Clocks

Almost all organisms evolved endogenous circadian (ca. 24 hr) clocks in order to adapt to cyclically recurring conditions across the 24 hr light-dark cycle [•3]. At the cellular level, the circadian system is a cell-autonomous timekeeping mechanism based on autoregulatory transcriptional–translational loops (TTLs) based on delayed negative feedback. The “positive limb” of the core TTL consists of the transcriptional activators BMAL1 (ARNTL), CLOCK, and NPAS2, which heterodimerize and bind E-box promoters of the transcriptional repressor genes

CRY1/2 and *PER1/2/3*. PER and CRY proteins form the "negative limb" of the loop by eventually inhibiting BMAL1/CLOCK/NPAS2 and thereby their own transcription. Other components, such as RORA/B/C (activators) and REV-ERBα/β (inhibitors) modulate oscillations of core clock gene expression [4]. Clock gene transcription factors also drive rhythmic expression of many "clock-controlled genes" (CCGs) not essential for the core clock mechanism itself. In fact, ~10–20% of the genome is rhythmically expressed in each tissue, and ~50% of all genes are rhythmically expressed in one tissue or another [5, 6]. As clock outputs, CCGs directly or indirectly regulate numerous physiological processes, from homeostatic control to behavior, ensuring optimal synchronization between biological functions and the environment over the course of the day. In this way, the circadian system has influence over a wide range of physiological processes, including many that influence metabolism, brain function, and behavior [•3, 7].

In mammals, circadian clocks throughout the brain and body are organized in a hierarchical fashion and are mainly controlled by the brain's central pacemaker, the suprachiasmatic nucleus (SCN), which is localized in the anterior hypothalamus [••8]. The SCN is synchronized to the environment by light, the main *Zeitgeber* (German: *time giver*), through the retino-hypothalamic tract. By neuronal efferent projections directing oscillatory changes in body temperature, endocrine signals, and behavior, the SCN controls circadian rhythms of peripheral clocks, ensuring that physiological processes throughout the body are optimally synchronized.

Metabolic comorbidity in Psychiatric Disorders

Major psychiatric disorders such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are associated with increased risks of metabolic disturbances: obesity, diabetes mellitus type 2, hypertension, and hyperlipidemia [1, 9-•13]. This cluster of symptoms, commonly known as Metabolic Syndrome [14], increases cardiovascular risk and therefore mortality in psychiatric patients [12, 15, 16]. Antipsychotics, mood stabilizers, and antidepressants used to treat psychiatric disorders have metabolic side effects, but metabolic disturbances in psychiatric patients also occur independently of drug effects. For instance, dyslipidemia and insulin resistance may precede start of medication in SCZ [17-19]. The close

relationship between psychiatric disorders and metabolic disturbances has led to the concept of a "metabolic mood syndrome", positing the existence of common biological mechanisms underlying both conditions [20-23]. Despite evidence of shared risk and overlapping pathophysiology, there is only a limited understanding of the specific biological mechanisms predisposing patients to comorbidity of psychiatric and metabolic disorders. Factors such as regulation of reward, chronic stress, and energy utilization have been proposed [24, 25], but the causal interactions among these variables remain poorly understood [13].

Disturbed Circadian Clocks as the Basis of Metabolic and Psychiatric Disorders

Disturbed biological rhythms such as those seen in sleep disorders (e.g. circadian rhythm sleep disorder and sleep apnea) and shift workers have been shown to elevate the risk of both metabolic and psychiatric disorders, including obesity, type-2 diabetes, depression, and suicide [26-31]. Therefore, we hypothesize that the circadian clock system may serve as a central modulator of higher brain functions and metabolism by coordinating key systems and physiological processes, such as the reward system, the stress response, and energy utilization; and that disturbed brain clocks may alter fundamental metabolic, cognitive, and affective functions. Although clocks in the liver, adrenals, pancreas, and other endocrine organs play crucial roles in metabolic processes at the local level, they are all controlled by central clocks in the brain [32]. As a consequence, genetic or environmental perturbations of clock function in brain areas critical for regulation of energy balance, arousal, and motivated behavior may contribute to frequent co-morbidity between psychiatric and metabolic disorders (Figure 1).

