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The concept of "metabolic jet lag" in the pathophysiology of bipolar disorder: implications for research and clinical care

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Abstract

Bipolar disorder (BD) is a potentially chronic mental disorder marked by recurrent depressive and manic episodes, circadian rhythm disruption, and changes in energetic metabolism. "Metabolic jet lag" refers to a state of shift in circadian patterns of energy homeostasis, affecting neuroendocrine, immune, and adipose tissue function, expressed through behavioral changes such as irregularities in sleep and appetite. Risk factors include genetic variation, mitochondrial dysfunction, lifestyle factors, poor gut microbiome health and abnormalities in hunger, satiety, and hedonistic function. Evidence suggests metabolic jet lag is a core component of BD pathophysiology, as individuals with BD frequently exhibit irregular eating rhythms and circadian desynchronization of their energetic metabolism, which is associated with unfavorable clinical outcomes. Although current diagnostic criteria lack any assessment of eating rhythms, technological advancements including mobile phone applications and ecological momentary assessment allow for the reliable tracking of biological rhythms. Overall, methodological refinement of metabolic jet lag assessment will increase knowledge in this field and stimulate the development of interventions targeting metabolic rhythms, such as time-restricted eating.

Review

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Introduction

Bipolar disorders (BDs) are a group of common, complex, and multidimensional mental disorders that affect mood, cognition, and behavior. They are classified into two main types, BD type I and BD type II. BD type I is characterized by the presence of one or more manic episodes, whereas BD type II includes both a hypomanic episode and a major depressive episode. Depressive components of either subgroup are the most prevalent and difficult to treat.[1,2] Depression in BD is more likely to be accompanied by atypical symptoms, such as increased sleep and appetite, as well as fatigue.[1] The implications for those who are affected by these disorders are significant, as it impacts their physical and mental health while also being inconsistent by nature which complicates both living and treating the disorder. Ideal treatment strategies should address both manic and depressive groups of symptoms, treat acute episodes, prevent relapses and recurrences, restore functioning, and cause no or limited side effects. These goals are not always achieved by individuals living with BD, even with the adoption of evidence-based approaches.[3]

Although frequently referred to as a mood disorder, the mental and behavioral manifestations of BD go far beyond mood. Individuals with BD exhibit widespread dysfunction across multiple central and peripheral systems including abnormalities in arousal, attention, cognition, neuroendocrine function, and even neurostructural changes.[4] Another dimension of BD psychopathology is circadian rhythm disruption, with changes in the sleep–wake cycle being the most replicated.[5-7] Most individuals with BD exhibit different degrees of circadian desynchronization in different moments of their illness trajectory, resembling "jet lag" via unfavorable side effects such as abnormal sleep, metabolic disturbances, and low energy.[8] In addition, there is a bi-directional relationship between circadian disruption and manic and depressive symptoms, with sleep deprivation being a trigger for manic symptoms and mood episodes being accompanied by circadian dysfunction.[9,10] One of the most robust illness triggers is jet lag itself.[11]

Circadian rhythms are influenced both by the main endogenous biological clock, a distinct group of cells located in the anterior hypothalamus, and by information from both internal and external inputs, via light, sounds, feeding, exercise, and activity scheduling.[12] Neurobiological underpinnings of this association include but are not restricted to genetic factors, chronotypes, presence of sleep disturbances (eg, obstructive sleep apnea), hormones (eg, melatonin), and immune-inflammatory mediators.[5] The genetic control of circadian rhythm maintenance is composed of a molecular feedback loop of approximately 20 genes, known as "clock genes."[13] Studies have suggested a role for the suprachiasmatic nucleus (SCN) and related genes in emotional regulation.[4] In addition, disruptions in circadian rhythm have been implicated in a variety of adverse health effects, including mood and metabolic disturbances.[4,14] Metabolic syndrome is approximately twice as common in BD when compared to the general population and is associated with worsened mood symptoms, reduced treatment efficacy, and an unfavorable clinical course.[15,16] Further, dysfunctional circadian rhythms have been linked to an increased susceptibility to mood switching and treatment resistance.[17] It is evident that a complex and multi-directional relationship exists between synchrony of circadian clocks, metabolic homeostasis, and mood disorders.

