The effects of shift work induced circadian disruption on human health and its countermeasures

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Introduction

It is estimated that 0.7 billion of the world's population is engaged in shift work[1] and that most of these people are involved in professions that are highly vital for the society's functioning. These workers include healthcare practitioners, pilots and flight attendants, police and fire fighters as well as the hospitality industry. The impacts of shift work on the human body are adverse as they cause disruptions to the circadian system. Circadian rhythms refer to changes in an individual's behaviour, mental health and physical well-being that take place over a cycle of 24 hours. These cycles are controlled by a central biological clock, or an oscillator, called the suprachiasmatic nucleus. The suprachiasmatic nucleus is located in the hypothalamus, and smaller peripheral clocks are situated in almost all the tissues and organs in the body[2]. While it is understood that shift work leaves a negative impact on the body, further research is required to understand how these factors affect cognition and well-being. In addition to this, there is a shortage of information over the possible treatments or interventions aimed at those suffering from the consequences arising as a result of disrupted sleep cycles. The aim of this research paper is to understand how disruptions to the circadian rhythms of the sleep-wake cycle that arise from shift work impact cognition and overall well-being, and what potential interventions or strategies can be developed to mitigate these effects. This paper is a literature review addressing circadian rhythms, effects of shift work on the circadian rhythm, how these disruptions to the circadian rhythm affect the body, and interventions that can be made to alleviate the adverse effects in cases where shift work cannot be avoided.

Overview of Circadian Rhythms

As stated earlier, circadian rhythms are changes in the body over a 24-hour period controlled by the suprachiasmatic nucleus and various oscillators in the body [3]. Circadian rhythms have five characteristic properties. The first is that circadian rhythms are self sustained, which means that they are capable of existing and are expressed without any external cues such as light and temperature, suggesting that there is an inner timekeeping mechanism. All circadian rhythms have a cycle that is close to but not exactly 24 hours and can be synchronised by external factors, also called zeitgebers. The reason why the cycle does not last exactly 24 hours is because it allows for the inner clock to be constantly adjusting to the light dark cycle. The last two properties of circadian rhythms are that they are ubiquitous, as they exist in a wide range of species and mechanisms, and they are conserved across species at the cellular level. Even unicellular organisms such as algae have the same rhythm as highly complex mammals like human beings [3].

While circadian systems are self sustained, they also have an ability to be aligned with the external light dark cycle in a process known as entrainment. The most prominent zeitgeber or external factor that entrains the sleep-wake cycle is the light and dark cycle. The light dark cycle depends on two factors- the timing of light exposure and the intensity of the light. Exposure to light towards the beginning of the individual's dark period would cause a phase delay while exposure towards the end would cause a phase advance. Similarly, exposure to bright light

could cause the cycle to become longer in a few species or cause it to shorten in others. The ability for light to induce circadian phase shifts is due to the presence of intrinsically photosensitive retinal ganglion cells (ipRGCs) that are stimulated by light due to the activation of the photopigment melanopsin. Melanopsin signaling communicates with the SCN, SCN, which ultimately activates the pineal gland to control the release of the sleep hormone melatonin[4] Other zeitgebers that affect the sleep cycle include temperature, social interactions and exercise[3].

In order to understand the genetics of the circadian system, *Drosophila* (fruit flies), *Neurospora* (fungi), cyanobacteria and mice were historically used. Due to circadian rhythms being ubiquitous, even though the specific genes that are expressed in each organism vary, the process that controls the phasic expression of genes across these species remains mostly the same. The circadian system operates in a feedback loop called the transcription translational feedback loop (TTFL)which takes place inside the cell. This loop consists of a positive arm and a negative arm. During the day, the levels of the negative arm continue to increase until they are able to suppress the activity of the positive arm, by translocating into the nucleus. Once they enter the nucleus, they are degraded, allowing the positive arm to start the cycle again. This entire process takes approximately 24 hours, which accounts for the near 24 hour length of the circadian rhythm[5].