Circadian Disruption in Psychiatric Disorders

Perturbed rhythms are core features of psychiatric disorders.

Disruption of biological rhythms is a hallmark of several neuropsychiatric disorders including MDD [33, 34], BD [33, 35], SCZ [36], and substance use disorders [37]. Patients with psychiatric disorders often show perturbations in rhythmic processes like the sleep-wake cycle, appetite, social interaction, activity, and endocrine function [33, 34, 38]. For example, many depressed patients display sleep disturbances, lower amplitude of circadian temperature rhythms, and

abnormal circadian pattern of cortisol secretion [39]. Similarly, bipolar patients show highly variable daily activity and sleep timing and altered body temperature and melatonin secretion rhythms [40]. Conversely, environmental perturbation of circadian rhythms, e.g. caused by shift work, disrupts sleep and eating patterns [41, 42], and has been linked to increased risk of MDD and sleep disorders. Chronotherapeutic interventions such as bright light [43-45], sleep deprivation [46, 45] and shifts of sleep timing [45] have been shown to produce antidepressant effects. Supporting the role of circadian rhythms in mood regulation and other brain functions, candidate gene studies have linked the clock with a number of psychiatric disorders [34, 47, 48].

Animal models of clock dysfunction.

Animal models carrying mutations in clock genes often show behaviors comparable to human symptoms of depression or mania [49]. The best studied clock gene model of a mood disorder is the *Clock-Δ19* mouse [50], which carries a dominant-negative mutation in the essential circadian clock gene *Clock*, and displays manic-like behavioral features of hyperactivity, impulsivity, increased preference for psychostimulants and decreased sleep. When treated with the mood stabilizer lithium, the majority of these behavioral features are normalized [51]. Mutations in other clock genes also produce various affective or cognitive disturbances in mice: *Per1*$^{Brdm1-/-}$ mutant mice display a depression-like phenotype, and *Cry1*$^{-/-}$*; Cry2*$^{-/-}$ mutant mice display higher anxiety levels, sensitivity to psychostimulant drugs, and perturbed cognitive functions such as recognition memory [49].

Circadian Disruption in Metabolic Disorders

Circadian disruption increases metabolic risk in humans.

Under ideal conditions, external and internal timing cues are synchronized and contribute to the coordination of physiological processes throughout the body. However, when the relationship between timing cues such as food and light is altered, inputs to the clock may become misaligned. Feeding time affects the phase of the clocks in peripheral tissues, which can uncouple rhythms of peripheral metabolic processes from the primarily light-driven SCN

clock [52]. As a consequence, eating at inappropriate times was shown to contribute to weight gain and the development of symptoms related to diabetes and cardiometabolic syndrome in rodents and humans [53-••55]. Since such effects are independent of total daily food intake, it was hypothesized that the loss of coordination between the central clock and subsidiary clocks in peripheral clocks in different organs and presumably in different brain nuclei may cause disrupted energy utilization and metabolic dysfunction [••55-58]. Accordingly, circadian misalignment based on sleep deprivation, night time feeding, exposure to light at night, and shift work all increase the risk of obesity, type 2 diabetes and cardiovascular disease [1, ••55, 59, 60].

Circadian regulation of neuroendocrine function.

Circadian regulation of neuroendocrine systems has been shown in rodents and humans [59, 61]. The expression and regulation of many rate-limiting enzymes, transporters, and receptors (and other key components) of processes such as digestion/absorption, hormonal secretion, glucose and lipid homeostasis are under circadian control [57, 62]. In the liver, an organ with a major role in the coordination of energy utilization, local circadian clocks, together with inputs from the SCN central clock and from nutritional signals, coordinate glucose synthesis and storage [••63]. The pancreas releases insulin in response to nutritional challenges but also according to a circadian oscillation; as a result, there is variation in glucose tolerance and insulin action across the day [1, 64]. CLOCK and BMAL1, core components of the clock machinery, along with Rev-erbα/β and Rorα/β, have major roles regulating gluconeogenesis and lipid metabolism throughout the day [57, ••63, 65]. Adipose tissue activity, such as lipolysis, lipid biosynthesis, and release of the adipose-derived satiety hormone leptin is also under circadian control [61].