The study of energy intake and expenditure in mood disorders represents a unique opportunity to integrate transdisciplinary lines of research, such as chronobiology and metabolic physiology with the goal of improved patient outcomes.[18,19] The objective of this study is to comprehensively review the clinical and mechanistic findings from different lines of evidence suggesting that imbalances in rhythmic regulation of metabolic processes are involved in the pathophysiology of BD and discuss the implications of these findings for research and clinical care.

The concept of metabolic jet lag

"Metabolic jet lag" is a recently introduced concept in the literature, designating a state of dramatic shift in circadian patterns of energy homeostasis, including but not being restricted to hormone release, adipose tissue function, and immune function which is expressed through behavioral changes including irregular sleep and feeding.[20] Under physiological conditions, metabolic rhythms are related to cyclical changes in biochemical pathways which are integral for the body to respond to the environmental changes that happen during night and day cycles.[20] The existence of such changes is thought to provide organisms with a significant evolutionary advantage, as it allows the body to anticipate nutrient needs and guarantee optimal energetic capacity during the active hours of the day.[21]

Metabolic jet lag constitutes a desynchronization between external cues and the temporal order of the main circadian clock and has been linked to a variety of detrimental health outcomes. For example, it is well known that shift workers or individuals consistently traveling between time zones are disproportionately affected by coronary disease, obesity, and metabolic syndrome.[22-24] Conversely, individuals affected by increased weight and obesity are more prone to circadian rhythmic alterations.[25] The bi-directional link between circadian rhythmicity and metabolic health adds to the complexity in understanding the underlying mechanisms.

Several factors are involved in the pathophysiology of metabolic jet lag. The most relevant are described in the following sections.

Genetic predisposition

It is known that BD is a heritable mood disorder and recently it has been suggested that circadian disruption, a risk factor for BD, may also be heritable.[4] The circadian rhythm is regulated by a variety of transcription and translation pathways, described in detail elsewhere.[20,26] Although specific genetic variation predisposing to metabolic jet lag has yet to be identified, genetic mutations in multiple clock genes are known to result in an array of health effects, including metabolic abnormalities. For example, deletion of the melatonin receptor has been shown to result in systemic insulin resistance, increased fat mass, leptin resistance, and diabetes in mice. In addition, mice lacking *BMAL1* or the leptin receptor demonstrated weight gain and a shifted rhythm of food intake.[27] Studies in humans have also outlined multiple clock gene polymorphisms which are linked to obesity and metabolic syndrome including *BMAL1*, *CRY2*, and the melatonin receptor.[26]

It is also possible that a genetic predisposition to metabolic or sleep dysfunction may result in circadian rhythm abnormalities, further exacerbating metabolic jet lag in the afflicted individual. For example, mutations in *PER2* have been associated with sleep–wake disorders which are more commonly diagnosed in individuals with BD compared to the general population.[28,29] Specifically, delayed sleep–wake phase disorder results in a loss of synchrony between sleep–wake and day–night cycles and is associated with potentiated relapse and the onset of mania.[29]

Irregular eating rhythms

The timing of energy intake is an important peripheral cue, influencing the regulation of circadian function. Adjusting regular meal times can reset peripheral clocks, placing them out of sync with the SCN.[30] In fact, a disorganized eating pattern is both an indicator of and contributor to metabolic jet lag which is related to a higher risk of obesity, metabolic syndrome, diabetes mellitus, and even some forms of cancer.[31-33]

Eating rhythms have been shown to influence body weight and energy metabolism, even when the same amount of food is consumed because energy balance does not promote expenditure during the night hours and therefore calories are stored as fat.[34] Weight gain and increased risk of cardiometabolic diseases have been observed regardless of overall food intake when eating patterns were out of sync with the SCN clock.[20,27,30] Rodent studies have demonstrated that restoring meal timing during the active phase improves metabolic abnormalities associated with jet lag and reduces obesity, indicating a protective effect of routine feeding.[35]

Although exact mechanisms underlying the adverse effects of irregular eating rhythms remain unknown, research indicates that meal timing and physiological processes of the circadian cycle may interact to influence how metabolic systems respond to meals differently over the 24-hour day. For example, human subjects who consumed a high-calorie breakfast showed reduced weight gain, adipose tissue, fasting glucose, triglycerides, and insulin compared to subjects who consumed a high-calorie dinner late in the evening when melatonin levels are highest.[27] Additionally, a cross-sectional study of college-aged individuals demonstrated that participants who consumed most of their calories closer to the onset of melatonin secretion at night had more body fat than individuals who consumed most of their calories in the day.[36] Furthermore, irregular eating times associated with shift work have been