In the *Drosophila* clock, the positive arm consists of CLOCK and CYCLE, which are master transcription factors. These form a heterodimer and start the transcription process by binding to the E boxes at specific promoters and activating them. The negative arm is made up of *period (per)* and *timeless (tim),* which join together and build up in the cytoplasm. This dimer translocates into the nucleus during the evening where it binds to the CLOCK-CYCLE dimer and inhibits their function. In the morning, light causes *tim* to break down. Without *tim, per* is less stable and is also broken down by a proteasome-dependent pathway. There are additional loops as well, such as the prevention of CLOCK and CYCLE gene expression, regulation of the forward loop of the positive arm, and the loop to reduce CLOCK expression and increase the *per* transcription[5].

The mammalian/mouse transcription translation feedback loop is quite similar to that of the *Drosophila.* Instead of the positive loop consisting of CYCLE, mammals contain BMAL1 as well as CLOCK which form the heterodimer. The negative loop is made up of PERIOD (PER) and CRYPTOCHROME (CRY), which perform the same function as *per* and *tim* in flies. While *per* acts as the main negative regulator in flies, the mouse/mammal circadian system consists of mPER1, mPER2 and mPER3. Each of them play an individual role in maintaining the clock at a molecular level. mPER3, for example, plays a regulatory role in maintaining the circadian rhythm in peripheral tissues [5]. mPER2 and mPER1 have similar roles,with mPER2 acting as a positive regulator for the CLOCK-BMAL1 transcription and mPER1 aiding the SCN in light entrainment[6]. The mammalian/mouse feedback loop also consists of secondary loops which are more complex, and affect different proteins [5].

The Effects of Shift Work on the Circadian System

Shift work occurs when at least a portion of a worker's shift is between 7pm and 6am, and often requires conflicting sleep-wake schedules that differ from the natural sleep-wake cycle [7]. The criteria for shift work includes insomnia/hypersomnia with an overall reduction of sleep time, shift work schedule for 3 months, disturbed sleep wake pattern on the 14 day sleep log and the absence of any other condition to explain the sleep disorder. This often results in desynchrony between the work cycle and the natural cycle, similar to the jet lag experienced by those traveling across numerous time zones, resulting in problems with both sleep and wakefulness [7,8]. This desynchrony is caused by the conflicting drives of a "homeostatic pressure" to sleep and a "circadian alerting signal" that encourages wakefulness [7]. Entrainment to a new time zone/schedule for both the central and peripheral clocks is a slow process, and this is further slowed down by external synchronisers during the night which promote a day-oriented schedule, such as light exposure or feeding during the night. The time taken for the circadian rhythm to fully adapt to the new schedule varies between workers, and usually takes place with the help of deliberate intervention."

In daytime workers who have a regular sleep-wake schedule, cortisol normally peaks during the day and melatonin during the night. Cortisol levels peak particularly in the morning and are responsible for the body remaining awake throughout the day [9]. Melatonin levels are almost nonexistent during the day and are at their highest during the night, when they help the body fall asleep, because the dim light triggers the iPRGCs to produce more melatonin [4]. These hormones are influenced more by the endogenous circadian rhythm rather than the homeostasis negative feedback loop [10]. The lack of entrainment, or the delay of entrainment of levels of cortisol and melatonin in night shift workers, result in the levels of these hormones peaking at inappropriate times. For example, cortisol levels peak during the sleep time for shift workers and are at their lowest during the night when they are awake [11]. This reduction in cortisol levels for shift workers during their waking period could contribute to reduction in productivity and performance in their workplace, which could be particularly dangerous in healthcare workers who are responsible for the health of others, or overnight drivers who must maintain alertness on the road.

The tolerance to shift work differs between individuals and factors that typically impact the tolerance are the duration of the shifts, timing of the shifts and consistency of the shift work schedule. There are other human-level factors that also contribute to the tolerance such as their history with shift work, familial and social responsibilities, amount of time spent in bed, any collateral sleep disorders and/or medical and psychiatric conditions, and their medications [7]. Despite all of these factors, only 3% percent of the population adapts fully to shift work schedules, with 25% experiencing only partial entrainment and the remaining 72%experiencing no circadian adaptation. Another study conducted on patrol officers, showed that 44% of them spontaneously entrained to their night shifts. The researchers measured melatonin levels in the saliva, subjective alertness and performance, and also conducted a psychomotor vigilance test. [11.]. The timed exposure to bright light and stable daytime schedules are known to promote partial circadian entrainment. The likelihood of shift workers to adapt to their shift work schedule increases with the intensity of light exposure during the night. A study conducted with a group of nurses showed that the adapted nurses tended to expose themselves to light during the evening and night and reduced their daytime light exposure [10]. The time of the day and circadian phase

during which a shift worker goes to sleep can also affect the duration of the main sleep episode and the daytime sleep duration, contributing to impaired sleep schedules.

