Jurnal Sains Kesihatan Malaysia **18** (1) 2020: 47 - 61
DOI : http://dx.doi.org/10.17576/JSKM-2020-1801-07

Kertas Asli/*Original Article*s

The Effects of Circadian Rhythm Disruption towards Metabolic Stress and Mental Health: A Review

(Kesan Gangguan Ritma Sirkadian terhadap Stres Metabolik dan Kesihatan Mental: Satu Tinjauan Kepustakaan)

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ABSTRACT

This review aims to present an overview of current research findings on the possible effects of circadian rhythm (CR) disruption towards metabolic stress and mental health. CR can be described as an internal biological clock that regulates our body functions, based on our sleep/wake cycle. Any time that our normal 24-hour circadian rhythm is altered or interrupted, it will have physiological and psychological impacts. However, in today's demanding working world, most of us are working defying the normal conditions without realising the significant drawbacks of it. Therefore, this review summarises the findings from several researches on the physiological (metabolic stress) and psychological (cognitive functioning and mental health) impacts of the CR disruption in order to assist people to have a holistic view on the effects of CR to our mind and body. Evidences that linked these aspects to health circumstances of shift workers have also been highlighted.

Keywords: Circadian rhythm; metabolic stress; sleep/wake cycle; cognitive performance; mental health; shift workers

ABSTRAK

Tinjauan ini bertujuan untuk menunjukkan gambaran keseluruhan penemuan penyelidikan semasa mengenai kesan gangguan ritma sirkadian (RS) terhadap stres metabolik dan kesihatan mental. Ritma sirkadian (RS) didefinisikan sebagai jam biologi dalaman yang mengawal fungsi badan kita berdasarkan kitaran tidur/jaga kita. Jika RS 24-jam kita yang biasa terganggu, ia akan memberi kesan kepada sistem fisiologi dan psikologi kita. Walau bagaimanapun, dalam era globalisasi ini, kebanyakan individu bekerja pada luar waktu normal tanpa menyedari kesan buruknya. Oleh itu, tinjauan ini merumuskan penemuan daripada beberapa kajian mengenai kesan gangguan RS terhadap sistem fisiologi (stres metabolik) dan psikologi (fungsi kognitif dan kesihatan mental) kita agar dapat membantu masyarakat kita untuk mempunyai pandangan holistik terhadap kesan RS ke atas minda dan badan kita. Kesimpulan yang menghubungkan aspek-aspek ini dengan keadaan kesihatan pekerja syif juga telah dibincangkan.

Kata Kunci: Ritma sirkadian; stres metabolik; kitaran tidur/jaga; prestasi kognitif; kesihatan mental; pekerja syif

INTRODUCTION

Humans are made as diurnal species, opposite of nocturnal ones where we are created to be active in daylight and inactive at night. This type of behaviour is controlled by a built-in mechanism called circadian rhythm (CR), which is located in the brain. The CR or biological clock, circadian clock, etc. is known as the 24-hour day and night cycle which makes every life on earth becomes dependent on this environmental cue, or also known as 'Zeitgebers' (German word that means 'time givers'). CR disruption through routine changes especially sleep or meal time affects the natural relationship between rest/activity cycle and light /dark cycle of the environment.

Although humans are created diurnal, these days many conditions require someone to work defying the normal conditions. For example, with the increase demand in industrialised countries has urged the employers to offer a service of 24 hours to produce continuous production. Some career may require their staffs to work around the clock such as medical officers, nurses, police officers and fire fighters to offer services in kind anytime in need. In the meantime, some organisation applies labour cost savings, consequently the workforce become smaller and urge the employees to work outside traditional hours (07:00 am to 6.00 pm), which is referred as shift work (Siebenaler & McGovern 1991). The shift work design may disrupt sleep/wake configuration because the workers need to stay

awake at night and disregard the light/dark cycle which eventually will lead to the disrupt of circadian rhythm of the brain and body.

Besides that, airliners also typically work at irregular schedules, long working hours, early starts times and night work. In relation to this, they often report jet-lag symptoms such as difficulty to initiate sleep, poor alertness and fatigue (Samel et al. 1995). This is believed due to the disruption of CR timing caused by the transmeridian flight (flight across time zones). Main attributes of normal CR are the light/dark cycle and social cues (Wulff et al. 2012). But a rapid change of time zones makes it difficult for the CR system to re-entrain immediately (Weyer 1980) which results in the alignment of CR with the timing of departure not the timing of local (Winget et al. 1984). This explains how the desynchronization of CR causes jet lag symptoms.

Therefore, this review will discuss on how the upsetting of circadian system can exert influence on metabolism, cognitive functioning and mental health. Evidences that linked these aspects to health circumstances of shift workers have also been highlighted.

CIRCADIAN RHYTHM (CR)

All free-living organisms are regulated by the 24-h light and dark cycle produced by earth's rotation. All bodily processes such as sleep, hormonal secretions, digestion are governed by the circadian rhythm, an internal biological clock that aligns internal metabolism as well as physiological and behavioural attributes to changes in the 24-hour light and dark cycle. The biological clock programmed in the body's genetic material is being controlled by the suprachiasmatic nucleus (SCN) of the brain's hypothalamus, allowing the appropriate phase of the rhythm to take place in the peripheral organs (Dixit et al. 2017; Mattson et al. 2014).

Sensory input is delivered to the SCN via retinohypothalamic tract from photosensitive ganglion cells in the retina making SCN is very receptive to light. This process optimizes CR system in the light/dark cycle every day. The CR is mainly influenced by melatonin that is secreted by the pineal gland in hypothalamus. It is tremendously low during daytime, high during night and decreased gradually at dawn (Arendt 1998).