The clock as a metabolic sensor

Food and metabolic cues contribute to the regulation of circadian clocks [7]. Meal schedule alterations can reset peripheral clocks such as in the liver, thereby uncoupling peripheral clocks from the SCN. This has been proposed as a cause of obesity and other metabolic disorders [59,

66]. Many cellular metabolic sensors act directly on core components of the clock, adjusting biological timing with metabolic status. For instance, SIRT1 is a class III histone deacetylase (HDAC) that detects NAD^+, an oscillating metabolite that reflects the energy level and the redox state of cells [7, 64]. SIRT1 is under regulation of metabolism related processes such as eating/fasting and has an impact on insulin sensitivity [64]. SIRT1 also stabilizes BMAL1/CLOCK heterodimers and PER2 protein, thereby linking metabolic state directly to the circadian clock [67]. Another cell energy status sensor, the heterotrimeric protein kinase AMP kinase (AMPK), directly modifies circadian clock components such as CRYs in response to AMP:ATP ratio variations caused by daily fasting/feeding cycles [68].

Circadian disruption in animal models.

Wild-type mice fed a high-fat diet exclusively during the rest period have accelerated weight gain compared with animals fed during the active period of the circadian cycle [53], whereas restricting feeding to the active period ameliorates metabolic abnormalities in these animals [69, 70]. Moreover, mice carrying clock gene mutations develop metabolic abnormalities [48]. BMAL1-deficient mice, for example, present deficient glycemic control and perturbed lipid mobilization [61, 65].

Clock gene mutations affect mood-related behavior and metabolism in mice

Interestingly, some clock gene mutations in mice lead to changes in both mood-related behavior and metabolic disorders (Table 1). While many mice with mutated clock genes have been characterized for metabolic or behavioral phenotypes, only a few have been characterized for both phenotypes. As described above, *Clock-d19* mice show mania-like behavior and metabolic abnormalities [51, 71]. *Clock-d19* mice are hyperphagic, and the timing of their feeding behavior lacks a normal circadian pattern, both of which may contribute to their obese phenotype. In addition, their glucose and lipid metabolism is disturbed, resulting in hyperglycemia, hypoinsulinemia, and hyperlipidemia. Like the *Clock-d19* mice, $Per2^{Brdm1-/-}$ mice also show a mania-like behavior, arrhythmic food intake, hyperphagia, and, at least in the first four months of their life, increased body weight [72-75]. However, unlike *Clock-d19* mice, they

display hypoglycemia and increased glucose metabolism. Like *Per2*$^{Brdm1-/-}$ mice, *Per1*$^{Brdm1-/-}$ mice are hyperphagic and display increased glucose metabolism, but show depression-like behavior and are leaner than wild-type mice [72, 73].

Mutations of the *Cry1* and *Cry2* genes also lead to mood-related behavior and metabolic phenotypes. *Cry1*$^{-/-}$ mice show anxiety-like behavior [76]. However, compared to WT controls, the loss of *Cry1* protects them from obesity under high-fat diet (HFD) conditions [77]. *Cry2*$^{-/-}$ mice show anxiety- and depression-like behavior [76, 78], but their body weight is comparable to WT mice under normal diet and HFD [77]. The loss of either *Cry1* or *Cry2* leads to arrhythmic feeding behavior and impaired glucose tolerance [79]. When both *Cry* genes are deleted, mice also exhibit anxiety-like behavior and metabolic disturbances. Although *Cry1*$^{-/-}$*; Cry2*$^{-/-}$ double mutants are hypophagic, they gain more weight under HFD than WT mice. Their obese phenotype under HFD may be explained by their metabolic abnormalities, including hyperinsulinemia, hyperglycemia, impaired glucose tolerance, insulin resistance, and increased lipid uptake [79, 80].

