CIRCADIAN RHYTHMS, SLEEP AND MOOD ACROSS THE PERINATAL PERIOD

A LONGITUDINAL INVESTIGATION OF CIRCADIAN RHYTHMS AND SLEEP DISTURBANCES ACROSS THE PERINATAL PERIOD IN WOMEN AT LOW AND HIGH RISK OF POSTPARTUM DEPRESSION

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ABSTRACT

Postpartum depression (PPD) remains a serious mood disorder without a known etiology. PPD has a prevalence of 7-15% in the general population. Women with a history of a mood disorder are at an even higher risk for the development of PPD. Work over the last few decades has established a strong association between circadian rhythm and sleep disturbances and mood disorders, such as Major Depressive Disorder (MDD) and Bipolar Disorder (BD). Despite the breadth of evidence associating circadian rhythm disruption and depressive mood episodes, literature establishing a connection between circadian rhythms and changes in mood across the perinatal period is lacking. The work outlined in this thesis aimed to address this gap by examining the association between circadian rhythm and sleep disturbances across the perinatal period and their association with changes in mood in women at high and low risk of PPD development. A total of 87 women were studied, 45 healthy controls and 42 women with a mood history. Women were interviewed during the third trimester of pregnancy and between six to twelve weeks postpartum. Sleep and circadian rhythms were measured using both subjectively with self-reported questionnaires and objectively with actigraphy. Our results show that women at high and low risk showed higher disruption differ in subjective circadian rhythmicity, as well as in both subjective and objective parameters of sleep. Specifically, women at high risk for postpartum were found to have lower sleep efficiency, as measured by actigraphy, in the postpartum. In addition, subjective and objective parameters of sleep and circadian rhythms are associated with changes in depressive symptoms across the perinatal period. Our findings suggest that stabilizing circadian rhythms and improving sleep quality throughout the perinatal period can prevent postpartum mood worsening, particularly for those women at greatest risk.

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LIST OF ABBREVIATIONS

Arginine-vasopressin (AVP)

Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL)

Bipolar Disorder (BD)

Central SCN subnucleus (SCNce)

Circadian Locomotor Output Cycles Kaput (Clock)

Cryptochrome (Cry)

Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)

Dim light melatonin onset (DLMO)

Electroencephalograms (EEG)

Gamma-aminobutyric acid (GABA)

Gastrin-releasing peptide (GRP)

Gene Wide Association Studies (GWAS)

Geniculo-hypothalamic tract (GHT)

Hamilton Depression Rating Scale (HAMD)

Hypothalamic–pituitary–adrenal (HPA)

Major Depressive Disorder (MDD)

Major Depressive Episode (MDE)

Neuronal PAS domain-containing protein 2 (NPAS2)

Neuropeptide Y (NPY)

Paraventricular Thalamic Nucleus (PVT)

Period (Per)

Postpartum Depression (PPD)

Retinal ganglion cells (RGC)

Retinohypothalamic Tract (RHT)

Seasonal Affective Disorder (SAD)

Sleep efficiency (SE)

Sleep onset latency (SOL)

Socioeconomic status (SES)

Suprachiasmatic Nucleus (SCN)

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Total sleep time (TST)

Transcription Translation Feedback Loop (TTFL)

Vasoactive intestinal polypeptide (VIP)

Wake after sleep onset (WASO)

DECLERTION OF ACADEMIC ACHIEVEMENT

This thesis consists of five chapters. Chapter 1 provides the background and rationale for the research study. Chapters 2 and 3 are manuscripts, submitted to peer review journals. Chapter 4 outlines the rational and methods for the genotyping of a circadian rhythm gene polymorphism and its potential association with Postpartum Depression. Finally, Chapter 5 discusses the results, limitations and possible future directions. The study itself was designed by Dr. Benicio Frey and me. All figures contained in the thesis were produced by me.

I conducted all of the recruitment at the Women's Health Concerns Clinic and Community Midwives of Hamilton. Data collection (including blood draw) and management, DNA extraction, and data interpretation, was also carried out by me in fulfilment of the thesis requirements. Apart from the non-parametric circadian rhythms analysis (inter-daily stability and intra-daily variability circadian parameters) carried out by William Simpson, all remaining data analysis was done by me, with support from Dr. Streiner and Dr. Minuzzi. I am grateful to all contributors.

CHAPTER 1

General Introduction

Postpartum Depression (PPD) remains a serious and prevalent mood disorder, despite decades of extensive research. The mechanism involved in the etiology of PPD is yet to be identified. As a result, it remains imperative to determine the neurobiology behind this mood disorder, as well as establish proper clinical markers for its development. Literature suggests that the circadian system plays an important role in mood regulation. In fact, decades of work have associated circadian rhythm disruption with mood disorders such as Major Depressive Disorder (MDD) and Bipolar Disorder (BD). This system, however, has not been well studied in regards to the etiology of PPD.