As CR is being controlled by SCN, and the SCN acts as the master pacemaker in the brain. It orchestrates the timing rhythms in other regions of the brain and throughout the body where the secretion of hormones and peptide implicate the rhythms in the brain. Environmental factors such as food and stress may influence the rhythms both in brain and the body (Mc Clung 2011).

CR is also a cycle between sleepiness and alertness at regular interval or known as sleep/wake cycle. As stated by Mc Clung (2011), SCN are responsive to light. When it's dark at night, the eyes will send a signal to the thalamus to alert the body tiredness. Hence, the SCN sends a signal to the body to release the melatonin, the hormone that is responsible to make the body tired. Having a regular sleep habit helps CR to work at its best. When the regular pattern of the CR is disrupted, it can lead to mood disruption, cognitive deficits and even metabolic stress as all the hormones are related to the functions are interlinked with SCN.

CIRCADIAN RHYTHM AND SLEEP

Sleep is a vital process in any life cycle. There are two types of sleep which are Non Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. NREM sleep encompasses four stages. Stage 1, is the sleep onset marked by theta wave or slow wave where the noise is screened out from surrounding but we are still aware of any loud noise. In stage 2, our body temperature starts to drop, breathing and heart rates slows down and the sleep spindles and K-complex waves alternate each other. Delta waves marked a deep sleep which can be achieved in stage 3 and 4 (Matheson et al. 2007). These phases are important in restoring energy, releasing growth hormones and strengthening immune system. During REM sleep, eyes roll rapidly, breathing become faster and we dream vividly. This phase is essential for memory consolidating, problem solving and information processing which includes the encoding of information into long-term memory.

The neurophysiology of sleep and wakefulness is regulated by the action of sleep-promoting neurons in the anterior hypothalamus and sleep inhibiting neurons in the lateral and posterior hypothalamus on the arousal promoting systems in the brain stem (Behn et al. 2007 & 2008; Schott & Hobson 2002). The excitatory neurotransmitter such as noradrenaline, serotonin, histamine, acetylcholine and orexin are secreted in the brainstem, midbrain and basal forebrain structures during wake state. The inhibitory neurotransmitter such as GABA from ventrolateral preoptic nucleus (VLPO) secretion is suppressed.

Moreover, during sleep, NREM stages decreases arousal by all aminergic and cholinergic neurotransmitters are inhibited through VLPO mediated GABA and galanin release. While during REM sleep the release of aminergic neurotransmitter of the brainstem is inhibited, but acetylcholine and orexin are released. GABA and galanin that are released from the brainstem and VLPN act to inhibit aminergic brainstem neurons (Wulf et al. 2010). It was

reported that the normal secretions of the hormones will be interrupted if the CR is disrupted especially in the sleep deprived state.

CR has a very evident function in organism's biological activities, but the sleep/wake cycle is undeniably the most visible aspect in exhibiting the role of CR. In the sleep/wake cycle, the body temperature regulates the day-night routine to wake up in the morning and to sleep at night. When the circadian rhythm resets every 24 hours, the external temporal environment by light, temperature and food can be synchronised with the body functions (Dixit et al. 2017). As the sleep/wake cycle involves in the interplay between sleep homeostatic mechanism and CR system, Reichert et al. (2016) concluded that a change in homeostatic sleep pressure and circadian timing interfere with human behaviour concerning working memory, performance and underlying brain activity.

According to National Sleep Foundation (2017), a good night sleep consists of more sleep time on the bed (at least 85% of the total time), falling asleep in 30 minutes or less, waking up no more once per night and being awake for 20 minutes or less after initially falling asleep. While the duration of sleeping hours varies according to the age (Ohayon et al. 2017).

With the daunting demand to keep up with all the daily life, many people deprived their sleep to compensate with the tasks. Many choose to sleep less than 7 hours to cope with the demand, such amount can be considered of being deprived (Ohayon et al. 2017). According to Naitoh et al. (1990) sleep deprivation can be divided into sub categories which are total sleep deprivation, partial sleep deprivation and selective sleep deprivation. Total sleep deprivation can be defined as no sleep at least 24-hour cycle. Partial sleep deprivation occurs in an individual where a person sleeps less than usual.

Insufficient amount of sleep can give impacts to cognitive functioning, mood, work performance and quality of life (Kaliyaperumal et al. 2017; Alhola & Polo-Kantola 2007). Moreover, many scientists are being aware of the health risks due to sleep disorder. The inability to sleep may compromise with the secretion of insulin, suggesting the relation between sleep and diabetes (Khandelwal et al. 2017; Shan et al. 2015) which may cause weight gain (Marks & Landaira 2015).

CIRCADIAN RHYTHM AND METABOLIC STRESS

As CR also plays an important role in the metabolism process, circadian misalignment from a disturbed sleep/wake cycle can result in metabolic diseases incorporating glucose content, blood pressure, triglycerides (TG) and cardiorespiratory competency (Neil-Sztramko et al. 2014). Studies have shown that adverse effects for interference in circadian melatonin are associated with cardiovascular diseases, obesity and diabetes risks (Joseph & Golden 2017; Kim et al. 2015; Rutters et al. 2014; Shanmugam et al. 2013).