How Do Circadian Rhythms and Shift Work Affect the Human Body

A) Cardiovascular System

The suprachiasmatic nucleus controls the cardiovascular system both directly and indirectly. It directly affects the cardiovascular system by controlling the autonomic nervous system–responsible for regulating blood pressure and heart rate [12]-and the endocrine system, such as glucocorticoid rhythms which regulate cardiac function [13].It indirectly affects the cardiovascular system by synchronizing local clocks in cardiac tissues which act as peripheral clocks. The cardiac system benefits from the circadian system by anticipating and preparing for external stimuli [14]. Cardiac muscle cells (cardiomyocytes) in rats exhibit rhythmic clock gene expression, and *in vivo* studies show that about 3-16% of the transcribed genes in the cardiac transcriptome-the protein coding part of an organism's genome are regulated by circadian rhythms [15].

Mice that were in an experimental "shift work" paradigm showed decreased levels of cardiomyocytes and reduced expression of key genes in cardiac hypertrophic (add brief definition) pathways [16]. Additionally, circadian rhythms in kidney tissues, immune function and cholesterol pathways can overall impact cardiovascular functions. Simulated shift work protocols in humans showed that circadian misalignment during night shifts increased wake-time blood pressure, 24-hour average systolic blood pressure and diastolic blood pressure. The shift work protocols also decreased the healthy sleep-associated systolic blood pressure dipping effect leading to increased risk of cardiovascular diseases and mortality. Circadian misalignment also has negative effects on the cardioprotective parasympathetic (vagal) activity, suggesting that parasympathetic changes may contribute more to increased risk of cardiovascular diseases rather than sympathetic changes [16]. A study conducted in Japan showed that male workers that participated in rotating shift work had 2.32 times higher risk from ischemic heart diseases compared with a day time or fixed night time worker [17]. Other studies with mice showed that desynchrony between the central and the peripheral clocks contributed towards the progression of cardiovascular disorders. Studies with mice which were subjected to a disrupted 20-hour cycle resulted in lower cardiac function, fibrosis and impaired contractility [14].

B) Digestive System

Circadian rhythms drive behavioral activities and one of them includes the feeding system. Because the feeding system is photo-period dependent, animals tend to have a stable feeding schedule. Many feeding hormones such as insulin, glucagon and leptin fluctuate throughout the day to anticipate feeding [18]. Peripheral tissue clocks are shown to not be dependent on the SCN function and can persist and be entrained by external factors, such as the timing of food intake [19]. Previous research demonstrates that animals with SCN lesions can be entrained by food alone [20,] and several experiments conducted on mice have indicated that feeding schedules can affect their behavioral activity. This rhythm however is terminated in darkness and an ad lib food routine [18]. The ability of circadian clocks to coordinate multiple tissues is used in coordinating

the simultaneous activity of the digestive and the metabolic pathways such as carbohydrate digestion and glucose metabolism [19]. When the circadian rhythm is disrupted, this results in an increased risk for obesity and metabolic disruption. Sleep disruption alone is known to affect caloric intake, leptin resistance and glucose utilization [18].

In the liver, reentrainment of the genes that align with meal time is driven by feeding and only a portion of the rhythmic liver genome is directly under clock control. Circadian regulation in the liver impacts important metabolic pathways such as the nucleotide synthesis and mitochondrial processing of fats and carbohydrates [21], [22]. Clock mutations in the liver cells, such as the conditional loss of BMAL1 function resulted in increased oxidative stress and elevated plasma concentrations of triglycerides and cholesterol [23],[24]. CRYPTOCHROME (CRY) is also known to regulate gluconeogenesis, lipid metabolism and oxidative pathways in a hepatic specific manner [25]. Insufficient sleep is also linked with the increased risk of Non-Alcoholic Fatty Liver Disease (NAFLD) [26]. Additionally, circadian disruption is also linked with Hepatocellular Carcinoma (HCC) and animal models showed that altered circadian pathways could aggravate HCC [27].