The goal of this work was to investigate parameters of circadian rhythms and sleep during the perinatal period in women with and without a history of a mood disorder and to examine if this disruption is associated with worsening in postpartum mood symptoms. This was done through a clinical approach utilizing both subjective (Chapter 2) and objective measures (Chapter 3) of circadian rhythms and sleep. A pilot molecular approach was also applied to examine if differences in the polymorphism of a circadian gene were associated with a history of a mood disorder and vulnerability to PPD development (Chapter 4). It is hoped that findings from this work will serve to support the development of methods that are more effective and efficient in a clinical setting for decreasing postpartum mood worsening, as well as to support the offer of alternative preventative and treatment approaches for depressed mood by targeting circadian rhythm stabilization.

Postpartum Depression (Description)

Many women experience depressive symptoms in the first two weeks following childbirth. This is termed postpartum blues, with prevalence ratings ranging from 24-84% (O'Hara & Wisner 2014). On the same spectrum, a smaller percentage of women, 0.1-0.2%, develop postpartum psychosis, typically observed in women with a history of bipolar disorder (Sit et al. 2006). However, 7-15% of women develop more chronic and serious depressive symptoms termed Postpartum Depression (PPD) (O'Hara & Wisner 2014; Gaillard et al. 2014; Gavin et al. 2005). According to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), a diagnosis of PPD (now acknowledged as peripartum depression) is contingent on the diagnosis of a major depressive episode (MDE) with peripartum onset, in that the episode occurs during pregnancy or in the first four weeks following birth (American Psychiatric Association [APA] 2013). However, studies have shown that PPD may develop after the first month postpartum, and so this time-frame has been widely challenged (Kettunen et al. 2014; O'Hara & Wisner 2014).

Clinical symptoms of PPD include, but are not limited to, changes in sleep pattern (insomnia or hypersomnia), changes in appetite, and feelings of sadness and guilt; symptoms similar to a MDE (Norhayati et al. 2014). However, unique to depression in the postpartum, women feel an undermined confidence in the care of their infant, possibly showing poor parenting practices (Bobo & Yawn 2014) and unsuccessful breast feeding (Dias & Figueiredo 2015). Some mothers also show insensitivity to the infant's distress or may become overly-active and hostile (Murray, Cooper & Fearon 2014). Women with PPD often perceive poor bonding with their baby (Baines, Wittkowski & Wieck 2013). Substance abuse is also associated

with depressive symptoms in the postpartum, and may develop especially in unmarried and/or unemployed women and women who smoke (Chapman & Wu 2013). In severe and chronic cases of PPD suicidal ideation or attempt may result. A recent large-scale, retrospective cohort study found 3.4% of 8,394 women reported suicidal ideation at six weeks postpartum (Kim et al. 2015). Moreover, up to 10-20% of postpartum deaths are attributable to PPD (Tabb et al. 2013; Lindahl, Pearson & Colpe 2005).

PPD is also a serious concern for the reason that it not only severely impacts the patient, in regards to domains such as health status (Van der Woude, Pijnenborg & de Vries 2015), quality of life (Darcy et al. 2011; Webster et al. 2011) and cognition (Pio de Almeida et al. 2012), but also that of the infant or whole family (Letourneau et al. 2012). Concerning the infant, the mother-infant bond is consistently shown to be stressed in cases where PPD develops (Ohoka et al. 2014; O'Higgins et al. 2013; Moehler et al. 2006). Moreover, behavioural, cognitive, and emotional difficulties have long been observed in children of mothers depressed in the postnatal period (Stein et al. 2014; Field 2010). For instance, Feldman et al. (2009) found that maternal depression at 9 months postpartum was associated with poor infant emotion regulation (showing more negative emotionality), less mature regulatory behaviours and low social engagement. Furthermore, studies show that teenagers of mothers who suffered from PPD are at greater risk for the development of psychiatric disorders themselves (Murray et al. 2011).

PPD is also associated with a negative impact on the family unit as a whole. For example, Beestin et al. (2014) used narrative interviews to explore how partner's PPD affected 14 fathers. The men in the study stated that their partner's PPD produced a sense of absence,

which often led to compensatory fathering in an attempt to fill the void. This finding was replicated by Goodman et al. (2014) in a longitudinal study, finding paternal compensatory behaviour predominantly during the first six months of maternal PPD. Moreover, PPD of both mothers and fathers is associated with impaired bonding with infant, particularly in situations where marital relationship is deteriorating (Kerstis et al. 2015). Other studies also highlight that depressive symptoms in the postpartum are bidirectionally associated with marital relationship quality (Mamun et al. 2009).