Daily patterns of energy expenditure, hormones, and lipids involved in energy metabolism (e.g. leptin, ghrelin, glucose, insulin, catecholamines, fatty acids, triglycerides) are regulated by sleep and circadian rhythms (Depner et al. 2014). Epidemiological and experimental studies have demonstrated that sleep quality and quantity are important determinants of whole-body metabolism and the sleep deprivation can have a major impact on the metabolic processes and may constitute underlying mechanisms responsible in part for the increasing prevalence of metabolic disorders such as obesity and diabetes (Briançon-Marjollet et al. 2015; Morris et al. 2012; Van Cauter et al. 2008). The commonly used metabolic stress markers are glucose, triglycerides, cortisol, blood pressure and heart rate (Arimi Fitri et al. 2015; Roselina Mokhtar et al. 2019; Nik Nur Izzati & Suzana Shahar 2018).

The endogenous CR also plays a role in the regulation of glucose metabolism, as such circadian misalignment by insufficient sleep may induce imbalance of metabolism leading to insulin sensitivity and diabetes, as well as hormonal rhythm problems to explain obesity, such as the dysregulation of leptin, that is the hormone that tells you when to stop eating which increased during sleep, and ghrelin known as the "hunger hormone" that decreased during sleep (Kim, Jeong & Hong 2015). In relation to this, other epidemiological studies have also associated poor sleep quality to obesity, while chronic disruptions of CR mostly from sleep alteration and meal frequency intake develop a higher chance for cardiovascular diseases, certain types of cancer and neurodegenerative diseases (Mattson et al. 2014; Morris et al. 2012; Stevens et al. 2014).

The complexity of disrupted metabolism can be further demonstrated by observations of elevated levels of pro-inflammatory cytokines. The bulk of the evidence stems from sleep restriction studies which indicate that poor sleep is associated with an exaggerated inflammatory response indicated by increased circulating concentrations of the proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α (Mullington et al. 2010), and C-reactive protein (CRP) (Ferrie et al. 2013). These markers of inflammation have been associated with chronic inflammation state and contribute to the risk of a wide spectrum of medical conditions. Increases in circulating markers of inflammation, such as high sensitivity C-reactive protein and interleukin-6 (IL-6), predict cardiovascular events, hypertension, weight gain, and type 2 diabetes (Barzilay et al. 2001; Irwin et al. 2016).

More recently, with the introduction of high sensitivity CRP (hsCRP) assays, very low level sub-clinical levels of CRP became detectable in serum and plasma. These levels were found to be associated with future risk for the development of cardiovascular disorder (CVD), even in healthy, asymptomatic men and women (Ridker 2001). HsCRP is not the only inflammatory marker of risk in CVD currently available; however, it is arguably the most clinically useful because it is relatively stable across weeks and months (Glynn et al. 2009), has a long half-life of 15–19 hours and does not show a diurnal rhythm (Meier-Ewert et al. 2001).

The sleep-wake cycle is often one of the first responses to acute inflammation and infection and that the reciprocal effect of sleep on the immune system in acute states is often protective and restorative. For example, slow wave sleep can attenuate proinflammatory immune responses while sleep deprivation can aggravate those responses. Sleep influences two primary effector systems, the HPA axis and the sympathetic nervous system, which together shift the basal gene expression profile toward increased pro-inflammatory responses. Activation of β-adrenergic signalling induces increases in NF-κB, inflammatory gene expression, production of proinflammatory cytokines, and markers of systemic inflammation. Given that normal nocturnal sleep is associated with a drop in sympathetic outflow, activation of the sympathetic effector pathway is one of the biologically plausible mechanism to explain the associations between sleep disturbance, short sleep duration, and increases in markers of inflammation (Irwin et al. 2016).

Recent studies have also given attention to cohort-based studies involving pregnant women's metabolic condition. A meta-analysis by Reutrakul and Van Cauter (2014) indicated that irregular glucose metabolism among pregnant women was prevalent with diabetes. Gestational diabetes mellitus was related to short duration of sleep and higher daytime sleepiness, affecting detrimentally on maternal and fatal health.

Another circumstance that has an impact on CR is social jet lag, which is referred to individual's differential sleep pattern on the weekend and during working weekdays. In an attempt to associate metabolic syndrome and type-2 diabetes mellitus with social jet-lag, a population-based study by Koopman et al. (2017) measured usual bedtime and wake times of elderly during weekdays and weekend using Munich Chronotype Questionnaire (MCTQ), as well as fasting blood glucose sample to assess the levels of glucose and enzymatic techniques to evaluate HDL and TG. Analysis on HDL and TG found that metabolic syndromes were associated with individuals having more than 2 hours of social jet-lag, as compared to those with less than 1 hour of social jet-lag. Furthermore, greater risks of diabetes mellitus was significantly correlated with participants who reported more than 2 hours of social jet lag as determined by higher levels of glucose and waist circumference.

Similarly, Rutters et al. (2014) in their experimental study portrayed that in comparison to participants experiencing more than or equal to 1 hour of social jet lag, participants who had more than or equal to 2 hours of social jet-lag reported decreased amount of sleep in a week, more physically inactive and increased resting heart rate, putting them at a higher risk for cardiovascular diseases and diabetes.

Wani et al. (2017) studied on the effect of metabolic syndrome on more serious illness. Metabolic syndrome defined by impaired glucose metabolism and type-2 diabetes mellitus was examined with breast cancer risks. Drawn 10ml of blood sample from breast cancer case group and control group was tested for fasting plasma glucose, and levels of serum TG, HDL, low-density lipoprotein (LDL) and serum cholesterol. Findings concluded that patients who were initially affected by metabolic syndrome would commit for higher risks of developing breast cancer from stronger association with serum TG levels and fasting blood glucose levels. Meanwhile, breast cancer was not predicted by low HDL since significant difference could not be observed by the level of HDL in case group and control group.

