

**DISTURBANCE OF CIRCADIAN RHYTHM AS A CHARACTERISTICAL  
DEPRESSION SYMPTOM**



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**ABSTRACT:**

Internal expressions of the solar day, known as circadian rhythms, are what make it possible for organisms to adjust to changes in the environment that are predictable across time. These about 24-hour rhythms are regulated by molecular clockworks that are housed inside the brain. These clockworks are set back to exactly 24 hours on a daily basis when they are exposed to the light–dark cycle. Through both humoral and neuronal communication, the mammalian hypothalamus, which houses the "master clock," transmits information about the passage of time to the rest of the body. There is a connection between mood disorders and circadian rhythms, and this connection goes in both directions. Mood disorders are frequently linked to disturbances in the circadian clock-controlled responses of the body, such as sleep and cortisol secretion.

**Keyword:** Circadian Clock-Controlled, Master Clock, Humoral, Neuronal Communication,

**INTRODUCTION**

The span of one day in the life of a living organism is characterised by a diverse spectrum of cyclical physiological shifts. The cycle of sleep and wakefulness is the daily regularity that is most noticeable in animals, including humans. In addition to changes in core body

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temperature, physiological rhythms may be observed in the release of hormones like cortisol as well as the functioning of a variety of organ systems. Alterations in mood are also seen in people during the course of a 24-hour cycle. Particular mood disorders have been linked to shifts in a variety of circadian rhythms throughout the body. In recent years, we have made enormous strides in our knowledge of the molecular and cellular mechanisms involved in the creation and synchronisation of circadian rhythms.

These systems are responsible for the body's internal 24-hour clock. Recent research has uncovered new information that sheds light on the biology of mood disorders, as well as new possibilities for chronotherapeutic treatment methods. The circadian irregularities that are associated with unipolar depression are the primary topic of discussion in this article. Circadian irregularities seen in seasonal affective disorder or bipolar disorder as well as other mood disorders have been extensively researched elsewhere and are just briefly mentioned here for clarity. Recent discoveries on the processes that control the circadian clock are discussed in this article, with a focus placed on the physiological foundations that support healthy sleep-wake regulation. The next part of this article presents converging data that supports the role that circadian and sleep disruptions play in the pathogenesis of mood disorders, with a particular emphasis on unipolar depression. In addition, unique and effective treatment techniques that have a direct impact on both circadian and unipolar depression are presented.

### **Central and peripheral oscillators**

The endogenous, cyclic rhythmicity of a wide variety of biological and behavioural processes is present in all living creatures. This rhythmicity may be found in all living things. An oscillator, also known as a system of components that work together to produce a rhythmic output, is what's responsible for the cyclic rhythmicity of a certain chemical or biological activity. In species as varied as cyanobacteria, the fungus *Neurospora*, and *Drosophila* (and more recently in the mammalian brain), oscillators have been investigated in great depth at the cellular and molecular levels. Recent research has indicated that circadian oscillators may also be found in the peripheral tissues of mammalian organisms, including the liver, the heart, and the fibroblasts. The term "circadian rhythm" comes from the Latin phrase "circa diem," which means "about the day," and refers to cycles that are approximately 24 hours long. Cycles that are either shorter or longer than the 24-hour cycle are referred to as "ultradian" or "infradian" rhythmicity, respectively. These biological cyclic cycles are both produced and

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sustained by the body's own internal mechanisms. Human participants who are removed from all environmental signals that indicate the passage of time continue to exhibit stable cycles in their physiological processes even when they are observed over extended periods of time. The majority of these cycles, however, fluctuate with durations that are somewhat different from 24 hours (typically longer), and as a result, they lose synchronisation with the day-night cycle that the planet experiences. In addition, synchronicity may be lost among some cyclic functions, which results in a certain degree of "internal desynchronization." It is now abundantly obvious that a central pacemaker in mammals is responsible for conducting the orchestration of the many oscillator systems in mammals. Synchronization of different endogenous processes among each other is known to improve the chances of survival of all living things. The adaptability of the pacemaker, which allows it to be trained to respond either directly or indirectly to zeitgebers, or time givers, from the outside, is another factor that contributes to the organism's high rate of survival.