PPD remains a serious health concern for a couple of reasons. For one thing, the biological mechanism underpinning PPD remains elusive. PPD is also often misdiagnosed or missed altogether by primary health teams (Cooper and Murray 1998). Studies have found that up to half of PPD cases may remain undetected (Hendrick 2003; Ramsay and Torbet 1993). Many women do not seek help for depression in postpartum (McGarry et al. 2009). Even for those cases of PPD that are detected, not all women receive treatment (Flynn et al. 2006; Yonkers et al. 2009). This is attributable to both the failure to disclose symptoms by the patient, because they are ashamed or unaware of PPD, as well as the similarity of depressive symptoms and expected postpartum symptoms, such as fatigue or loss of appetite (Matthey and Ross-Hamid, 2011; Dennis and Chung-Lee 2006). To address these problems it is important to determine the risk factors for PPD, to screen for them during pregnancy, as well as take preventative measures across the perinatal period to avoid PPD development.

Risk Factors of Postpartum Depression (Social and Biological)

To date, multiple risk factors have been studied in relation to the development of PPD. These risk factors fall into four broad categories: social, obstetrical, clinical, and biological.

Various meta-analyses have revealed that poor social support, poor marital relationship, stressful life-events (such as physical abuse by partner), low socioeconomic status (SES), being single and unwanted pregnancy are among the low to moderate social risk factors for PPD development (O'Hara & Wisner 2014; Gaillard et al. 2014). Numerous obstetrical factors, such as mode of delivery, delivery and/or postpartum complications (such as infection), and pain during delivery, have also been moderately associated with subsequent PPD development (Csatordai et al. 2007; Gaillard et al. 2014; Johnstone et al. 2001). In addition, having an infant with a very low birth weight has also been attributable to PPD risk (Davis et al. 2003), as supported by a recent cross-sectional study conducted by Helle et al. (2015).

On the other hand, it has also been shown that many clinical features are associated with high to moderate risk of PPD development. Among them are a history of a mood disorder, anxiety and/or depression during pregnancy, high neuroticism, postpartum blues and low self-esteem (O'Hara & Wisner 2014; Kettunen et al. 2014; Gaillard et al. 2014; Dorheim et al. 2014). Some studies have found that up to 20% of women with a history of BD or MDD will develop PPD (Payne et al. 2007). In addition, risk is found to be even greater if a woman has had a previous history of PPD (Viguera et al. 2011; Cooper & Murray 1995).

The aforementioned findings highlight the extensive focus given to the epidemiology of PPD. This breadth is due to the fact that the perinatal period is a unique time in woman's life where multiple changes occur. Specifically, there are alterations in a woman's biological, psychosocial and environmental domains. Alterations in any of these areas may impact vulnerability to depression onset and so all have been studied. However, work has also been

done to determine the biological underpinnings of PPD. The approaches to determining the mechanisms underlying PPD have been genetic, epigenetic and endocrine in nature.

In regards to endocrine markers, much focus has been given to the role of placental (particularly placental corticotropin-releasing hormone) (Glynn & Sandman 2014; Yim et al. 2009) and hypothalamic–pituitary–adrenal (HPA) axis hormones (primarily cortisol) (Glynn et al. 2013; Groer & Morgan 2007). Some attention has also been given to the thyroid system (Sylven et al. 2013; Albacar et al. 2010; McCoy et al. 2008; Kent et al. 1999) and inflammatory markers (Osborne & Monk 2013; Blackmore et al. 2011; Groer & Morgan 2007; Maes et al. 1999). These two systems, in particular, have been considered because of their associations with Major Depressive Disorder, but establishing associations between them and PPD development have remained poor (Schiller, Meltzer-Brody & Rubinow 2015; Skalkidou et al. 2009; Scrandis et al. 2008). In relation to genetic approaches, multiple studies have explored various genetic factors, predominantly polymorphisms, 35 of which were recently reviewed by Figueiredo et al. (2014). Despite this extensive work, to date, there is no consensus as to the biological mechanism underlying PPD development as conflicting results are often reported and most findings are not replicated. Moreover, hormonal changes alone may not explain the development of PPD, as males are also vulnerable to developing postpartum depression (Demontigny et al. 2013; Godderis et al. 2011).