In relation to this, Anjum et al. (2014) exhibited melatonin influence on the occurrence of breast cancer using samples of urine. Chronic melatonin reduction as a result of alternating night shifts interrupted its secretion pattern which indicated carcinogenic mechanism relating to higher breast cancer risk. In several studies to explain disrupted nocturnal melatonin on breast cancer, higher daytime sleepiness, night-time work and reproductive hormones production were correlated with lower levels of urinary 6-sulfatoxymelatonin, encouraging an increased risk of breast cancer among night-shift female workers (Davis et al. 2012; Mirick et al. 2013).

Evidence for the treatment of sleep and circadian problems to improve metabolic health is emerging, thus to optimize public health recommendations based around sleep deficiency and metabolic dysfunction, a better understanding of the physiological mechanisms by which sleep problems contribute to metabolic disorders is needed.

CIRCADIAN RHYTHM ON MOOD AND PSYCHOLOGICAL WELLBEING

Mood is an affective state of feeling that people experience that can be categorized as positive affect and negative affect. Positive affect is a mood dimension encompasses

particular positive emotions where excitement at the high end and boredom, tiredness at the low end. A negative affect means a mood dimensions containing nervousness, stress at the high end and relaxation, tranquillity at the low end.

Individuals with mood disorders often display abnormal rhythmicity of body temperature, cortisol and melatonin levels, blood pressure, and sleep/wake cycles suggesting circadian rhythm disruption (Wirz-Justice 2006). As mood are concurrently associated with the neurotransmitter secretes by the brain in the limbic system, sleep disruption destabilize circadian physiology thus exacerbating abnormal pattern of neurotransmitter released. A state of internal de-synchronization may also occur including hormonal and behavioural rhythm (Schibler 2007). Although major mood and rewards related circuits has its own endogenous rhythm that synchronized by SCN, it can also be desynchronized by SCN under certain conditions. Individual circadian genes play key roles in this mood-related circuits in both regulating activities 24-hour per day and even ultradian synchronization of neuronal firing within and between various brain structures.

Abnormalities in sleeping behaviour are one of the sign for the diagnosis of mood disorders in the classification used in Diagnostic and Statistical Manual of Mental Disorder 5. Previous researches have shown that CR misalignment is closely related with sleep disorders. The most common sleep disorder, insomnia, is known to contribute to psychiatric disorder, and was reported in a number of studies relating to interruption in the circadian system. In a review analysis by Soehner et al. (2013) about insomnia comorbidity to schizophrenia, it was concluded that a low total of sleep time resulting from higher sleep-wake disturbances, had increased psychotic symptoms such as delusions, hallucinations, as well as disorganised thinking and behaviour, with prolonged sleep latency was related to higher thinking disturbance. It was also reported that, for Major Depressive Disorder (MDD), 90% of the patients report difficulties in initiating and maintaining sleep resulting changes in their sleep profile. Similarly, irregularity and disruption of sleep/wake cycle have been identified as the triggers for manic episodes in Bipolar Disorder patients. In relation to these findings, it was reported that ensuring stable and adequate sleep is one of the main therapy in the process of intervening individuals with mood disorders (Plante & Winkelmen 2008).

In relation to above-mentioned findings, researches of disrupted CR on cabin crews and mental health problems were taken into account due to transmeridian travel. Izadi and Ahmadinejad (2015) reviewed that mental disorders such as depression, anxiety, paranoid schizophrenia and mania symptoms may be instigated by jet-lag, causing long hours of flights for airliners especially for flights crossing time zone and alternating work schedule. A study by McNeely et al. (2014) which compared the mental health status of flight attendants and general U. S. population found that the rate of sleep disorders, depression, anxiety and fatigue were higher among the flight attendants.

Having said that, Inder, Crowe and Porter (2016) had exhibited that mood episodes with transmeridian travel and jet-lag precipitated if the individuals had history of mood disorders and without adherence to medication. On the other hand, as transmeridian travel mostly triggered conflict between endogenous CR sleep timing and the sleep / wake period in the new time zone due to shortened sleep duration, episodes of depression and manic / hypomanic were more related to westward travel than eastward travel. Because westward's travel endogenous CR resets after 92 minutes each day, and 52 minutes earlier after eastward flight, thus it is more notable for individuals in westward travel to remain sleeping since the circadian signal for alertness is activated during the desired sleep period (Inder et al. 2016; Zee & Goldsteinland 2010).

On the other hand, it has been highlighted that there are close interconnections and reciprocal regulation between the circadian clock and the stress response system in which the circadian clock genes regulate the physiological sensitivity to, and rhythmic release of glucocorticoids (GC). In turn, GCs have reciprocal effects on the clock. The common mechanism by which circadian clock genes affect multiple psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD); is the modulation of the stress response (Landgraf et al. 2014).

According to the Diathesis–Stress Model, the effect of CR disruption can be seen as an environmental challenge factor that combines with the genetic factor in causing mental disorders. Therefore, the chronic factors of CR disruption and environmental stresses can weaken the individual's physiological ability to act with these stresses. Failure to this endurance system exposes individuals to mental disorders.