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repeatedly linked to obesity, abnormal insulin functioning, and metabolic syndrome in the literature.[22,37-40]

Abnormalities in hunger, satiety, and hedonic aspects

In humans, the behavior of obtaining food and eating is highly complex and requires the integration of multiple systems. For example, it requires the interpretation of interoceptive inputs, such as the sensations of hunger and satiety, which fluctuate dynamically over time based on the energy status.[41] It also has to be integrated with the hedonic aspects of eating, which are partially independent of the energetic needs.[42] Viewed through an evolutionary lens, obtaining food requires activity to facilitate the gathering of food (eg, foraging) and the navigation of associated risks (eg, hunting). Eating according to the socially determined times also requires learning and memory which are at least partially dependent on hippocampal activity, through the integration of past experiences with current signals from exteroception and internal energy balance. The hypothalamus plays an important role in learned control of eating behavior, highlighted by the inability of subjects with bilateral hippocampal damage to interpret interoceptive inputs such as hunger and satiety.[41] A disconnect between energy requirements and the interpretation of hunger was observed as maintained hunger ratings throughout eating phases. This confirmed that these systems can process independently but require communication to operate effectively. Overall, negative health consequences arise if humans do not receive or interpret energy requirements sufficiently, including metabolic jet lag.[41]

Nutritional content

Although the timing of meals is important to maintaining metabolic synchrony with the circadian clock, studies have also indicated an important role of nutritional content. Specifically, diets with a high content of fat and sugar have been linked to disturbances in circadian rhythms. In animals, 1 week of high-fat diet was sufficient to cause a prolongation of the circadian period compared to a regular diet, an effect that was independent of changes in body weight.[43] More recently, studies have indicated an underlying mechanism for this observation in which the nutritional content of food has been shown to alter the expression of clock genes. For example, obesity caused by a high-fat diet was shown to alter the expression of clock genes in the liver and kidneys.[27] In addition, disruption of intestinal L cells and pancreatic beta cells was shown in mice following obesogenic feeding, providing some explanation for the development of metabolic abnormalities on a high-fat diet.[44]

Gut microbiome health

The gut microbiome may be a factor whereby diet and meal timing impact metabolic and circadian dysfunction. The composition and functioning of the gut microbiome oscillate with the 24-hour clock. The gut epithelium interacts with different microbes throughout the course of the day and some bacteria are even entrained with melatonin levels.[45] Furthermore, a bi-directional relationship has been proposed in which the microbiome may also influence clock gene expression in response to diet.[46] In particular, a high-fat diet has been shown to reduce microbial diversity and patterns of metabolite production which in turn modulates clock gene expression in hepatocytes. Conversely, germ-free mice demonstrated impaired clock gene expression on both low- and high-fat diets, even when light and dark signals remained intact.[47] Therefore, gut microbiota may mediate the effects of dietary content on circadian abnormalities as the microbiome was needed to see the effects of diet on clock function. Overall, it is evident that both meal timing and composition are important factors in maintaining microbial function and, therefore, circadian alignment.

Sedentary lifestyle

Another facet of lifestyle that may predispose an individual to metabolic jet lag includes insufficient exercise or a sedentary lifestyle which has been linked to the desynchrony between metabolism and the circadian cycle. In humans, physical activity exhibits an approximate 24-hour circadian cycle and acts as a zeitgeber to entrain circadian clocks in peripheral tissues such as skeletal muscle, liver, and lungs. This has been confirmed in both animal and human studies.[48] From an evolutionary perspective, energy metabolism is optimized throughout the day–night cycle to allow humans to travel long distances for food during the waking hours. Conversely, limited physical activity may indicate the body is recovering from an injury or sickness and is associated with inflammatory responses.[49] Therefore, energy expenditure responds to environmental adversity and is also an important external cue for maintaining circadian synchronization.