Circadian rhythms are crucial in the gut, as they allow the gastrointestinal tract to anticipate and prepare for heightened digestion before meals. The small intestine and colon also have circadian functioning which help in enzyme secretion and nutrient absorption [28]. As they are self renewing tissues, the small intestine and colon also exhibit circadian rhythms in processes such as cell proliferation and migration [29]. The circadian rhythms in the gut are not fully predictive and are influenced by the gut microbiome and the abundance of food. Several epidemiological studies show that there is an increased risk of colorectal tumors in shift workers, and animal models such as mice (mice) show that the loss of circadian function could increase intestinal tumorigenesis [30]. Shift workers also demonstrated an increased risk of Inflammatory Bowel Disease (IBD) and the genetic loss of circadian clock components increased the severity of colitis in mouse models by affecting the regenerative proliferation, mucus producing cells and inflammation pathways [19].

C) Reproductive System

Regulation of the reproductive hormones by the circadian system is necessary for fertility, and changes in the circadian rhythms have shown to negatively affect reproductive capacity [24]. Regulation of the estrus cycle, luteinizing hormone levels, sperm production and maturation as well as the timing of insemination and fertilization are controlled by clock genes. Fertility hormones also have the ability to influence clock-gene expression, suggesting that these interactions go two ways.

In the female reproductive system, the placenta acts as a peripheral oscillator [31] and most of the fertility hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone sex-hormone binding globulin (SHBG) display circadian rhythmicity [32]. Moreover, estrogen receptors are expressed in the SCN, suggesting that there might be a link between estrogen synthesis and the circadian rhythm [33]. Women often working later in the day and doing shift work reported changes in their menstrual cycle. These changes could occur as a result of alterations in the patterns of ovarian and pituitary hormone secretion, such as changes in FSH concentrations [34]. Women who work in shifts often report having decreased

sleep. Female shift workers also have a higher tendency for producing premature/low birth weight babies, spontaneous abortion and subfecundity [34]. A mouse model of shift work that put mice in 22-hour and 26-hour light-dark cycles, showed that there was a reduction in the percentage of animals that mated in the 22 and 26-hour cycle compared with that of the mice in the 24 hour light-dark cycle. The difference in cycles, however, had little effect when pregnant mice were put in the same model, suggesting that entrainment to the new light-dark cycle might be necessary for copulation and conception but may not have an effect on pregnancy outcomes afterwards [35].

In the male reproductive system, the circadian rhythm helps to regulate fertility. BMAL1 is located mainly in the Leydig cells,which produce steroid hormones to ensure the maturation of spermatozoa and the sexual characteristics, and CLOCK is expressed more in the cytoplasm of round spermatids [36],[37]. A study was conducted in which the CLOCK gene expression in the testes of male mice was reduced or removed completely. This resulted in a lower *in vitro* fertilization rate, lower blastula formation rate, as well as lower acrosin activity. Melatonin levels were also found to be lower in semen samples with low and poor fertilization rates and its suppression is also linked with the decline of sperm motility and concentration. Melatonin is shown to have protected sperm cells from oxidative damage by lowering the amount of free radicals, and also preserves mouse spermatogenesis. In another study conducted, the testosterone levels of men who slept for 5 hours at night decreased by 10-15% compared with the general population [38].

D) Nervous System

The nervous system is separated into two main components - the central nervous system (including the brain and spinal cord), and the peripheral nervous system [39], which consists of the nerves outside of the brain and spinal cord. The peripheral nervous system is further divided into the somatic nervous system and the autonomic nervous system (ANS), which connects your brain to your internal organs and functions automatically . Circadian rhythms regulate the brain and the body's functions, ANS balance, and the CNS/ANS interaction, which involves complex neural pathways and non-neuronal factors. The autonomic nervous system regulates heart rate, respiration, hormone secretion, smooth muscle activity and biological sensors to maintain a homeostatic balance [40]. For example, the peak in cortisol levels in the morning is associated with sympathetic activation, which involves your fight or flight response when you are stressed or active. The interactions between the central and the autonomic nervous system change with timing throughout the day and the sleep schedule.