Aarti et al. (2013) reported that the link between the sleep and circadian rhythms (SCRD) and the neuropsychiatric disease, especially in schizophrenia, bipolar disorder and major depression, can be explained in a more cyclic relationship rather than a linear relationship whereby psychiatric disorders results in SCRD as a result of stress axis, social isolation and/or medication. Based on the cyclic relationship, it was explained that the psychiatric disorders and SCRD reinforce one another and share common and overlapping mechanisms. Impairment in neurotransmission/ neurodevelopment, and cognitive/health issues can make an impact on both the sleep/circadian and psychiatric axis,

while stress, social isolation and medication resulting from psychiatric disorders can lead to sleep/circadian disruption (Figure 1).

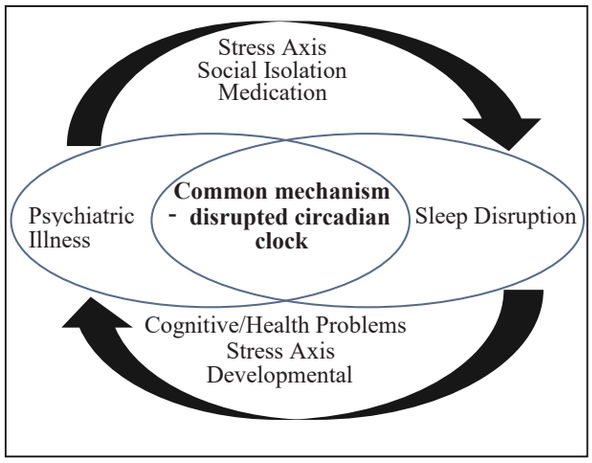

FIGURE 1 Links between SCRD and psychiatric illness
Source: Aarti et al. (2013)

CIRCARDIAN RHYTHM AND DEPRESSION

Depression is a common and serious medical illness that negatively affects how you feel, the way you think and how you act (APA 2013). The results of the previous study showed that the inconsistency of CR often leads to the presence of the symptoms of major depression (Emens et al. 2009). Aarti et al. (2013) reported that the connection between the circadian system and depression has been evident since the 1960s and 70s, when it was found that the patients with depression lose 24-hour rhythmicity in cortisol secretion.

In discussing about depression, insomnia, as a matter of fact, was revealed as a symptom in psychiatric disorder that was most likely relevant to depression (Cordoba et al. 2017; Luca et al. 2013). As accentuated by Salgado-Delgado et al. (2011), variation in depressed mood, was therefore common if the individuals experienced improved mood state in the evening since their sleep/wake cycle was already disturbed due to having insomnia at night and hypersomnia during the day. Since the homeostatic mechanism in circadian system functioned to regulate the sleep/wake cycle, by right, if the person was always sleepy during daytime from shorter sleep duration, sleep debt was more likely to occur, causing the person to sleep in longer time. But this case was unable to be experienced by depressed individuals because of alteration in both of their homeostatic function and circadian rhythms.

Turek (2007) reported that CR disruption could lead to depression in two general ways, (1) disorganisation within the circadian system could itself lead to neurobiological dysfunction and (2) a circadian disturbance of the normal sleep–wake cycle could facilitate or exacerbate the depressed state. It was reported that the type of rhythm abnormality is found to be highly variable in the depressed condition, including phase advance or phase delay of rhythms such as the early occurrence of many physiological events in patients with depression compared to normal individuals; as well as an increase or decrease in the amplitude of various rhythms.

This finding also explained that the expression of most rhythms at the behavioural, physiological, and biochemical levels is controlled by the assimilation of information from the circadian clock and the sleep–wake state. This shows that the circadian and sleep control centres have evolved together to ensure that the timing in the internal and external environments is coordinated in such a way to maximize the survival of the species.

In addition, the seasonal affective disorder (SAD) has also been associated with the CR disruption (Aarti et al. 2013). SAD is a sub-type of depression where individuals experience depressive symptoms and show hypersomnia only in the winter months. Previous studies revealed that variation in polymorphisms in the three circadian clock genes, NPAS2 (neuronal Per-Arnt-Sim domain protein 2), PER2 (period homolog 2) and ARNTL (aryl hydrocarbon receptor nuclear translocator-like); and in OPN4; are keys to the pathogenesis of SAD (Partonen et al. 2007; Roecklein et al. 2009, 2012; Wulf et al. 2010).

These researches discovered that, as a function of day length, the polymorphisms in OPN4 varies individuals sleep onset and chronotype. OPN4 is the photopigment of the photosensitive retinal ganglion cells, which directly signal light information to the suprachiasmatic nucleus as well as the ventrolateral preoptic nuclei (VLPO) (Gooley et al. 2003). These findings explain clearly that some forms of depression might be linked directly to the photic pathways that regulate circadian rhythms and sleep.

CIRCARDIAN RHYTHM AND BIPOLAR DISORDER

Bipolar disorders are brain disorders that cause changes in a person's mood, energy and ability to function (APA 2013). The connection between the CR disruption and bipolar disorder (BD) also has been well documented in the past and current research. Takaesu et al. (2016) explained the dysfunction of CR due to sleep disturbance among euthymic bipolar disorder (BD) patients. Participants went through a clinical interview and had a sleep log for researchers to monitor participants' sleeping pattern before they were categorised for sleep disorder according to International Classification of Sleep Disorders-3rd Edition

(ICSD-3). Prevalence between circadian rhythm sleep-wake disorder (CRSWD) and bipolar disorder using Montgomery-Asberg Depression Rating Scale and Young Mania Rating Scale were strong, especially if the individuals had family history of psychiatric disorders and suicide.