A lot of focus has also been given to sleep disruption in association with PPD development, an idea that will be further explored in subsequent sections of the introduction. However, the disruption of sleep and the above-mentioned systems as seen during the perinatal period and in mood disorders may be better attributed to another dysfunctional system. The

circadian rhythm system and its potential disruption during the perinatal period has been understudied in relation to PPD development. The dysfunction of this system may better combine the findings from the other work on risk factors and biological underpinnings of this disorder to explain PPD development (McClung 2013; Landgraf et al. 2014).

Circadian Rhythms (description, physiology and genetics)

Numerous physiological and behavioural processes follow a biological rhythm of approximately 24-hours. These include, but are not limited to, the sleep-wake cycle (process C), metabolic cycle, hormonal control (e.g. melatonin, cortisol), temperature regulation, sociality, and timing of feeding. Light is the primary zeitgeber entraining these processes to a 24 hour cycle (Albers, Lydic & Moore-Ede 1984; van Esseveldt, Lehman & Boer 2000); the endogenous component diverges slightly from 24 hours (Allan et al. 1999; Wever 1975). The circadian rhythmicity of these processes is primarily regulated by outputs from the Suprachiasmatic Nucleus (SCN), a bilateral structure. Although previously described (Suburo & Pellegrino de Iraldi 1969), the understanding that the SCN is the master clock was evidenced by various animal studies, pioneering with the rodent lesion studies of Moore & Eichler (1972) and Stephan & Zucker (1972). This was followed by similar results from the rat studies of Ibuka and Kawamura (1975) and finally confirmed as the master clock region of mammals (Turek 1985; Miller et al. 1996; Reppert et al. 2002). Determining that circadian control is mediated by a structure with a specific location has allowed the past few decades to focus in depth on the anatomy, entrainment and communication of the SCN.

The SCN is located in the anterior ventral portion of the hypothalamus, positioned astride the supraoptic commissures by the third ventricle (Morin 2013; Welsh, Takahashi & Kay

2010). Containing approximately 10,000 neurons, this pacemaker is organized into two components; a core (dorsomedial) enveloped by a shell (ventrolateral) (Welsh, Takahashi & Kay 2010). Retinal input is transferred to the core (Welsh, Takahashi & Kay 2010). The majority of the connections between these two SCN components stem from the core to the shell, with many less seen projecting from shell to core (Welsh, Takahashi & Kay 2010). Certain mammals, such as the rat and hamster, also show the presence of a central SCN subnucleus (SCNce) (Morin 2013). The SCN contains a variety of neuron classes, all of which appear to contain gamma-aminobutyric acid (GABA) (Morin 2013; Welsh, Takahashi & Kay 2010; Abrahamson & Moore, 2001). The neuronal classes are distinguished by neuropeptide markers. For example, approximately 1000 neurons of the core contain vasoactive intestinal polypeptide (VIP), while about 2000 neurons of the shell contain arginine vasopressin (AVP), among many others (Welsh, Takahashi & Kay 2010).

As aforementioned, the SCN is predominantly entrained by light cues. These photic cues are conveyed from the retina to the SCN via the retinohypothalamic tract (RHT). The development of improved tracing methods resulted in the discovery of such a pathway in the rat in early work (Hendrickson et al 1972; Moore & Len 1972). Since, the existence of this tract has been confirmed in other mammals, such as the skunk (May, DeSantis & Mead 1985), the macaque monkey (Moore 1993), and humans (Sadun, Schaechter & Smith 1984; Hannibal et al. 2004). It is now understood that the specialized retinal ganglion cells (RGC) contain the photopigment melanopsin. This allows the RGC to process and pass on photic information to the core region of the SCN to phase-set the nucleus (Brancaccio et al.2014; Morin 2013). This portion of the circuitry appears to be highly specific with low plasticity, in that complete and

bilateral lesions to the SCN in early development lead to no alternative connectivity of the retinohypothalamic projections with other brain areas (Mosko & Moore 1979). Work by Harrington and Rusak (1988) done in hamsters suggested that the geniculo-hypothalamic tract (GHT) appeared to also be involved in mediating the photoentrainment of the SCN. GHT terminals on the SCN have also been noted in mice and rats (Morin 2013).

The SCN also receives inputs from other brain areas. The SCN is heavily interconnected with its neighbouring nuclei, such as the medial preoptic area (MPOA) and subparaventricular zone (sPVz), among others (Morin 2013). In addition, the median raphe nucleus also has projections to the SCN, transmitting serotonergic input effecting circadian rhythm regulation (Meyer-Bernstein EL & Morin1996; Morin 2013). Although the SCN mediates nighttime melatonin secretion from the pineal gland to generate temporal cues, melatonin is able to feedback onto the SCN (Kalsbeek et al. 2004). This became known through the discovery of melatonin receptors in the SCN (Laitinen & Saavedra 1990; Kalsbeek et al. 2004), as well as through studies observing changes in circadian rhythmicity in rodents by administering melatonin (Kalsbeek et al. 2004; Pitrosky et al. 1999).