Sedentary lifestyles are associated with a variety of unfavorable health effects, including cardiometabolic issues such as worsened glycemic control, blood pressure, and triglyceride levels.[50] Sedentary activity is reported to significantly increase glucose and insulin resistance in participants after only 5 days, including a 67% greater insulin response to a glucose load.[51] Exercise is a promoter of health in humans as well as an important circadian entrainment cue. Therefore, the widespread benefits of physical activity are important to consider in resisting the development of metabolic jet lag.[52]

Disturbances in mitochondrial metabolism

Mitochondria are organelles responsible for the generation of energy in eukaryotic cells. Dysfunctional mitochondrial function has been consistently demonstrated in several severe mental disorders, including BD. In fact, BD is often conceptualized as a mitochondrial disorder, where mania and depression are considered states of up- and down-regulation of mitochondrial function, respectively.[53] In addition, the prevalence of BD in mitochondrial diseases is about 20 times higher than in the general population.[54] The mitochondria of individuals with BD demonstrate significant differences in morphology and dynamics when compared with healthy individuals.[18] Early observation of variations of mitochondrial morphology date from 30 years ago, when Uchiyama described that mitochondria from rat hepatocytes changed their tubular structure from the light to dark phase.[55] After this, it was demonstrated that mitochondria continuously fuse and divide, move, and are removed, depending on the energetic needs of the cells.[21] The endosymbiotic theory states that mitochondria were once independent bacteria, consumed by an early eukaryotic cell; therefore, it is plausible that these organelles have their own circadian clock.[56]

Current evidence suggests that mitochondria are both influenced by circadian rhythm and exert effects on biological rhythms. Circadian factors are known to be critical regulators of mitochondrial function and demonstrate an important role in the maintenance of metabolic health.[53] Specifically, changes in the clock genes

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Table 1. Factors Contributing to the Pathophysiology of Metabolic Jet Lag

Type of risk factor	Evidence	Protective factor
Genetic predisposition	• Deletion of melatonin receptor → systemic insulin resistance, increased fat mass, leptin resistance, diabetes • Deletion of *BMAL1* → weight gain, abnormal eating rhythm • Deletion of leptin receptor → weight gain, abnormal eating rhythm • Clock gene polymorphisms in *BMAL1*, CRY2, melatonin receptor → linked to obesity and metabolic syndrome • PER2 mutations → de-synchrony between the sleep–wake and day–night cycles	Lack of genetic predisposition to metabolic dysfunction or circadian rhythm abnormalities
Eating rhythm	• Irregular eating rhythms have been related to a higher risk of obesity, metabolic syndrome, diabetes mellitus, and cancer • Food intake during the resting phase promotes weight gain and obesity	Restoration of routine meal timing during the active phase and fasting during the rest phase
Hunger, satiety, and hedonic aspects	• Disconnect between energy requirements and the interpretation of hunger	Hunger, satiety, and hedonic cues in sync with energy needs
Nutritional content	• Diets high in fat and sugar disturb circadian rhythmicity and alter clock gene expression	Balanced diet, moderate fat, and sugar intake
Gut microbiome	• Gut microbiota mediate the effects of dietary content on circadian abnormalities	Healthy and diverse gut microbiome
Physical activity	• Sedentary lifestyle is associated with cardiometabolic issues, glucose and insulin resistance, worsened glycemic control, blood pressure, and triglyceride levels	Regular exercise
Mitochondrial function	• Changes in clock genes are related to abnormalities in mitochondrial dynamics • Mitochondrial function impacts clock gene expression through AMPK	Healthy mitochondrial function

Abbreviation: AMPK, adenosine monophosphate activated protein kinase.

are related to abnormalities in mitochondrial dynamics, but the opposite also happens. Adenosine monophosphate-activated protein kinase (AMPK) is responsive to AMT/ATP ratios and works to maintain energy balance as well as promoting biogenesis.[21] AMPK provides a link between mitochondrial functioning and clock transcription and gene expression, having the power to destabilize circadian functioning should an imbalance occur.[21] Therefore, specific mitochondrial enzymes and proteins may influence metabolic rhythms associated with changing circadian function and could be of interest as a contributing factor in altered energy homeostasis in BD (Table 1).