A review paper by Melo et al. (2016) reported that the substantial majority of studies identified a disruption of circadian rhythm and an evening preference in patients with BD, independently of mood status. Findings of this study suggest the alterations in daily profiles of melatonin levels and cortisol, act as the reinforcers for the circadian dysregulations in patients with BD. As cited in this paper, few studies reported that the circadian disruption in BD were more frequent in patients with depression than in euthymic patients (Ashman et al. 1999; Krane-Gartiser 2014; Pinho et al. 2016; Rosa et al. 2013).

A recent study reported that the increased light exposure in the spring, results in acute circadian rhythm shifting which causes misalignment between the endogenous and environmental circadian rhythms. It was explained that during the onset of spring, the circadian rhythm of a healthy individual advances in line with the earlier time of sunrise. However, in depressed patients with a delayed endogenous circadian rhythm, exposure to bright light early in the morning during the spring delays their circadian rhythm further. The significantly more delayed circadian rhythm is then able to trigger a mixed/manic episode or emotional instability, directing to a possible suicide attempt in susceptible individuals (Cho & Lee 2018). A similar finding was reported by Moon et al. (2016) in which the biochemical circadian rhythms in manic episodes of bipolar patients were reported as significantly advanced compared to controls, whereas the mixed manic episodes and depressive episodes were reported to be associated with phase delays in circadian rhythm.

The role of melatonin was prominent to explain manic episodes among BD patients. As a result of disturbed circadian profile, the differential patterns of melatonin secretion were observed during advanced phase for manic episode and during phase delayed for phase for depressive episode (Hickie et al. 2013). This means patients who experienced mania were most likely to fall asleep at several hours advanced than normal sleeping time, while individuals who were depressed had a later sleeping hour as well as having more difficulty waking up at a desired time. Consistently, Moon et al. (2016) found that most reported cases of acute manic and depressive episodes had approximately 7 hours sleep advanced and 4 to 5 hours sleep delayed sleep, respectively. Hickie et al. (2013) also concluded that the severity in amplitude responses from rate changes of melatonin secretion is related to mood disorders, indicating that acute depression was dependent on the degree of sleep disturbance.

CIRCADIAN RHYTHM AND SCHIZOPHRENIA

Schizophrenia is a serious mental illness characterized by incoherent or illogical thoughts, bizarre behaviour and speech, and delusions or hallucinations, such as hearing voices (APA 2013). Schizophrenia has also been associated with the CR disruption. The prevalence of sleep and circadian rhythm disruption (SCRD) in patients with schizophrenia has been documented to be as high as 80% and has been portrayed as a hallmark of the disorder (Cohrs 2008; Krysta 2017). Monti et al. (2013) reported that most of the sleep disturbances in patients with schizophrenia appear to be caused by abnormalities of the circadian system as indicated by misalignments of the endogenous circadian cycle and the sleep-wake cycle.

This finding explained that the circadian misalignments leading to sleep-wake disruption may also be credited to secondary effects such as insufficient light exposure and weak social zeitgebers that lead to circadian desynchronisation and lack of entrainment. As cited in this study, there are several studies have reported the similar findings and further explained that these circadian misalignments range from delayed and advanced sleep phase, free running rest-activity patterns to irregular sleep-wake patterns (Bromundt, et al. 2011; Pritchett et al. 2012; Wulff et al. 2006). Wulff et al. (2012) also reported that the rest–activity and melatonin rhythms of patients with schizophrenia are often fragmented, unstable, and phase shifted and therefore not well synchronised to the environmental light/dark cycle.

The relation between CR disruption and schizophrenia was further supported by Pritchett et al. (2012), whereby the intervention of SCRD was reported to show improvements in both the sleep quality and psychiatric symptoms of schizophrenia patients. Furthermore, this study has highlighted that the negative symptoms of schizophrenia might also be sensitive to SCRD as the circadian disruption was proven to increase the negative mood, irritability and affective volatility in healthy individuals.

CIRCADIAN RHYTHM DISRUPTION AFFECTS COGNITIVE PERFORMANCES

The misalignment between the circadian pacemaker and behavioural/environmental cycles increases cognitive vulnerability on sustained attention, cognitive throughput, information processing and visual-motor performance over multiple days (Sarah Laxhmi Chellappa et al. 2018; Kyriacou & Hasting 2010). Working memory (WM) implies a combination of storage and manipulation (Baddeley 2012). The WM framework proposed by Dr Alan Baddeley

is widely accepted as he regard WM as a multifaceted function that captures visual and auditory information, directs attention and coordinates processes which demonstrate strong link between WM and attention control. Thus, working memory is vital in everyday task because it holds the ability of an individual to control attention when facing distraction.

This ability is essential in performing cognitive activities such as maintaining attention, following directions, execute multi step procedure and complex reasoning. It is agreeable by many psychologist that 50% of the variance in general intelligence of an individuals can be explained by working memory capacity differences. In fact, it provides mental workspace which we can hold information while mentally engaged in other activities. Impairs in WM deficits can be seen in people with attention problems, people with learning disabilities, stroke patient and traumatic brain injury patient (Stern 2009).

Since focused attention and working memory (WM) takes place during wake state, loss of sleep may contribute to lapses in cognition due to destabilization of the state. It exacerbates the risk of dysfunctional of executive attention, working memory, and divergent higher cognitive function (Durmer & Dingers 2005). They had added sleep deprivation may incur involuntary micro sleep, slow response time, the decline in short term recall and WM performance, decrease the ability of learning of cognitive tasks, loss of situational awareness, performance decrease as task duration increased and main task promote by prefrontal cortex increase in response suppression errors.