These studies show that genetic perturbations of circadian rhythms simultaneously alter both mood regulation and central metabolic functions. Effects across multiple clock genes argue against an incidental non-circadian pleiotropic effect. It is not yet clear whether the metabolic phenotypes in these mice are based on disturbed rhythms in the brain or in peripheral tissues (e.g. liver or white adipose tissue). However, the co-ocurrence of both mood-related behavior and metabolic phenotypes suggests a dysfunction of brain clocks.

The circadian clock synchronizes motivated behavior with homeostatic state.

In order to synchronize behavior with daily changes in the environment, a timekeeping mechanism is required to coordinate neurophysiological processes such as cognition, arousal, motivation, reward, and stress response, processes that are disturbed in most psychiatric disorders. The hypothalamus is an integrated energy sensing center capable of integrating such processes with metabolic status [81] and circadian cues. The interconnectivity of systems in

brain areas such as the lateral hypothalamus (LH), the SCN, and midbrain structures is mediated by a number of neuropeptides and hormones, including dopamine (DA), glucocorticoids (GC), hypocretin/orexin (ORX), melanocyte concentrating hormone (MCH), and leptin. Importantly, all of these components are simultaneously key regulators of cognitive/affective function and metabolism. Their concerted action is orchestrated by the circadian system, ensuring that cognitive function and behavioral output are in phase with proper homeostatic state [••82]. For example, for optimal Darwinian fitness it is important that behavioral arousal, feeding, and propensity to explore the environment are synchronized with the right phase of the daily cycle.

In the following paragraphs, we will highlight the overlap of cognitive/affective and metabolic circuitries and the importance of proper circadian regulation among these different systems in order to simultaneously coordinate behavior and metabolic outputs (Figure 2).

The Stress System: Glucocorticoids

The hypothalamic–pituitary–adrenal (HPA) axis is involved in regulating metabolic activity in response to environmental demands and stress. GC release is under control of the HPA axis, which is strongly regulated by the circadian system. Consequently, GC release shows a pronounced circadian rhythm, with peak levels in the early morning, promoting arousal after sleep and gluconeogenesis after overnight fasting [81]. The brain regions controlling this process include the paraventricular nucleus of the hypothalamus, which releases corticotropin-releasing hormone (CRH) to signal the anterior pituitary to release adrenocorticotropic hormone (ACTH) in an oscillatory manner. The adrenal glands respond to ACTH by stimulating the synthesis of GC and its release into the systemic circulation. GCs then inhibit their own release through a negative feedback loop. Accumulating evidence indicates that the circadian clock system and HPA axis interconnect at multiple levels [83-••85]. The molecular clock can control rhythmic expression of glucocorticoid receptors (GR) in a tissue-specific fashion, as well as GR sensitivity across the day [83]. Conversely, GCs feedback on the clock, having an important role in synchronizing peripheral oscillators [83, 84] via GC responsive elements (GREs) in the promoter regions of several clock genes.

However, not all GC release is regulated in a circadian manner. In response to low blood sugar or sympathetic activation, GCs are also released in a pulsatile manner. GCs induce expression of phosphoenolpyruvate carboxykinase 1 (Pck1), a rate-limiting gluconeogenic enzyme in the liver, therefore increasing gluconeogenesis. Glucose homeostasis is achieved in part via suppression of Pck1 expression by the CRY genes [79]. Chronic activation of pulsatile GC release in response to stress can alter the circadian release of GCs, and this aberrant regulation of the HPA axis has been identified as a common pathway in both metabolic and neuropsychiatric syndromes, such as diabetes, obesity, and mood disorders [83, 86]. Abdominal obesity is associated with abnormal diurnal variation of GC release, with increased basal and stress-induced GC levels [87]. Similarly, MDD patients often display hypercortisolism [88] and hyperglycemia [89]. Another common feature of depression is loss of HPA feedback inhibition, revealed by testing with GC agonists like dexamethasone [90]. Importantly, therapeutic interventions that alleviate depression often reverse elevated cortisol and ameliorate hyperglycemia as well [•13, 91-93].