In turn, the SCN communicates with other brain areas and the innumerable peripheral circadian oscillators to induce circadian control of specific tissue phases. It does this through both electrical activity and chemical signals. The SCN has efferent projections to local areas, such as the other nuclei of the hypothalamus, thalamus and ventral tegmental area (Schnell, Albrecht & Sandrelli 2014; Welsh, Takahashi & Kay 2010; Leak & Moore 2001). In particular, the SCN has known GABAergic projections to the paraventricular nucleus of the hypothalamus, as revealed by a rat study (Kalsbeek et al. 2004). Withdrawal of these inputs, as mediated by the SCN, is found to control plasma glucose concentrations (Kalsbeek et al. 2004).

As discussed above, the SCN also connects to the pineal gland, wherein melatonin is the efferent endocrine output (Pevet & Challet 2011). Moreover, other animal studies also revealed that the SCN shell projects densely to the medial preoptic area and more sparsely to other brain areas (Leak & Moore 2001).

In regards to chemical signals, the SCN communicates via neurotransmitters such as arginine-vasopressin (AVP), neuropeptide Y (NPY), gastrin-releasing peptide (GRP) and vasoactive intestinal polypeptide (VIP) (Brancaccio et al.2014). These neurotransmitters maintain interneuronal synchrony and are released by the associated different subtypes of neurons within the SCN, which have a specific localization (Brancaccio et al.2014; Hastings, Brancaccio & Maywood 2014). For example, the GRP and VIPergic neurons are found in the ventrolateral (core) region of the SCN, while the AVP neurons are found in the shell region (Brancaccio et al.2014). Neurons characterized by VIP are found to be the retinorecipient neurons of the SCN (Hastings, Brancaccio & Maywood 2014).

The 24-hour cyclic communicative nature of these cues is regulated by a shared transcription translation feedback loop (TTFL) found within each individual SCN cell (Hastings, Brancaccio & Maywood 2014). Specifically, as shown in Figure 1, the TTFL functions through the timed transcription of key genes: period (per) and cryptochrome (cry) (Brancaccio et al. 2014). These genes are activated by Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL/BMAL1)/ Circadian Locomotor Output Cycles Kaput (CLOCK) dimers (helix-loop-helix transcription factors), as well as by ARNTL (BMAL1)/ Neuronal PAS domain-containing protein 2 (NPAS2) dimers in the forebrain which bind to E-boxes in the promoters of Cry and Per (Landgraf, McCarthy & Welsh 2014; Brancaccio et al. 2014; Schnell, Albrecht & Sandrelli 2014;

Hastings, Brancaccio & Maywood 2014; Koike et al. 2012; Garcia et al. 2000). The promoter region of the per gene is also mediated by secondary messengers such as cAMP/Ca 2 Responsive Elements (CRE) (Brancaccio et al. 2014; Brancaccio et al. 2013). As Per and Cry accumulate, the BMAL1/CLOCK dimers are inhibited (Brancaccio et al. 2014). In turn, Per and Cry are degraded and so the cycle continues (Brancaccio et al.2014). Although this is the main TTFL, it is influenced by other loops, involving RORA and Rev-Erba/b genes (Hastings, Brancaccio & Maywood 2014). However, similar feedback loops have been found in other mammalian cells and tissues as well (Brancaccio et al. 2014; Welsh et al. 2004). The interplay of this extensive, collective physiological network sets up the hierarchical circadian system, critical for the appropriate timing of metabolism and behaviour.