Circadian dysfunction is often associated with a higher risk of brain disorders that include psychiatric conditions like depression.Chronic shift workers are more vulnerable to various diseases and have a higher risk of psychiatric disorders [41]. Most evidence linking brain disorders is correlational rather than causal but even in brain disorders where circadian disruption is not the primary case, it has been shown that stabilizing sleep-wake patterns may alleviate the symptoms [41]. A study conducted with 11,450 Canadian nurses showed a strong relationship between work schedule and depression, especially with those having rapidly changing or undefined work schedules [42]. Another survey conducted by US National Health and Nutrition

found out that flight attendants are 2-5.7 times more likely to experience sleep disorders, depression, anxiety and fatigue compared to the general population [43].

In older adults, weak circadian rhythms and fragmented patterns of activity are risk factors for developing dementia. Single nucleotide polymorphisms (SNPs) in CLOCK and BMAL1 are linked to an increased risk of Alzheimer's, and SNPs in BMAL1 and PER1 are linked to Parkinson's disease [41].Individuals with these diseases have also been found to exhibit lower melatonin rhythm amplitudes, excessive sleepiness, and disturbances in the sleep wake cycle, including later sleep onsets. Additionally, although individuals with Alzheimer's disease still exhibit cycling clock gene expression, they lose the typical phase coherence within and across the regions [41] .

E) Cognitive Function

Shift work often leads to decreased and impaired sleep which could contribute to a range of cognitive problems, such as a decrease in alertness and concentration, and an increase in reaction time [44]. These are measured most often by the psychomotor vigilance test which provides information about reaction times and lapses, and is also sensitive to the effects of sleep loss. Shift work also causes partial or total sleep deprivation which could lead to prolonged wakefulness. Prolonged wakefulness has been shown to have adverse effects on cognitive function [45]. Previous research has shown that disruption of the circadian cycles can increase the human error rates due to slower reaction times and decreased attention span [46]. Evidence shows that the main cause for several industry related accidents such as Chernobyl and Three Mile Island have all occurred during the middle of the night, and the main cause for these accidents have been investigated to be shift work and human error [47]. The risk of errors and accidents increase by 15% in the evening and 28% at night compared with day shifts. In addition, it is shown that the likelihood of errors and accidents in consecutive shifts increases by 17% and 36% on the third and fourth night respectively [48].

Insufficient sleep could also lead to episodes of microsleep–the person may appear to be awake but their brain will not process any information and may have lapses in attention [49]. These attentional lapses have been thought of as the main reason for the decrease in cognitive function during sleep deprivation [45]. According to the "sleep based neurological perspective," sleep deprivation may impact cognitive function by interfering with the function of certain brain areas [50.] The most famous theory in this category—the prefrontal vulnerability hypothesis—suggests that sleep deprivation affects functions that depend on the prefrontal cortex, such as language, executive functions, divergent thinking and creativity. Shift workers have also reported psychological problems such as bad mood, depression, irritability, anxiety, personality changes and difficulty with personal relationships [48].

F) Endocrine system

In the endocrine system, daily rhythms may be influenced by both intrinsic and extrinsic factors. During sleep, cellular repair takes place and hormones such as melatonin and corticosterone transmit signals from the hypothalamic and brain stem nuclei to the rest of the body to prepare it

for changes in food activity, rest and physical activity that occurs on a daily basis [51]. Various tissues, such as the adrenal gland and the pancreas both have local tissue oscillators. The adrenal molecular clock controls the Adrenocorticotropic hormone (ACTH) sensitivity and it has also been shown that the disruption of local clocks in the pancreatic Beta cells influence insulin secretion [52].

Extended periods of desynchrony between circadian rhythms and the endocrine system (of what)are linked with altered immune function, tumor growth, reduced body temperature and an increase in adiposity. In an animal study conducted, mice that did not have the BMAL1 gene had lower levels of circulating insulin, but the levels of adiponectin and leptin were higher [25]. Genetic manipulation of the circadian clock has also been shown to affect the sensitivity of insulin. If the positive clock component is affected, the sensitivity of the insulin increases and vice versa [25]. Shift work results in the misalignment of cortisol and melatonin rhythms, and is linked to an increase in the risk of developing cardiometabolic disease. This is due to an increase in the postprandial levels of several hormones such as insulin, glucose and triacylglycerol in the night shift, an increase in the energy intake and circulating triglycerides, along with reduced insulin sensitivity and postprandial ghrelin release. Observations in night shift workers show that shift work leads to changes in feeding patterns, leading to increased food intake during the normal rest period. This leads to an increase in obesity and increased accumulation of abdominal fat—a sign of unbalance in metabolism [53]. Additionally, the atypical levels of cortisol at the beginning of the shift work wake episode could lead to insulin resistance and hyperglycemia. Moreover, decreased leptin levels reduces energy spent and increases the appetite. If this is maintained over a long period of time, it could lead to the development of obesity [54].