BD as a dysregulated energy expenditure illness

A high prevalence of metabolic abnormalities in individuals with BD, especially in those with multiple mood episodes, is well documented.[57] Metabolic abnormalities are frequent in the mood disorder population, with approximately 50% of patients having obesity, diabetes mellitus, and/or insulin resistance.[58,59] Although there is a well-documented influence of iatrogenic and lifestyle factors on metabolic dysfunction in BD, they do not account for all the differences observed.[60] For example, individuals with BD exhibit severe metabolic abnormalities even in the absence of pharmacotherapy.[61,62] It is believed that metabolic dysfunction is a core component of disease pathophysiology and contributes significantly to mortality in individuals with BD, including increased rates of death due to cardiovascular disease when compared with the general population.[59] Understanding the etiology of metabolic abnormalities will allow for the prevention of further disease progression, limiting mortality in these individuals.

Taking these data together, it is not unexpected that replicated evidence indicates that energy metabolism plays a critical role in both normal and abnormal brain function.[60] The human brain constitutes 2% of the body mass yet consumes 25% of the energy substrates,[63] suggesting that changes in energy regulation significantly affect neural function. In addition, evidence indicates that brain energy metabolism plays an important role in human behavior, through the control of both energy intake and expenditure.[64] Certain neural networks including dopamine transmission in cortico-striatal pathways are considered to be a potential mechanism explaining this finding as well as indicators of energy status, such as glucose and insulin. In fact, studies have linked disrupted insulin signaling in the brain with reduced dopamine transmission and disordered mood symptoms.[65]

Research has repeatedly demonstrated that individuals with mood disorders exhibit abnormal brain energy metabolism.[60,66,67] For example, markers of dysfunctional energy regulation have been identified in individuals with mood disorders including increased lactate and lower pH,[68] as well as oscillating energy generation in which body temperature is higher in mania and lower in depression.[69] In addition, reduced cerebral glucose metabolic rates during depressive episodes have been identified in both major depressive disorder and BD.[70]

As a result of dysfunctional energy metabolism in mood disorders, evidence indicates that molecular and cellular pathways mediating energy expenditure are downregulated.[71] Behaviorally, this has been expressed as reduced physical activity during depressive episodes, revealed through accelerometry studies.[72] In addition, individuals with mood disorders exhibit a reduced willingness to expend physical effort for rewards when compared with healthy controls, indicating motivational changes and reward system dysfunction.[73] Recent work has associated this finding with altered peripheral insulin signaling in individuals with depression, although more work is needed to identify a mechanistic link.[74,75] According to the "selfish brain" theory, glucose utilization is prioritized for use by the brain through the inhibition of insulin secretion from the pancreas. This mechanism enhances the uptake of glucose to the central nervous system which is an insulin-independent process.[60] Therefore, reduced physical activity in individuals with altered brain energy regulation may signify another compensatory mechanism acting to conserve energy in states of homeostatic imbalance such as those observed in mood disorders.

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Insulin is a key hormone involved in the regulation of brain energy metabolism, mediating food intake, energy expenditure, adipose tissue accumulation, and peripheral metabolism.[76-78] Brain insulin signaling has also been implicated in the mesolimbic dopamine system and influences brain activity related to reward behavior.[79] Therefore, the actions of insulin demonstrate high relevance to the study of mood disorder etiology.[80,81] In fact, brain insulin resistance has already been described as a potential mechanism for abnormalities in mood.[82] Despite this evidence, to our knowledge, no study has yet to evaluate the relationship between brain insulin signaling and energy expenditure in individuals with BD.

BD as an illness of metabolic let lag

Historically, circadian rhythms of energy regulation have allowed our human ancestors to allocate metabolic resources according to the occurrence of activities across the day and night cycle. The influence of metabolic jet lag is becoming increasingly relevant to humans as we continue to adopt social and personal habits that stray from the daylight cycle and protrude into the resting period. Misalignment between internal physiology and behavior is detrimental to many aspects of human health. The high prevalence and impact of metabolic dysfunction in individuals with BD support the view that metabolic jet lag may be a key aspect of the pathophysiology and disease progression.[83]

Metabolic abnormalities are significantly higher in BD compared to the general population and have been linked to unfavorable illness trajectories.[15] Specifically, laboratory markers indicate elevated serum triglycerides and glycosylated hemoglobin, hyperinsulinemia, insulin resistance, and lowered HDL, compared with healthy controls.[84] These increased blood markers of metabolic syndrome have been associated with decreased treatment efficacy and worsened disease course in BD.[85] Individuals with BD also demonstrate a greater prevalence of obesity when compared with the general population. Obese BD individuals are more likely to have major depressive episodes, accumulate medical conditions, and become treatment resistant.[86] Studies have revealed evidence of structural and neurobiological changes associated with obesity that may contribute to the progression of BD, although more work is needed to identify the exact underlying mechanisms responsible.[87]