Figure 1 – The Core Transcription Translation Feedback Loop

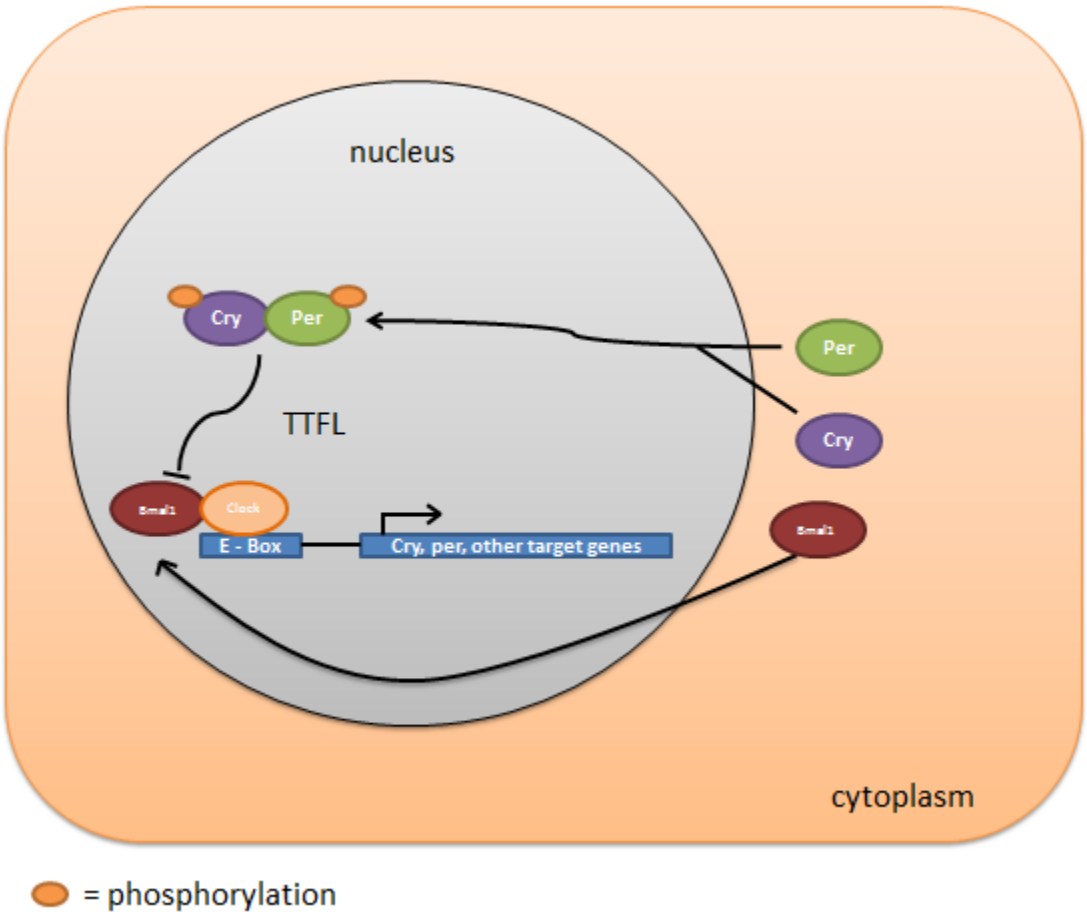

Figure legend: The core Transcription Translation Feedback Loop oscillates with a period of 24 hours. Transcription factors CLOCK and BMAL1 heterodimerize and bind to the EBox of the *Cry* and *Per* promoters. This results in the transcription and translation of these two genes, which then heterodimerize to form a CRY and PER complex that is translocated back to the nucleus from the cytoplasm to inhibit the CLOCK and BMAL1 heterodimer. As CRY and PER are degraded, the cycle repeats.

The Sleep-Wake System and its Association with the Circadian Rhythm System

The most accepted model of the sleep-wake cycle, based on mathematical modeling, postulates that the cycle is governed by two processes termed process C (circadian control) and process S (homeostatic control) (Skeldon, Dijk & Dirk 2014; Borbely & Acherman 1989). Process C mediates the temporal nature of the sleep-wake cycle by electrical input from the efferents of the SCN (Goel et al. 2014). This process is often viewed more so as contributing to alertness than sleep promotion (Goel et al. 2014). On the other hand, process S governs sleep need. To explain process S simply; as one remains awake, pressure mounts for one to sleep and once sleep is attained, the pressure is removed. This process has also been shown to be more contributory to NREM sleep; specifically electroencephalograms (EEG) delta power, in comparison to process C which influences such sleep associated factors as body temperature changes and melatonin levels (Curie et al. 2013; Wurts & Edgar 2000; Dijk et al. 1995).

Light input has been found to be associated with the regulation of both of these processes (LeGates et al. 2014) and the paraventricular thalamic nucleus (PVT) has recently been implicated in the integration of both processes in order to control the cycle (Colavito et al. 2014). Collectively, both processes establish sleep length and are critical to establishing a proper sleep-wake cycle (LeGates et al. 2014). Furthermore, the strong relationship between the processes suggests that changes in either domain can disrupt the partnered system. For example, evidence suggests homeostatic information may also influence circadian gene expression (Curie et al. 2013; Wurts & Edgar 2000). Franken et al. (2007) showed evidence for this system cross-talk by observing the relationship between *Per2* expression (process C marker) and EEG delta power (process S marker) in various sleep deprivation models in mice.