Interaction of the HPA axis with Leptin

HPA axis activity is fine-tuned by leptin, an adipose tissue-derived hormone with a major role in feeding behavior and energy homeostasis. Leptin binds to its receptors in the hypothalamus and midbrain, providing information about the availability of peripheral energy stores [94]. Leptin release is under circadian control, displaying circadian oscillations that are antiphasic to cortisol [95]. High leptin levels inhibit GC actions in the medial hypothalamus [96], and thereby suppress appetite and stimulate energy expenditure. When fat stores are reduced, lower leptin levels enhance GC release, activating brain circuits that drive food intake [97]. These data suggest that the interaction between leptin and cortisol rhythms represents a relevant pathway by which neuroendocrine circuitry integrates the stress response and energy homeostasis [95, 98]. Thus, impaired HPA–leptin interactions may contribute to the development of metabolic disruption [58, 95]. Furthermore, it has been proposed that leptin´s negative feedback on the HPA axis and subsequent downregulation of cortisol hyper-reactivity may have an antidepressant effect in animal models [94] and in humans [99, 100]. Dysfunctional leptin

activity at its midbrain and hypothalamic receptors may therefore contribute to the comorbidity of obesity and mood disorders [87]. Because the circadian clock coordinates both leptin release and activity of the HPA axis, disturbances of circadian rhythms may well contribute to co-morbid metabolic and psychiatric disorders by changing energy expenditure and food intake patterns as well as the ability to react appropriately to stress [84].

The motivation and reward system: dopamine

Dysfunction of reward processing and motivation are central features of affective disorders, SCZ, and substance use disorders [17, •101-103]. The key components of the reward circuit are the dopaminergic neurons of the midbrain ventral tegmental area (VTA), which project to the nucleus accumbens (NAc) and to the medial prefrontal cortex (mPFC). The hippocampus, amygdala, and other brain regions are also key components in the circuits regulating reward and motivated behaviors, including hedonic feeding behavior.

Dopamine and the clock

Reward processing is under circadian control, with reward salience varying throughout the day. Healthy humans show diurnal variation in mood [104, 105] and reward [106], and this process may be perturbed by psychiatric illness, stress, or misalignment of circadian cues. For example, drug-seeking behaviors and mesolimbic dopaminergic activity show prominent diurnal variation in models of psychostimulant dependence [26, 107]. In VTA DA neurons, the CLOCK/BMAL1 complex regulates rhythmic expression of tyrosine hydroxylase (TH) [108, 109], the rate limiting enzyme in the synthesis of DA. In target regions receiving dopaminergic inputs from the VTA, the sensitivity of DA receptors is also under circadian control [110].

Conversely, the reward system also regulates the circadian system. Reward presentation (such as food and psychostimulants) is capable of influencing circadian timing [111], and psychostimulants affect clock gene expression in the mesolimbic system, circadian behavior, and the molecular activity of the clock [38, 102, 112]. Moreover, DA enhances the activity of the BMAL1/CLOCK complex and induces *Per1* expression [113].

The reward system intersects with the HPA axis and metabolic regulators.

Midbrain DA circuitry has connections to the HPA axis, connecting the rhythmic reward system with the rhythmic stress response system. TH expression is controlled by GC hormones, and exposure to repeated or chronic stress is associated with increased TH expression. In addition, elevated CRF or GC receptor inactivation affects the sensitivity of DA-dependent reward pathways [38, 83]. Evidence indicates that leptin´s modulation of feeding behavior is in part due to its action on VTA DA neurons. Leptin inhibits the firing of DA reward neurons, resulting in reduced motivated food intake [••114]. Conversely, DA is also involved in the control of leptin release in humans [115]. By promoting hedonic drive and exploration of the environment, DA serves as a mediator that couples energy sensing pathways with voluntary energy expenditure [116]. Accordingly, in humans, DA antagonists reduce locomotor activity and promote hyperlipidemia and hyperglycemia independently of weight gain [117], whereas stimulant medications such as amphetamines promote weight loss [118].