Abnormalities in insulin and glucose regulation are also routinely observed in individuals with BD, linked to worsened mood symptoms, and reduced therapeutic efficacy of lithium.[58,88] In fact, a diagnosis of type II diabetes mellitus is three times as common in individuals with BD compared to healthy individuals.[85] As a hormone that acts within brain regions such as the amygdala, hypothalamus, and hippocampus, altered insulin signaling may disrupt the healthy functioning of neural tissues. Specifically, it is thought that reduced insulin sensitivity may lead to neurodegeneration in the aforementioned regions.[89,90] Cognitive impairment has also been linked to insulin resistance in individuals with BD, further supporting this point.[85]

A less-studied circadian somatic change in BD is related to appetite, which can widely differ in hypomanic, manic, and depressive episodes, similar to sleep–wake cycle abnormalities. Recent work has identified circadian desynchronized eating behavior as a prominent subgroup of BD, associated with more severe metabolic comorbidities and mood symptoms.[91] Under physiological conditions, most of us exhibit a rhythmic pattern in eating behaviors. However, patients with BD frequently describe oscillations or abnormalities in their appetite and eating habits, but most of these abnormalities have not been sufficiently explored.[92] Few studies have investigated eating rhythms in individuals with mental disorders, other than anorexia and bulimia, and very few of them were conducted in populations with BD.[93] The regular timing of meals is an important external cue for the circadian system; therefore, appetite changes may promote adverse effects along with circadian misalignment, as depicted in Figure 1.