For an example, a study conducted on crews that across the transmeridian shows that it has a short recovery period of CR and often requires coordination of CR in which it shows a decline in reaction-time, increased error in performing tasks and atrophic signs on frontal lobe (Cho 2001). In relation to this, Herxheimer and Waterhouse (2003) reported that the CR disruption which arises from the transmeridian flight procedures has also caused physiological and psychological syndrome such as drowsiness during the daytime, difficulty to sleep at night and agitation.

The implication of insufficient sleep on working memory had been widely studied by previous researches. One representation of sleep disturbance included Obstructive Sleep Apnea Syndrome (OSA) which contributed towards neurocognitive impairment as observed by Premkumar et al. (2013). In their study concerning individuals with sleep apnea, subtests of Digit Span and Letter-Number Sequencing of Wechsler Adult Intelligence Scale- Revised (WAISR) indicated global deficit score on working memory. The study by Premkumar et al. (2013) had also denoted the importance of good sleep on cognitive performance whereby enhanced sleep quality presented by higher melatonin levels was later shown to improve performance for Digit Span test. In relation to this, Miyata et al. (2013) tested working memory aspect among older adults using n-back test concluded that accuracy in responses decreased if participants only had sleep time of less than 5 hours compared to those who had more than 7-hour sleep as measured by Pittsburgh Sleep Quality Index (PSQI).

Nevertheless, there were still studies that showed significance of reduced sleep and working memory could not be established (Lovato et al. 2013; Richardson et al. 2018). From a between-subject quasi experimental study by Lovato et al. (2013), Double Span Memory test which is a computer-based working memory task was used to prove that no observable working memory impairment was found among older adults with insomnia when compared with good sleepers. According to Richardson et al. (2018), while worse performance on cognitive tasks were observed among Delayed Sleep-Wake Phase Disorder (SWPD) than good sleepers, no significant relationship was reported between adolescents with Delayed SWPD and good sleepers on working memory impairment. In spite of that, delayed SWPD participants did relatively show poor performance regarding thoughts organisation, concentration and daytime functioning due to reduced quality of sleep than those who had a good night sleep.

A cross-sectional study by Machi et al. (2012) indicated that physicians were reportedly having decreased sleep quality than normal population and post-shift fatigue was related to perceived difficulty in shift. As such, influence upon short-term memory decline was observed from remarkably lower recalling of words after day and overnight shifts using Repeatable Episodic Memory Test (REMT). While no difference was found for vigilance and memory between day and night shifts from Psychomotor Vigilance Task (PVT) and Rey Auditory Verbal Learning Test (RAVLT), off-duty sleep with on-duty supplementary naps were proven effective to maintain attention, learning and memory during working night-shift float (McDonald et al. 2013).

Following the connotation of a single night total insufficient sleep could weaken the encoding capacity of new memory, a parallel group design conducted by (Cousins et al. 2018) had showed that a significant poorer memory was observed in the sleep restricted group with 9-hour of sleep rather than the control group who had 5-hour bedtime. Performance in recognition task deteriorated after being sleep deprived, suggesting that the declined memory encoding among these adolescents would affect their learning ability on declarative information related to episodic or semantic memory negatively.

Mawdsley et al. (2014) who investigated the effect that sleep/wake cycle had upon item recognition and source

memory recollection found that shift workers performed significantly poorer in item recognition and source memory recollection tasks as compared to permanent-day workers during 12-hour retention interval wakefulness. Without analysis being mediated by night or day shifts, higher performance deficit was also shown by shift workers.

From the study above, it can be concluded that recognition of items and recollection of source were influenced by sleep, indicating the mnemonic processing involved in the stimuli was affecting shift workers more than permanent day workers. Having said that, the role of mnemonic in processing speed can be portrayed in the study done by Sandberg et al. (2016). It indicated that number-consonant mnemonic training which is changing numbers into consonant sounds then words by adding vowels could increase the magnitude of number recall from pre-assessment to post-assessment. As supported by Hampstead et al. (2012), information learning could be refined by mnemonic strategies.

The study by Giuntella et al. (2017) on China older workers identified an hour increase in the average sunset time with 20-minute reduction from reported sleep duration was associated with lower cognitive numerical skills among employed workers in the urban areas than rural areas. Older workers who lived in the city experienced 31-minute sleep reduction when socio-economic factors were controlled. The time zone settings, however, were less likely to affect farmers because they had better sleep quality and following the natural light in their activities compare to employed workers. The same thing applied for self-employed individuals who had flexibility in their work schedules. Emphasising the function of sleep with cognitive performance, old age cognitive and numerical skills were improved following an hour increase in average duration of sleep.

Apart from that, mild cognitive impairment (MCI) has been reported as one of the consequences of the CR disruption. Naismith et al. (2014) suggested that the melatonin secretion onset in patients with MCI which is earlier than the normal population of the same age, is related to poorer memory consolidation during the evening. The study also discussed that the circadian timing in MCI is also associated to diminished ability to form new episodic memories during the evening and overnight memory retention.

Circadian clock dysfunction also could promote neurodegeneration and perhaps contribute to Alzheimer Disease (AD) pathogenesis. Musiek et al. (2018) reported that preclinical AD is associated with rest-activity rhythm fragmentation, independent of age or sex. This finding demonstrating that circadian fragmentation occurs very early in the course of AD pathogenesis and precedes cognitive symptom onset. In addition, Lim et al. (2013) and Tranah et al. (2011) reported that decreased robustness of circadian rhythms has been associated with increased risk of future dementia in an elderly cohort, while sleep fragmentation appears to impart a higher risk of subsequent AD.