### **CIRCADIAN RHYTHM DISTURBANCE**

Because of the simplicity with which light exposure can be regulated, the majority of the data supporting the effects of atypical light exposure on emotional responses has been garnered from animal models, notably mice. This is because of the ease with which light exposure can be altered. One of the benefits of utilising rodents is that the majority of the species that are kept in laboratories are nocturnal. Because of this, the rodents are more active and alert throughout the night when they are exposed to light. Therefore, the presence of light throughout the night does not directly affect the sleep patterns of nocturnal animals. This is significant because the majority of the negative effects that disrupted circadian rhythms have on human mood are thought to be a result of disrupted sleep. However, studies conducted with nocturnal species have shown that this is not the only cause, as animals' ability to sleep normally is not affected when they are exposed to dim light at night. Studies in which diurnal rat species are exposed to light at night often produce emotional reactions that are comparable to those of nocturnal rodents. The generation of pineal melatonin is another another significant trait that distinguishes human beings from members of certain rodent species. Even though melatonin is produced during the dark phase by both nocturnal and diurnal animals, there are numerous popular laboratory strains of mice that do not exhibit any measurable pineal melatonin rhythms. Despite this, research conducted on Swiss Webster mice, who do not produce any melatonin in their pineal glands, and research conducted on

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Siberian hamsters, which have a strong pineal melatonin rhythm, have found that the effects of light at night on emotional reactions are quite comparable. This data seems to show that the suppression of melatonin by evening light is neither the sole nor even the predominant mechanism; yet, it may still be a key contributor in humans as well as a possible site of intervention.

### **Circadian rhythm disruption and major depressive disorder**

The major depressive disorder, also known as MDD, is distinguished by changes in mood, most commonly increased sadness and/or irritability, which are accompanied by at least one of the following psychophysiological symptoms: changes in sleep, sexual desire, or appetite; inability to experience pleasure; slowing of speech or actions; crying; and suicidal thoughts. In order to make a diagnosis of major depressive disorder (MDD), these symptoms need to last for at least two weeks and disrupt routine day-to-day activities. The Global Burden of Disease Consortium examined the global incidence and prevalence for 328 diseases in 195 countries from 1990–2016, and MDD ranked within the top ten leading causes of disease burden in all but four of the countries that were examined. This indicates that MDD affects a large number of people all over the world. The prevalence of major depressive disorder is on the rise around the globe; from 2005 to 2015, the number of persons who were clinically diagnosed with depression grew by approximately 18%. Notably, rates of major depressive disorder correlate with the modernization of society. This correlation may be a reflection of the increased circadian disruption (i.e., light at night, shift work, and jet lag) or the interaction between circadian disruption and other environmental factors that are experienced in modernised countries.

There have only been a limited number of research conducted on humans that have particularly looked at the link between circadian disturbance and MDD. The majority of human data mix all forms of depression. However, research on the link between shift employment and MDD has yielded mixed results in the studies that have been conducted. For instance, the frequency of major depressive disorder (MDD) among shift workers and night employees in a sample of about 4,000 South Koreans was dramatically elevated in comparison to daytime workers. Only women in a cohort of over 36,000 employees in Brazil were shown to have a significant association between night shift employment and major depressive disorder (MDD). In a French study, there was no correlation found between working shifts and major depressive disorder (MDD). If all of the different kinds of

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depression are considered together, then there is a definite relationship between shift work and depression. According to the findings of a meta-analysis that looked at 11 separate research, those who work the night shift are 40 percent more likely to have symptoms of depression than people who work during the day.

### **Symptoms of depression**

Data from clinical studies conducted on humans provide support for a significant relationship between MDD and circadian mechanisms. The signs and symptoms of depression change throughout the day; patients often report that their symptoms are at their worst in the morning or in the evening. Patients who have major depressive disorder (MDD) often exhibit more severe symptoms in the morning, which is thought to be connected with a more severe form of depression. Disruptions of biological rhythms are the underlying cause of the hallmarks of major depressive disorder (MDD). More specifically, alterations in sleep/wake states (decreased latency to rapid eye movement sleep, concurrent with increased rapid eye movement sleep and reduced slow wave sleep), social rhythms, hormone rhythms (reduced amplitude in melatonin and cortisol rhythms), and body temperature rhythms (reduced amplitude and increase in nocturnal body temperature) are observed. Clinical research has shown that the severity of major depressive disorder (MDD) is connected with the degree to which circadian rhythms are out of whack 82. In addition, the investigation of circadian patterns of gene expression within the postmortem brains of individuals with MDD reveals a decreased amplitude, shifted peaks, and an altered phase connection between genes, notably in canonical clock genes.