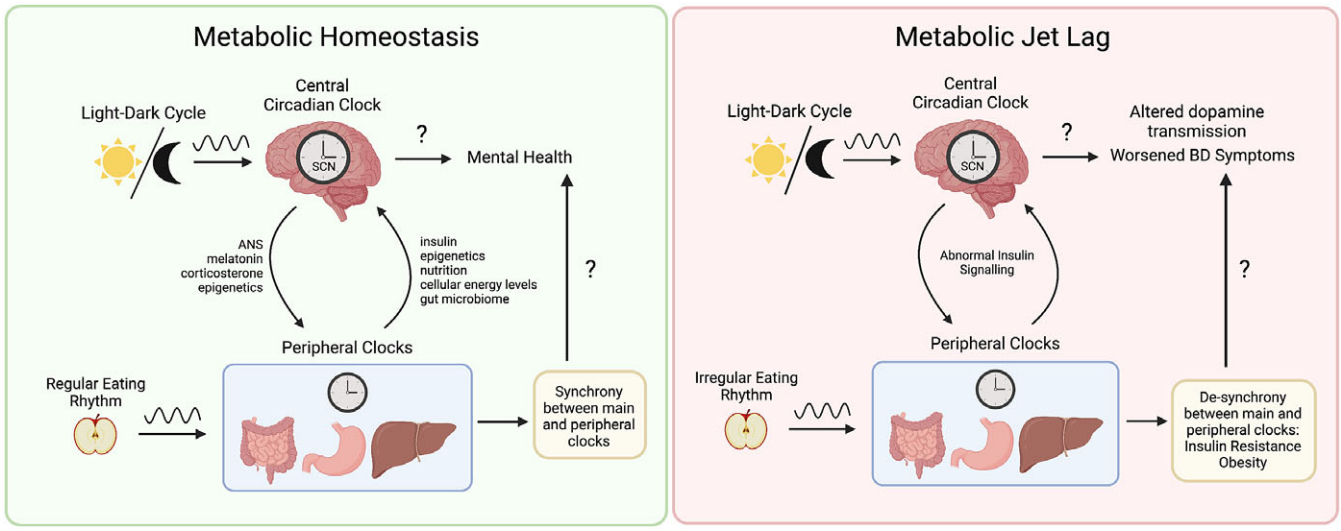

Figure 1. Metabolic jet lag as a core component of bipolar disorder (BD) pathophysiology. Synchrony between central and peripheral clocks is maintained by external cues such as the light–dark cycle and regular patterns of eating. The central circadian clock influences peripheral tissues through the autonomic nervous system, neurohormones such as melatonin and corticosterone, as well as epigenetic mechanisms such as control of metabolic enzyme gene expression. Conversely, metabolic function also influences the central circadian clock through insulin signaling, control of clock gene expression, mitochondrial function, energy expenditure, nutritional content, cellular energy levels, and via the gut–brain axis. Eating rhythms that are irregular and do not align with the light–dark cycle contribute to a variety of metabolic dysfunctions including insulin resistance and obesity. As a result, abnormal insulin signaling has been related to neurobiological changes including altered dopamine transmission. Ultimately, metabolic jet lag contributes to a worsened clinical course in BD including reduced quality of life and treatment efficacy, more frequent mood episodes, and shortened life span. The exact mechanisms underlying metabolic jet lag and worsened symptoms of BD remain unknown.

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Preliminary investigations using simple questionnaires suggest that eating rhythm dysfunction is present in BD during acute episodes and euthymia. This has been associated with symptom severity and poor quality of life.[94,95] Giglio *et al.*[95] showed that, although sleep disturbance is prevalent in BD, the disruption of eating rhythms is more strongly associated with executive functioning than with sleep rhythms in the interepisodic period.[92] Additionally, Allega *et al.*[94] used a self-report questionnaire to assess this biological disturbance during euthymia in BD, demonstrating that rhythms related to sleep, eating, and social activity are independent predictors of functioning and quality of life.[91] Additionally, Mondin *et al.*[96] showed that disrupted eating patterns are linked to obesity, diabetes, and cardiovascular disease and provided evidence that biological rhythm disruption may be a trait marker for mood disorders. More recently, a relationship between irregular eating patterns and mood instability has been proposed by Buyukkurt *et al.*[92] in which the temporal order of eating correlated with hypomanic symptoms. Overall, the alignment of internal and external cues is important to assess in individuals with BD and the role of eating rhythms and metabolic jet lag needs to be further understood.

Implications for research and clinical care

Considerations of metabolic jet lag and its role in the pathophysiology of BD are an important avenue for further research. Clinically, incorporating the assessment of eating rhythms is an important step for individuals with BD, especially considering common comorbidities which impact eating behavior, such as sleep–wake disorders, substance use disorders, and eating disorders.[97-99]

Improvements in the clinical assessment of eating rhythms

Currently available studies use very simple assessments in the evaluation of eating rhythms, including food diaries, 24-hour recalls, and food frequency questionnaires.[100] Food diaries are often tedious, posing a high burden to both the participant and researcher as well as challenging long-term compliance. Additionally, 24-hour recalls are often confounded by aspects of episodic memory and data interpretation with recall bias causing a significant threat to the accuracy of results. Finally, food frequency questionnaires are unable to fully assess eating patterns due to a lack of contextual information. Technological advances such as data entry apps and food tracking websites have reduced some of the burden associated with manual food tracking, although participant engagement is still required.

The use of ecological momentary assessment

The aforementioned methods contrast with the development of more sophisticated tools used to evaluate eating and nutrition, especially considering the current availability of smartphone apps which can be used for both active and passive monitoring of lifestyle factors, as part of a digital phenotyping approach. For example, ecological momentary assessment (EMA) is an active monitoring method in which human behavior is measured in a participant's natural environment, such as through a mobile phone. This method allows for real-time assessment of behaviors such as eating patterns over a certain period, possibly aiding in the early identification of abnormalities.[101] EMA requires little effort on behalf of the participant and avoids the effects of recall bias that are associated with other self-reporting methods, making it more effective than the standard food diary.[102]

EMA has been used in a variety of contexts, such as to identify the effects of fasting in eating disorders and the underlying cognitive aspects that may explain eating disorder behavior, as described by Levinson *et al.*[103]. Additionally, McHill *et al.* used time-stamped pictures from a mobile phone app to record feeding, demonstrating that food intake during the resting phase contributes to weight gain independent of dietary content or energy expenditure.[36] EMA has also demonstrated feasibility in the study of autoimmune disorders,[104] mood disorders,[105] alcohol abuse,[106] and other illnesses.[107] However, to our knowledge, there is not yet a study implementing EMA in the assessment of metabolic jet lag in individuals with BD. In addition, the optimal length of time to record with EMA for a reliable view of individuals' eating rhythms is yet to be determined and studies have collected data over a range of different time periods.