Countermeasures to the effects of shift work and impaired circadian rhythms

Majority of sleep-wake disorders are caused due to misalignment between the intrinsic and the external light-dark cycles. Hence, to treat sleep-wake disorders, a central objective is to reduce the misalignment between the two light-dark cycles. This could be done by using light, as it is a powerful zeitgeber and could shift the endogenous clock. Laboratory studies have shown that exposure to bright light 3-6 hours before the circadian nadir have shown significant shifts in circadian phase [55, 56]. This, however, is a challenge in real life as the circadian phase for shift workers can be anywhere across the 24-hour cycle and it is difficult for clinicians to determine the exact time of light exposure [57]. Additionally, the shift workers must maintain a consistent sleep-wake cycle 7 days a week in order to have complete circadian entrainment. Exogenous melatonin administration can also act as a potential zeitgeber and improve circadian adaptation among shift workers. However, as light is a stronger zeitgeber compared with melatonin, poorly timed light exposure could easily override the benefits of taking melatonin. Moreover, 1 mg, 2 mg, 3 mg and 4 mg of melatonin have all been shown to produce approximately the same amount of phase shifts in young adults (1.5 hours), which is less than that produced by bright light exposure [58].

Another way of combating problems associated with insufficient sleep can be by improving sleep quality. This could be done by practicing simple sleep hygiene such as avoiding alcohol and caffeine close to bedtime and by sleeping in an optimal sleeping environment that is dark, quiet and uncluttered.. Sleep anchoring—creating a sleep period that overlaps on both work and

non-work days—also helps to improve sleep quality by stabilizing circadian rhythms and increasing sleep duration. Planning strategic naps also increases total sleep time as well as increasing alertness and performance in shift workers. It has been shown that napping prior to and during shifts decreases reaction time, reduces fatigue and improves alertness [59]. Combining strategic naps with other countermeasures can also have a significant effect. For example, a study conducted with professional drivers working shifts showed that taking two ten-minute naps followed by ten minutes of bright light exposure reduced the risk of sleep onset during a simulated driving task [59] .

Drugs such as exogenous melatonin, ramelteon and tasimelteon have all shown to improve sleep in shift work simulation studies [60]. However, data from these samples are limited and it is also vital to control exposure to light, which could undermine the benefits of these drugs. Moreover, there are side effects such as dizziness, fatigue and nausea (ramelteon), and an increase in prolactin levels (melatonin and its agonists) [60]. Other drugs such as benzodiazepines improve sleep but have a small effect on alertness. Newer sedative-hypnotic agents which do not contain benzodiazepines enhance sleep as well performance for shift workers, but are associated with side effects such as anxiety and an irritable mood [7].

Conclusion

Shift work-induced circadian disruptions have profound impact on human physiology and cognition. The intricate interplay between circadian rhythms and various physiological systems, including the cardiovascular, digestive, reproductive, nervous, and endocrine systems, highlights the pervasive nature of circadian disruption beyond mere sleep disturbances. Shift work not only compromises physical health but also poses significant risks to cognitive function, increasing the likelihood of errors and accidents, particularly in safety-sensitive environments.

Furthermore, the exploration of potential countermeasures has revealed promising avenues for addressing the challenges associated with shift work. Strategies such as light exposure, melatonin administration, sleep hygiene practices, strategic napping, and pharmacological interventions offer practical approaches to enhance circadian adaptation and improve overall well-being among shift workers. However, the complexity of individual responses and the varying nature of circadian rhythms necessitate further research to optimize intervention strategies and tailor them to specific populations. Together with precise interventions and understanding support systems, it would be easier to enhance both individual well-being and social productivity.

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