### **Circadian rhythm disruption and anxiety**

Although a number of studies have demonstrated that working night shifts or having chronic jet lag might cause anxiety, more recent analysis imply that the mood changes may be the result of disrupted sleep rather than impaired circadian rhythms in and of themselves. For instance, a longitudinal study of day shift employees without a history of sleep disorders who migrated to rotating shift work schedules revealed increased anxiety associated with disrupted sleep. These participants had previously worked in jobs that did not include shift work. On the Hospital Anxiety and Depression Scale, nurses who suffer from Shift Work Disorder had significantly higher anxiety levels than other nurses. However, a questionnaire study of nurses found that quick transfers to night shift employment did not impact the participants' feelings of anxiety. It was found that experiencing jet lag, which was

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accomplished by undergoing a 7-h westward time shift by jet in five men preceding the study and, 1 month later, a 7-h eastward shift preceding, was associated with disrupted sleep and elevated anxiety and depression scores, particularly in simulated eastward travel. This was the case regardless of the direction of travel.

Research conducted on rats has shown that there is a connection between the circadian clock and anxiety-like diseases. For example, anxiety-like behaviour can be triggered by the targeted disruption of classical components of the molecular clock. Mice who have a mutation of the Clock gene called a 19 demonstrate less anxiety-like behaviour and have a lower level of fear in response to unpleasant stimuli when compared to mice that are wild-type. The 19 mutation in the Clock gene is sufficient to generate manic-like behaviour. Clock is notable for its regulation of cholecystokinin (CCK) production in the ventral tegmental region (VTA). In contrast, mice who lack both Per1 and Per2 exhibit enhanced anxiety-like behaviour, but mice that lack either Per1 or Per2 do not have changed anxiety-like reactions. Mice that are deficient in either Per1 or Per2 do not have altered anxiety-like responses. Anxiety-like behaviour is also produced by inhibiting Per1/Per2 expression in the nucleus accumbens (NAc) of wild-type mice, which suggests that these core clock components in the NAc play a causal role in regulating anxiety.

### **Inputs and outputs of the central pacemaker**

Light has the potential to function directly as a zeitgeber at peripheral oscillators in creatures that are relatively basic. When explanted and maintained in culture, several distinct tissues in *Drosophila* are photoreceptive and display circadian oscillations. These oscillations can be entrained by light. In such a system, light serves as the master coordinating signal, and a central pacemaker is not required because the system does not require one. The majority of an animal's tissues are not exposed to light, and the variety of cells and tissues that are receptive to light is narrowed down as the animal increases in complexity, size, and opaqueness.

### **REVIEW OF RELATED LITERATURE**

Depression may cause a wide range of symptoms, from a lack of desire and energy to thoughts of ending one's own life. Alterations in the sleep-wake cycle and the daily rhythms of hormone (such as cortisol and melatonin) release may also be seen in patients suffering from depression. The internal biological clock that is housed inside the hypothalamus suprachiasmatic nucleus is responsible for regulating both the sleep-wake cycle as well as the

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hormone cycles (SCN). As a result, an imbalance in the way the SCN's internal mechanism functions might potentially result in a disturbance of the body's temporal physiology as well as depression. Therefore, circadian symptoms in mood disorders have the potential to serve as key indicators in the diagnosis and treatment of depression. In animal models of depression, disruptions of daily rhythms in physiology and behaviour have also been documented. This provides an essential study tool for the understanding of the circadian processes that are implicated in mood disorders. This article presents a review that focuses on the changes in daily rhythms that are associated with depression, as well as how circadian disturbances could lead to changes in mood and behaviour that are similar to depression in people and rats respectively. By using animal models with circadian abnormalities and depressive-like behaviours, researchers will be able to gain a better understanding of the core timing processes that underlie depression and the ways in which treating the biological clock(s) may be able to enhance mood.

Again, gender inequalities may be found in the social support that is supplied by an individual's family. Women who are unemployed perceive the family environment as being an exceptionally powerful source of support, but males who are unemployed do not appear to experience the same benefit from this milieu (Holahan and moos, 2017).

In their relatively final study (N = 216), Retherford, Hildreth, and Goldsmith (2018) discovered that unemployed women were significantly more likely to receive support from their parents than from their partners, other relatives, or friends. This was the case regardless of whether the study was conducted in the United States or the United Kingdom.