Digital phenotyping also encompasses methods to collect data in a passive manner, that is, not requiring active input from the user such as with EMA. These methods typically use an individual's personal device, sometimes in conjunction with wearable sensors. This method of assessment utilizes data streams related to social activity, movement, and biological rhythms to identify human behavioral phenotypes.[108] Digital phenotyping demonstrates significant potential for capturing intra-individual differences over time, as well as improving the early detection of mood disorders and predicting health outcomes following clinical intervention.[109] Overall, more work is needed to determine the optimal technology for measuring biological rhythms such as eating, as well as implement their use in the clinical assessment of BD.

The integration of chronobiology in the study of mitochondrial dysfunction in BD

Although mitochondrial function and dysfunction have been previously investigated in BD,[110] to the best of our knowledge, no study has incorporated a chronobiological approach. It would be very helpful to understand if circadian lifestyle factors such as time of meals, exercise, and sleep are able to beneficially modulate mitochondrial function in BD and, in extension, if they can also be beneficial for general medical comorbidities.

Exploration of eating rhythms as a target for intervention

Additional research is required to identify more effective intervention strategies for the management of BD, especially for patients displaying circadian desynchronized eating. Further, the potential for adverse effects of pharmacotherapy on energy balance supports the need for adjunctive approaches for the prevention and management of metabolic comorbidities. Non-pharmaceutical interventions, especially those related to lifestyle choices, could support positive changes for those afflicted with this serious issue that impacts more people than is reported.[111] For example, interpersonal and social rhythm therapies have been shown to improve mood symptoms and prevent relapse in BD by helping patients establish routines to stabilize their circadian rhythms.[6,112,113]

Time-restricted eating (TRE) refers to the restriction of the daytime feeding window to 12–20 hours and demonstrates benefit to multiple aspects of human physiology, including the potential to counteract metabolic jet lag.[114] Although few studies of TRE have

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been conducted in humans, there is evidence that brain function and peripheral energy metabolism can be optimized with this method, including the promotion of ketone body synthesis. The role of ketone bodies in the brain has been linked to enhanced energy metabolism and ketosis is an increasingly attractive therapeutic target in BD.[115-117] Further, TRE allows for regulation of fat metabolism through hormones implicated in mood, such as leptin, adiponectin, and ghrelin.[118] TRE may be used to counteract certain metabolic abnormalities which have been linked to worsened mood disorder symptoms and the limited eating window allows a means to overcome circadian desynchronized eating.

Recently, Guerrero-Vargas *et al.*[119] demonstrated successful prevention of depressive- and anxiety-like behaviors in animal models of shift work upon adoption of a TRE window. Although there have been limited observational studies in humans, there is evidence that short-term calorie restriction similar to TRE may induce antidepressant effects in individuals with depression through a variety of molecular pathways.[120] Additionally, a recent cross-sectional study concluded that individuals over the age of 70 that have a feeding window of 8 hours are less likely to show signs of mental health distress, compared to those with no restriction on their feeding time.[114] Overall, more research is needed to delineate the role of TRE in the management of mood disorders, but current evidence is promising.

Conclusion

Disruptions in circadian rhythm adversely affect metabolic processes, and this is relevant to those with BD. Sleep–wake and feeding-fasting cycles are both affected by circadian rhythm disruption and are altered as features of BD, but it remains unclear whether the disruption is a result of physiological differences in those with BD, or if it is a contributing factor to the related disturbances. This review has explored important findings related to BD and the prevalence of metabolic dysfunction in this patient population, suggesting that altered energy regulation is a key contributing factor to disease pathophysiology.

Individuals with BD routinely exhibit signs of metabolic jet lag, and more work is needed to determine the link between biological rhythms such as meal timing and disease progression. Furthermore, it may be possible to limit unfavorable disease progression with interventions such as TRE, which improve the synchronization between energy metabolism and the circadian clock. As an emerging field in medicine, chrononutritional approaches to psychiatry show potential for improving BD symptoms, especially considering the unpredictable nature of pharmacological interventions and associated treatment resistance. As a 24-hour society, further research is needed to delineate the role of rhythm disruption in psychiatric illness. The incorporation of biological rhythm assessment in routine clinical care will allow the significant influence of lifestyle factors such as metabolic jet lag to be taken into consideration, a step toward improved treatment and patient outcomes.

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