Disruption of Circadian Rhythms

The SCN manifests an intrinsic rhythm, while remaining malleable to entrainment by other zeitgebers. Although the light-dark cycle is the primary zeitgeber entraining rhythms to a 24 hour period, other external and internal cues establish the varying rhythmicity of a multitude of discrete biological, and even social rhythms. Conflict can arise between changing endogenous and exogenous cues and one's hierarchical circadian system. This can result in rhythm disruption, manifesting in negative behavioural, emotional and cognitive outcomes. A primary example of circadian disruption negatively impacting ones' overall physiology is the condition of jet lag, resulting from a mismatch between the internal circadian system and external environment cues as a result of travel across time zones.

Circadian rhythm disruption can develop through two mechanisms. First, a dyssynchrony can develop between the circadian timing of the central and peripheral systems. Specifically, the clock genes of peripheral oscillators, of for example the liver and lung, may phase shift from the clock genes of the brain (Wirz-Justice 2006). This is deemed "internal desynchronization". This is because, although the SCN coordinates the timing or peripheral oscillators, they are known to maintain their own rhythms, resynchronizing at their own rates, and thus can fall out of sync with the master clock (Wirz-Justice 2006; Yamazaki et al. 2000). Alternatively, dissociation in circadian timing can develop between physiological rhythms and the external cue timing. This is referred to as "external desynchronization". Generally, this observed when internal rhythms are out of sync with the light-dark cycle. For example, a recent study comparing employees who work with or without a window in their work space found differences in melatonin and cortisol levels between groups, suggesting a desynchronization

between light exposure and hormonal rhythms (Harb et al. 2015). If both desynchronizations are manifest, this is termed a "double desynchronization" (Wirz-Justice, 2006).

Disruptions in rhythms can manifest as a result of various reasons. To study the effects of rhythm disruptions, various lab techniques have been developed. Animals can be exposed to varying zeitgebers to phase shift their cycles (Baron & Reid 2014). Naturally, chronotype, daylight saving time, jetlag, social jetlag (influence of, for example, school and work and the difference between the weekend and weekday), and circadian disorders can all misalign rhythms in people (Baron & Reid 2014; Schnell, Albrecht & Sandrelli 2014). Severe circadian disruptions have been associated with numerous negative health outcomes. The misalignment between the sleep/wake and day/night cycle is the most extensively studied (Baron & Reid 2014). The general misalignment of circadian rhythms has been associated with poor cardiovascular outcomes and increased risk of developing cancer and obesity (Baron & Reid 2014; Hastings, Reddy & Maywood 2003). Moreover, disruptions in timing between the pancreas, liver and skeletal muscles are also associated with insulin resistance (Hastings, Brancaccio & Maywood 2014; Shi et al. 2013). Circadian rhythm disruption, however, has also been extensively associated with mood disorders; the premise of this thesis.

Circadian Rhythm Disruptions and Mood Disorders

Although the etiology behind mood disorders remains uncertain, decades of work, in both humans and animals, have revealed a strong association between disrupted circadian rhythms and mood episodes in a variety of mood disorders. At the forefront of this work, studies have shown circadian disruption is associated with depressive mood disorders such as Seasonal Affective Disorder (SAD), Major Depressive Disorder, and Bipolar Disorder. More recently,

circadian disturbance has been shown not only during mood episodes in individuals with these disorders, but prior to their onset as well, acting as episode prodromes. These individuals may also show diurnal variability in their mood symptoms, such as morning worsening of mood (Kronfeld-Schor & Einat 2012; Morris et al. 2009; Wirz-Justice 2008; Tolle & Goetze 1987). There is also evidence that seasonality can affect mood episode onset or progression, as classified by SAD, which again, suggests a circadian component. Decades of work involving treatments targeting circadian rhythm stabilization, such as bright light or sleep deprivation therapy, in order to improve depressive symptoms have also had compelling results (Rudolf & Tolle 1978; Coogan & Thome 2011). Multiple reviews have already summarized this array of compelling evidence associating circadian rhythm disruption and mood disorders, particularly in individuals with MDD and BD (LeGates et al. 2014; Karatsoreos 2014; Schnell, Albrecht & Sandrelli 2014; Salvatore et al. 2012; McCarthy & Welsh 2012; Kronfeld-Schor & Einat 2012; Wirz-Justice 2006; Hallonquist, Goldberg & Brandes 1986).