On the other hand, Stokes and Levin (2016) found that unemployed men are more likely to seek support from friends other than from their close relations, as they prefer to keep family and work roles separate. This preference stems from the fact that unemployed men prefer to keep their family and work roles separate

While it is important to appreciate the positive impact that social support may have on psychological well-being, it is also important to acknowledge that it is possible for the home environment to amplify the negative impact that unemployment can have on both mental and physical health. It's possible that family responsibilities come with their own unique stresses, and that these stresses might become even more intense during unemployment. This is a scenario that is made worse by the fact that there is no way to leave the confines of the home setting (Hibbard and Pope 2013).

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The significance of keeping busy while unemployed has been demonstrated by a number of students who discovered that whether or not a man felt his time was being used productively was one of the best single predictors of mental health while unemployed. This factor accounted for twice as much variation as the total amount of time spent jobless or the individual's age (Hepworth, 2020).

### **RESEARCH METHODOLOGY**

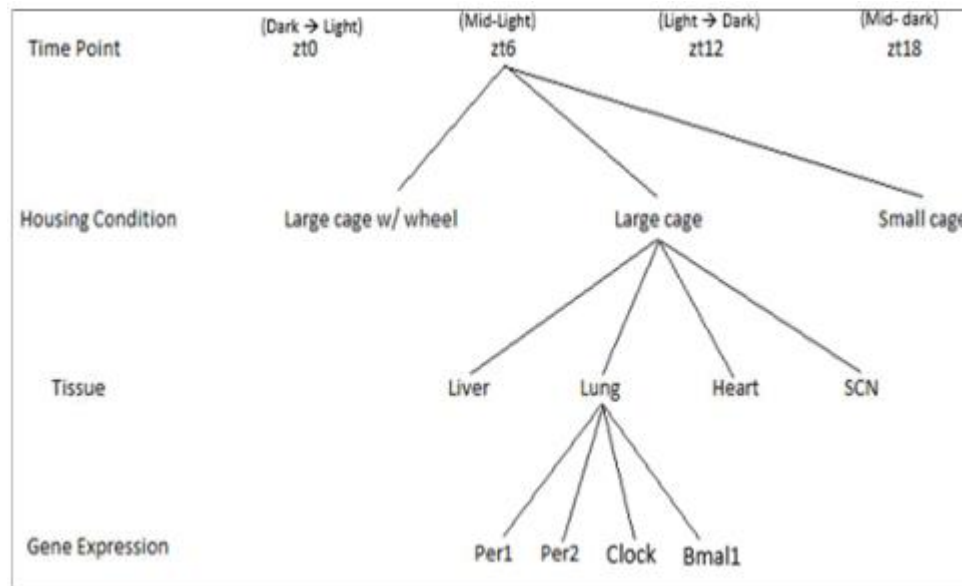
The animal facility at Kent State University used stock that was obtained from Jackson Laboratories to breed 75 mice of the C57BL/6J strain. These mice were bred in the facility. They were kept in communal settings with a light-dark cycle of 12:12 hours and had access to food and water on an as-needed basis. The animals ranged in age from 10 to 17 weeks and included 36 females and 39 males.

### **EXPERIMENTAL DESIGN**

The animals were single-housed throughout the experiment in one of three different sizes of cages: small cages (11.5"L x 7.5"W x 5"H), big cages (19"L x 10.5"W x 6.125"H), and large cages (19"L x 10.5"W x 6.125"H) with access to a wheel. A high temperature polycarbonate plastic was used to make all of the cages. For each group, 3 males and 3 females were employed, with the exception of the ZT 0 time point, where 3 extra males were introduced. For five weeks, they were kept in a 12 hr light: 12 hr dark cycle. The animals were allowed a week to become used to their new environment before spending a further 4 weeks in the appropriate cage setup. By cervical dislocation, all animals were killed at ZT 0 (light onset), ZT 6 (middle of the light phase), ZT 12 (start of the dark phase), and ZT 18 (middle of the dark phase) at the conclusion of the fifth week. The brains were taken, flash frozen, and kept at 80 degrees Celsius together with samples of liver, lung, and heart tissue.