The orexin/melanin-concentrating hormone neuronal system

In the LH two distinct neuronal populations produce MCH and ORX, respectively. The complementary functions of these two signaling molecules are crucially involved in regulating metabolism, feeding behavior and sleep/arousal. ORXs stimulate arousal, regulate glucose- lipid homeostasis, and increase energy expenditure [119, 120]. Furthermore, disruption or loss of ORX/MCH signaling is associated with obesity and diabetes mellitus [119, 120]. ORXs also participate in short-term regulation of food intake. The MCH neurons participate in sleep induction and maintenance, as well as in the long-term balance between hunger and energy expenditure, thereby regulating body weight [121, 122]. The ORX/MHC system and its downstream action is under control of the circadian clock [48]; lesions of the SCN eliminate ORX´s daily rhythm [123, 124], and *Clock*-mutant mice exhibit low ORX levels without a daily rhythm [71]. On the other hand, mice placed in constant light exhibit a robust circadian pattern of ORX activation, which may be involved in dark pulse resetting of the SCN circadian clock [125].

The ORX/MCH system appears to play a role in mood regulation as well, and the ORX/MCH system is discussed as a potential target for new antidepressant treatments [102, 126-128]. Both hypoactivity and hyperactivity of orexin signaling pathways have been found to be associated with depression [128]. Administration of MCH to the dorsal raphe nucleus in rats elicits depression-like behavior in the forced-swim test [129], whereas MCH receptor antagonists have anxiolytic/antidepressant properties, inhibit cocaine reward, and reduce food intake and body weight [129, 130]. CRF activates ORX neurons, indicating that the ORX/MCH system may be responsive to arousal and stress response systems [131], and orexins in turn also activate GC release [132]. In accordance with this idea, ORX-deficient mice show impaired "fight-or-flight" behavior [133]. Among other disrupted rhythms, obese and mania-like *Clock-d19* mice lose ORX oscillations [71]. But it remains unknown if the loss of ORX rhythms contributes to their obese and mania-like phenotype. In humans, ORX rhythms of depressed patients show slightly lower amplitudes [134]. Although these results suggest connections of the ORX/MCH system to the circadian system, further investigation is needed to fully understand the actual function of circadian ORX/MCH oscillations in the regulation of mood and energy metabolism.

The ORX/MCH system also has a bidirectional connection with the mesolimbic DA system, again demonstrating convergence between the energy homeostasis and reward systems. ORX projections to the VTA enhance DA release, promoting arousal, locomotion, and goal-directed behavior such as seeking drugs of abuse or palatable food [135]. In limbic structures such as the NAc, the MCH receptor is co-expressed with DA receptors [136] and acts as an important regulator of mesolimbic DA tone and responses to the rewarding effects of drugs and alcohol [137]. This regulation of DA tone by the ORX/MHC system is mediated by leptin [137, •138], providing information about peripheral energy status, and also, at least in part, by inputs from the master clock in the SCN [139]. In turn, ORX/MCH neuronal firing is also regulated by dopaminergic inputs [122, ••140].

Collectively, these data show an extensive interconnection between DA circuits and GC with ORX/MCH neurons, integrating circadian cues [125, 141, 142] with homeostatic control [143, 144], stress response [•138], and motivation [121, 145]. Importantly, the circadian clock has a central role regulating each of these systems and ensures proper synchronization among them. Thus, the circadian system is poised to play an essential role in synchronizing physiological processes and arousal state with higher brain functions, behavior, and the environment.

Conclusion

In this paper, we reviewed the central role of the clock in coordinating brain systems that regulate mood, reward, stress, and energy homeostasis, emphasizing the interconnections among these neurobiological circuits. We highlighted how optimal communication among stress, reward, and orexin systems require an intact circadian clock. Based on these observations, we propose that dysfunction in the clock may serve as an important mediator of metabolic co-morbidity in human patients with psychiatric disorders.

In individuals with genetic or environmental risk factors, disturbed synchronization among brain and peripheral circadian clocks may result in alterations in physiological timing that disturb energy regulation, cognitive functions, and behavior, ultimately leading to both metabolic and psychiatric disorders. Since metabolic and psychiatric features interact in the onset and progression of illness in affected patients, we propose that studying these processes from the perspective of biological timing may allow for the development of more comprehensive disease models, likely improving diagnosis and treatment strategies in the future.