CIRCADIAN DISRUPTION AMONG SHIFT WORKERS

Circadian misalignment prevalently stands out from shift work that includes working on permanent night shift or rotating shift schedules, either day or night that occurs in various fields such as healthcare, emergency services, manufacturing, retail and hospitality (NeilSztramko et al. 2014). According to Stevens et al. (2011), shift work is defined as covering more than 8 hours of organizational working time, up to 24 hours. Many of past studies have agreed that disruption of the circadian system is seen as relevant for shift workers, putting them at a major risk to be affected by health impairment. A recent review done by Khan et al. (2018) reported that despite the social inactivity and irregularity in habits, working in continuous irregular shifts causes serious health issues including sleep disorders, psychiatric disorders, cancer, and metabolic disorders.

In terms of physiological functioning, rotating night shift is associated with increased risk of type-2 diabetes among healthy nurses without diabetes, cardiovascular syndrome and cancer as proven by Pan et al. (2011), with the duration of shift work as another relative factor of type-2 diabetes risk between shift and non-shift workers. In a within-subject design, healthy participants were randomised into circadian alignment and misalignment conditions. During circadian alignment protocol, participants were required to check-in for sleep period between 11.00p.m to 7.00a.m for 7 days. Meanwhile, the circadian misalignment protocol asked them to sleep at the same duration (11.00pm to 7.00am) for 3 days and later switched to sleep span between 11.00a.m to 7.00p.m for the following day 4 to day 8. Both conditions were allocated with similar mixed meals at 8.00a.m during breakfast and at 8.00p.m for dinner. Post-prandial glucose tolerance was found lower when participants were under circadian misalignment protocol due to modulated insulin sensitivity. While this study was designated to show how metabolic pattern was affected from immediate interference to the circadian system, finding from this study suggested that elongated disruption to the circadian rhythm promotes poorer tolerance to glucose (Morris et al. 2015). These findings had manifested how distorted sleep was involved in the interplay to produce metabolic-related diseases.

Vogel et al. (2012) reported that the central trait of the shift work is the disruption of the physiologic rhythms of day and night in which the shift workers is being compelled to be functional in contradiction to the biological clock and the diurnal rhythm of the general population. This misalignment of the suprachiasmatic nucleus (in which the circadian clock resides) and peripheral organ clocks is often referred to as internal desynchronisation and seems to be interpreted by the body as a form of stress (Knauert et al. 2015). These would affect the sleep, alertness, performance and digestion system of the shift workers which in turn leads to the increased incidence of cardiovascular disease, metabolic syndrome, and elevated inflammatory markers.

With shift workers being known as commonly affected by sleep disorder, a study using actigraphy monitor used to keep track of human rest/activity cycles showed that nurses had been disclosed to have lower total of sleep time and sleep efficiency (Niu et al. 2013). In comparing between day and night shift working nurses, Aldalatony et al. (2018) revealed that night-shift nurses were significantly associated with depression as assessed by self-rated Depression Scale (SDS), with higher depression levels were reported among older nurses due to longer employment duration. As longer hours of working nights among nurses correlated significantly to Shift Work Disorder (SWD) characterised by sleepiness and insomnia, depression and anxiety were also among the higher complaints being reported by tertiary care nurses, followed by other sickness such as headaches, back pain, gastritis and menstrual disorders (Anbazhagan et al. 2016). In a cross-sectional study done by Anjum et al. (2011), night-shift schedule managed to show that changes to circadian patterns of blood pressure was related to night-shift work, with the workers reported of having fatigue, headache and insufficient quality of sleep.

The relationship between insomnia and shift-work schedule among factory workers was also explored, but mediated by the workers' chronotype. Chronotype is referred as the tendency for a person to prefer which times of the day he or she is most alert and active. From Song, Choi and Joo's (2016) cross-sectional study, shift workers were more prominent toward worse insomnia symptoms compared to day workers as evaluated by Insomnia Severity Index (ISI). Epworth Sleepiness Scale (ESS) showed more than 60% of clinically significant insomnia and daytime sleepiness among shift workers, regardless their chronotype which was assessed by Morningness-Eveningness Questionnaire (MEQ). In fact, this could also be driven by interference in the melatonin production that disturbed the regulation of homeostatic factor with respect to sleep tendency during the day, such that insomnia at night had facilitated falling asleep by the CR after a long wakefulness period (Maggio et al. 2013).

Apart from that, Kim and Duffy (2018) reported that older individuals are more prone to shift-work disorder and jet lag disorder than their younger counterparts because of reduced ability to sleep at adverse circadian phases. Shift-work disorder is characterized by an inability to obtain sufficient sleep during the day and difficulty remaining awake at night resulting from night work whereas jet lag disorder is an inability to sleep at night and/or remain awake throughout the day after traveling across several time zones. This condition is caused by the abrupt mismatch between internal biological time and external time resulting from rapid travel across time zones, and is typically self-limiting. Shift-work disorder can also affect day workers whose early morning shifts require very early rise times.

CONCLUSION

As nature function rhythmically, circadian rhythm is essential to keep it well-entrained with environmental signals such as natural light and social cues. The de-synchronization of circadian rhythm can be observed from physiological changes and markers which are body core temperature, metabolism stress and behavioural alterations. Thus, when the natural circadian rhythm is disrupted due to work requirements and changes in activity, it can seriously impact circadian timing systems resulting sleep disruption that can cause physiological and psychological stress.

ACKNOWLEDGEMENT

This review is funded by Dana Cabaran Perdana (DCP-2017-018/3) UKM.

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