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**Experiment #1's experimental layout. At four distinct timepoints, mice housed in each condition (LW, LC, and SC) were killed (ZT0, ZT6, ZT12, & ZT18). Each animal's liver, lung, heart, and SCN in the brain were removed. The mRNA expression of 4 distinct clock genes (Per1, Per2, Clock, and Bmal1) was assessed at the moment of sacrifice.**

### DATA ANALYSIS

Numerous physiological functions exhibit circadian rhythms. The most evident circadian rhythms in animals are those of sleep and awakening. Circadian and sleep disruptions have a significant role in the pathophysiology of mood disorders, which is supported by a large body of research. Sleep issues, abnormal circadian rhythms, and changes in mood during the day are common among depressed people. Chronotherapies, such as strong light exposure, sleep deprivation, and social rhythm treatments, may be beneficial additions to treatment for both non-seasonal and seasonal depression. Drugs that treat depression significantly affect sleep and circadian functions.

The two-way ANOVA was used to assess the data on gene expression (with time point and housing conditions as factors). The same time points were utilised to compare differences between experimental housing groups using Tukey-Kramer Multiple Comparison Tests. Using a three-way ANOVA, weight growth was examined (with diet, light treatment, and

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week as factors). Over the course of the 7-week trial, differences across light groups in each diet treatment were assessed using Dunnett's Two-Sided Multiple-Comparison Test.

Data were examined for body composition using a two-way ANOVA (with diet and lights treatments as factors). In order to ascertain differences between the light treatment groups in each diet treatment, Dunnett's Two-Sided Multiple Comparison Test was performed. The wheel element was included in each comparison when contrasting animals with wheels and those without wheels. Animals with wheels and those without were compared in terms of body composition using a three-way ANOVA (with lights, diet, and wheel as factors). Again, Dunnett's Two-Sided Multiple Comparison Test was employed to compare the differences between the diet groups with and without wheels and the light groups. Animals with wheels and those without were compared in terms of body weight using a four-way repeated measures ANOVA (with diet, lights, wheel, & week as factors). Pvalues less than 0.05 were regarded as statistically significant, and the mean and standard error of the mean were shown. All ANOVA and multiple comparison analyses were carried out using NCSS statistical software.

### Abbreviations used in this thesis and their corresponding definitions.

<b>SC</b>	Small Cage
<b>LC</b>	Large Cage
<b>LW</b>	Large Cage with Wheel
<b>HFD</b>	High Fat Diet
<b>ND</b>	Normal Diet
<b>PA</b>	Phase advance
<b>PD</b>	Phase Delay
<b>LD</b>	Light-Dark
<b>GTT</b>	Glucose Tolerance Test
<b>AUC</b>	Area under a curve

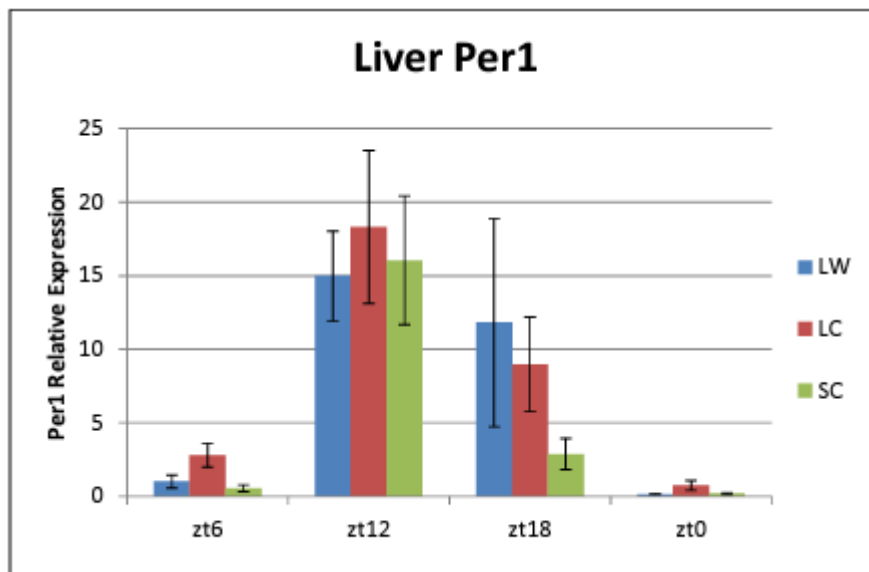
## RESULTS

### Experiment #1

In this study, mice were kept in large cages with wheels (LW), large cages (LC), and small cages (SC), and the expression of *Per1*, *Per2*, *Clock*, and *Bmal1* in numerous peripheral organs (liver, lungs, and heart) and the SCN was assessed at four distinct time periods (ZT 6, ZT 12, ZT 18, ZT 0). All of the day's major variations in *Per1*, *Per2*, *Clock*, and *Bmal1* were compatible with the SCN's and peripheral tissues' 24 h rhythmicity. In all peripheral tissues including the SCN, there were no discernible variations between housing situations in *Per1* and *Per2* expression (Figure 5, 7, 9, & 11). *Clock* and *Bmal1* expression varied significantly, with the majority of the variations occurring at either ZT 12 or ZT 18. There were no