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Figures

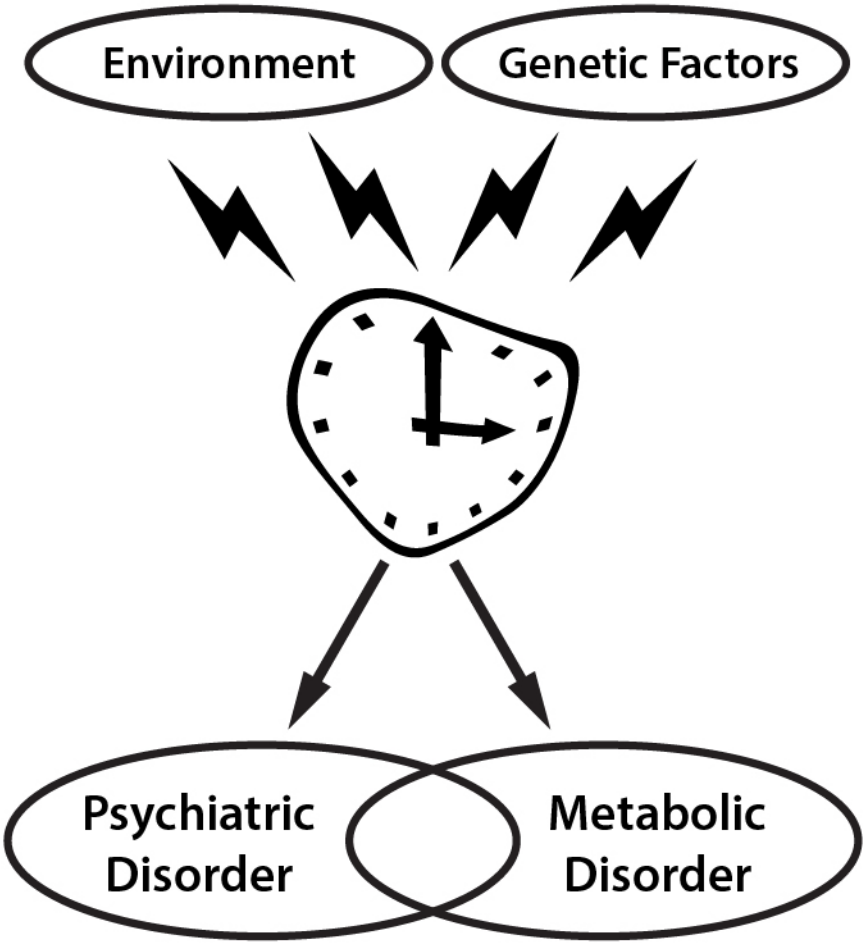

Figure 1: *Environmental and genetic factors can disturb circadian clocks throughout the brain and the rest of the body. Dysfunctional circadian rhythms may contribute to the simultaneous development of psychiatric and metabolic disorders.*