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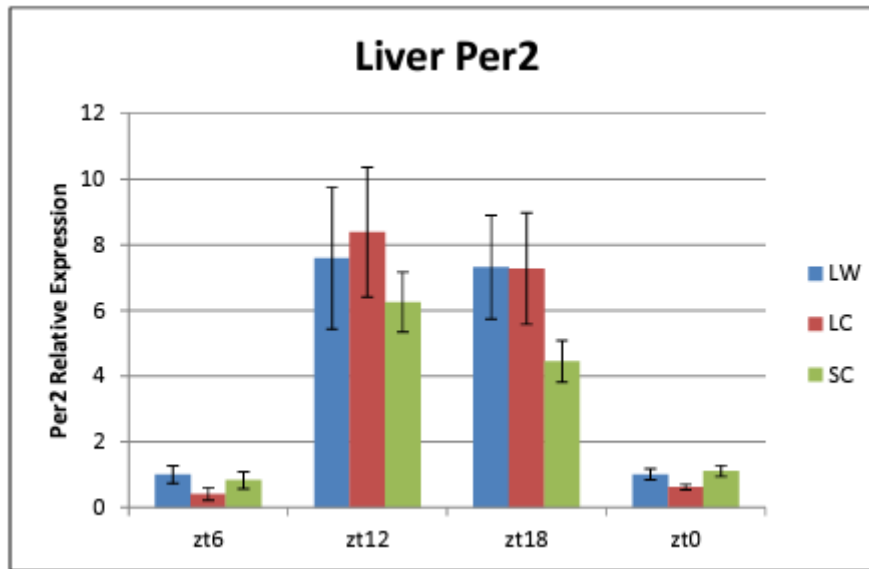
discernible changes in Clock expression between the liver and the heart (Figure 6a & 10a). But at ZT 18, Clock expression in the lungs was considerably higher in SC mice compared to LW and LC (p 0.000001). (Figure 8a). At ZT 18, Clock gene expression in the SCN was considerably lower in SC animals compared to LW (p=0.014) (Figure 12a). In the heart, there were no discernible variations in Bmal1 expression according to housing situations (p=0.29) (Figure 10b). At ZT 0, Bmal1 expression in the liver was considerably lower in SC animals compared to LW and LC (p = 0.00063). (Figure 6b). LW mice had considerably lower Bmal1 gene expression in the lungs than LC and SC at ZT 18 (p 0.000001); SC mice had significantly lower Bmal1 gene expression than LC and SC at ZT 0 (p 0.000001). (Figure 8b). At ZT 18, SC mice's Bmal1 gene expression in the SCN was considerably lower than that of LW and LC mice (p = 0.00011). (Figure 12b). Together, the varying sizes of the tiny cage and less so the presence of a moving wheel appeared to be the causes of the changes in clock gene expression between the housing circumstances. The most notable variations were also seen at ZT 18 (mid-active phase) and ZT 0. (end of active phase). Overall, the liver, lungs, and SCN showed altered clock gene expression due to various housing situations, but not the heart (Table 3).



(a)

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(b)

According to the time of day, Per1(a) and Per2(b) expression in the livers of LW, LC, and SC mice varied significantly ( $p < 0.05$ ). Housing circumstances and time of day had no discernible effects on Per1 and Per2 expression (Per 1,  $p = 0.76$ ; Per2,  $p = 0.61$ , respectively). The error bars show the standard error of the mean.

## CONCLUSIONS

Human behaviour and physiology are fundamentally regulated by circadian rhythms. On the other hand, disturbances of the circadian rhythm have been linked to a number of pathological processes, including depression. The primary symptoms of depression, such as a sad mood and sleep problems, follow circadian patterns in addition to irregularities in biological processes. Recent research has shown that the intensity of depressive symptoms corresponds with the degree of circadian misalignment.

In order to reduce findings variability, housing factors must be taken into account while assessing clock gene expression in experimental setups. Particularly during the active phase, the size of the cage may have a role in the modification of clock genes in the liver, lung, and SCN. In contrast to Per1 and Per2, Cage size mostly influenced Clock and Bmal1 expression, suggesting that measures of Clock and Bmal1 expression may be more appropriate when investigating the phase of the clock gene. HFD significantly increases weight gain. Animals that experience prolonged phase delay put on even more weight. However, the amount of weight gain that occurs as a result of phase delay is modest and unrelated to food or wheel

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access. Wheel running reduces increased weight gain while acting as a workout component. No matter which way the clock was shifted, simulating chronic jet lag consistently caused an increase in lean mass. HFD-induced weight gain is followed by a rise in fat mass and a reduction in glucose tolerance, which promotes the development of pre-diabetic symptoms. By replicating chronic jet lag, this study lends credence to the well-established adverse effects of circadian disturbance.

**References**

1. Albrecht, U., Eichele, G. (2003). The mammalian circadian clock. *Curr Opin Genet Dev*, 13(3),
2. Andrikopoulos, S., Blair, A.R., Deluca, N., Fam, B.C., Proietto, J. (2008). Evaluating the glucose tolerance test in mice. *Am J Physiol Endocrinol Metab*, 295(6), E132332.
3. Antle, M.C., Smith, V.M., Sterniczuk, R., Yamakawa, G.R., Rakai, B.D. (2009). Physiological responses of the circadian clock to acute light exposure at night. *Rev Endocr Metab Disord*, 10(4).
4. Arble, D.M., Bass, J., Laposky, A.D., Vitaterna, M.H., Turek, F.W. (2009). Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring)*, 17, 21002102.
5. Balsalobre, A. (2002). Clock genes in mammalian peripheral tissues. *Cell Tissue Res*, 309,.
6. Bartsch, C., Bartsch, H., Peschke, E. (2009). Light, melatonin and cancer: current results and future perspectives. *Biological Rhythm Research*, 40(1), 17-35.
7. Binder, E., Droste, S.K., Ohl, F., Reul, J.M., (2004). Regular voluntary exercise reduces anxiety-related behaviour and impulsiveness in mice. *Behav. Brain Res*, 155(2),
8. Buhr, E.D., Yoo, S.H., Takahashi, J.S. (2010). Temperature as a universal resetting cue for mammalian circadian oscillators. *Science*, 330(6002),
9. Buijs, R.M., Scheer, F.A., Kreier, F., Yi, C., Bos, N., Goncharuk, V.D., Kalsbeek, A. (2006). Organization of circadian functions: interaction with the body. *Prog Brain Res*, 153,
10. Castanon-Cervantes, O., Wu, M., Ehlen, J.C., Paul, K., Gamble, K.L., Johnson, R.L., Besing, R.C., Menaker, M., Gewirtz, A.T., Davidson, A.J. (2010). Dysregulation of inflammatory responses by chronic circadian disruption. *J Immunol*, 185(10),.

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11. Davidson, A.J., Sellix, M.T., Daniel, J., Yamazaki, S., Menaker, M., Block, G.D. (2006). Chronic jet-lag increases mortality in aged mice. *Curr Biol*, 16(21),
12. Davidson, A.J., Castanon-Cervantes, O., Leise, T.L., Molyneux, P.C., Harrington, M.E. (2009). Visualizing jet lag in the mouse suprachiasmatic nucleus and peripheral circadian timing system. *Eur J Neurosci*, 29(1),.
13. Debruyne, J.P., Noton, E., Lambert, C.M., Maywood, E.S., Weaver, D.R., Reppert, S.M. (2006). A clock shock: mouse CLOCK is not required for circadian oscillator function. *Neuron*, 50(3),.
14. Duman, C.H., Schlesinger, L., Russell, D.S., Duman, R.S. (2008). Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *BrainRes.* 1199, 148–158.
15. Esquirol, Y., Bongard, V., Mabile, L., Jonnier, B., Soulat, J.M., Perret, B. (2009). Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int*, 26(3),.
16. Fonken, L.K., Nelson, R.J. (2013). Dim light at night increases depressive-like responses in male C3H/HeNHsd mice. *Behav Brain Res*, 243,.