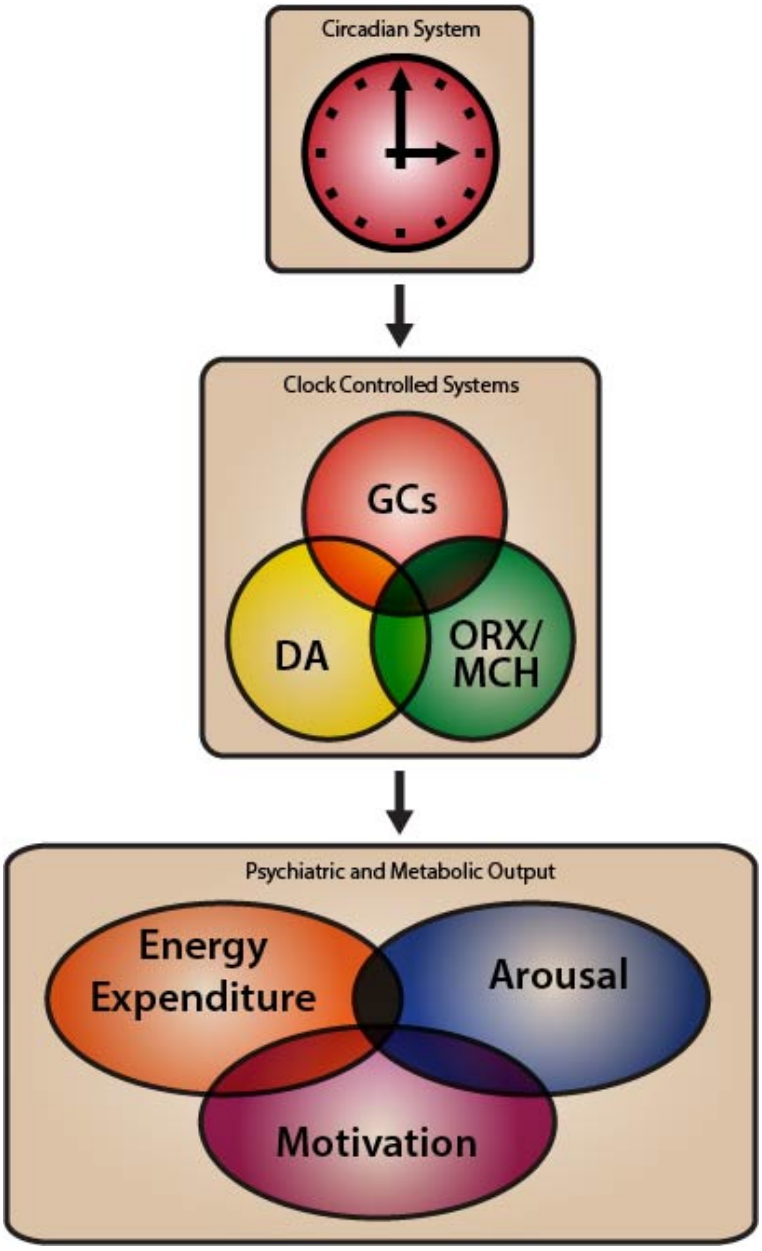

Figure 2: *By controlling glucocorticoids, dopamine, and orexin/MCH, the circadian clock regulates key facets of metabolism and higher brain functions, such as energy expenditure, arousal, and motivation.*

Table 1: Effects of Clock Gene Mutations on Mood, Food Intake, Glucose and Fat Metabolism, and Body Weight.

Genes	Mutants	Simplified mood phenotype	Feeding rhythm	Food intake	Glucose Metabolism	Fat Metabolism	Body weight	References
Clock	*Clock-d19*	Mania-like	Arrhythmic	Hyperphagic	Hyperglycemia, Hypoinsulinemia	Hyperlipidemia	↑	Roybal, 2007; Turek, 2005
Per	*Per1*$^{Brdm1-/-}$	Depression-like	N.D.	Hyperphagic	Elevated glucose metabolism	N.D.	↓	Abarca, 2002; Dallmann, 2006
	Per2$^{Brdm1-/-}$	Mania-like	Arrhythmic	Hyperphagic	Hypoglycemia, Elevated glucose metabolism	N.D.	↑ (young mice)	Abarca, 2002; Dallmann, 2006; Yang, 2009; Carvas, 2012
Cry	*Cry1*$^{-/-}$	Anxiety-like	N.D.	=	Impaired glucose tolerance	Reduced fat mass	↓ (HFD)	De Bundel, 2013; Lamia, 2011; Griebel, 2014
	Cry2$^{-/-}$	Anxiety-like Depression-like	N.D.	N.D.	Impaired glucose tolerance	N.D.	=	De Bundel, 2013; Savalli, 2015; Lamia, 2011; Griebel, 2014
	Cry1$^{-/-}$*; Cry2*$^{-/-}$	Anxiety-like	Arrhythmic	Hypophagia	Hyperglycemia, Impaired glucose tolerance, Hyperinsulinemia, Insulin resistance	Increased lipid uptake	↑ (HFD)	De Bundel, 2013; Lamia, 2011; Barclay, 2013

Note. N.D. = not determined; "=" = no change; ↕ = increased/decreased; HFD = high fat diet.