The Social Zeitgeber Theory proposes how the disruption of social zeitgebers (non-photic cues) by a life event can result in the disruption of physiologic rhythms, triggering depressive episodes (Ehlers et al. 1993; Ehlers et al. 1988). Grandin et al. (2006) reviewed the literature to examine support of this theory and found numerous examples of stressful life events, such as the loss of a loved one, being related to depressive and manic mood onset in a plethora of studies concerning BD. However, a recent study of students, who were either on the bipolar spectrum or matched healthy controls, found mixed support for this theory (Sylvia et al. 2009). This study found that stressful life events did not predict rhythm stability and in turn, rhythm stability did not predict mood symptoms, but stressful life events did predict bipolar symptoms and episodes (mostly depressive and not [hypo]manic symptoms).

Mood disorders can, however, also manifest in individuals with stable social cues. Therefore, this theory alone cannot be the full story as to the etiology of mood disorder development. The theory does provide a good basis for the notion that individuals may have differing vulnerability to circadian disturbance within their circadian system, influencing their risk for the development of mood episodes. Furthermore, the circadian system itself modulates other systems that have been implicated in mood disorder development, such as the HPA axis and monoaminergic neurotransmission, warranting the importance of this system in mood episode occurrence (Schnell, Albrecht & Sandrelli 2014). Another major factor that may underlie the vulnerability to develop mood disorders may be differing circadian rhythm genetics; an idea that is increasingly garnering attention in this field and will be discussed in the subsequent section.

Circadian Rhythm Genetics in Mood Disorders

MDD, and to a greater extent BD, have a high level of heritability. As a result, numerous studies have searched for a genetic basis that is shared among individuals who have these mood disorders. With the growing association between circadian rhythm disruption and affective disorders, literature exploring a link between circadian rhythm genetics and mood disorders has grown. Numerous associations between the two phenomena have already been found and summarized in reviews (Partonen 2012; Etain et al. 2011; Milhiet et al. 2011; McClung 2007).

The genetic approaches to determine a circadian genetic basis for psychiatric disorders have been various. For example, one group approached the study of this association by comparing gene expression of Clock, BMAL1, Period1, and Period2 mRNA between 30 individuals with a history of depression and 30 matched healthy controls from blood samples

(Gouin et al. 2010). They found that the levels of Clock and Period1 mRNA were elevated in individuals with a history of depression.

Many candidate gene approach studies have also been conducted, searching for associations between specific genes related to the circadian rhythm system and depressive mood disorders, such as MDD and BD. Specifically, polymorphisms, generally single-nucleotide polymorphisms (SNP), of circadian genes have been explored. In studies focused on individuals with MDD (as described below), associations were found for genes including ASMT (Galecki et al. 2010), CRY (Hua et al. 2014; Soria et al. 2010; Lavebratt et al. 2010b), NPAS2 (Soria et al. 2010), PER (Maglione et al. 2015), RORA (Lavebratt et al. 2010a; Maglione et al. 2015) and TIMELESS (Utge et al. 2010). Similarly, in relation to BD (as described below), associations have been found for ARNTL (Mansour et al. 2006), BMAL (Nievergelt et al. 2006), CLOCK (Soria et al. 2010; Lee et al. 2010), CRY (Lavebratt et al. 2010b), PER3 (Nievergelt et al. 2006), RORB (McGarth et al. 2009), TIMELESS (Mansour et al. 2006) and VIP (Soria et al. 2010). A recent study by Liu et al. (2015) also found that the rs2290036-C, a polymorphism of ARNTL, was over-represented in individuals who had psychotic features associated with their mood disorder (N=566) in comparison to controls (N=926). However, there are also studies that have investigated some of these candidate SNPs in these populations and have found no associations (Byrne et al. 2014; Calati et al. 2010; Crisafulli et al. 2013; Kishi et al. 2011).

It is of importance to this thesis to highlight the CLOCK 3111T/C SNP (rs1801260). The association of this particular SNP with depression has yielded mixed results. Some studies have found an association between this SNP and mood disorders (Dmitrzak-Weglarz et al. 2015; Lee et al. 2010; Serretti et al. 2003). On the other hand, other studies have not (Bailer et al. 2005; Desan et al. 2000; Kishi et al. 2011). This SNP has, however, been linked to sleep in association

with stressful life experiences (Antypa et al. 2012). It has also been linked to diurnal preference: morning or evening type (Katzenberg et al. 1998). This finding was, however, challenged by a study by Pedrazzoli et al. (2007), which did not find an association between the SNP and chronotype. These results suggest that the effect of this SNP may be small and warrants further research to determine its contribution to sleep, diurnal preference and/or mood disorders.

In addition, gene wide association studies (GWAS) studies have also sought to associate clock genes with depressive disorders. Although these studies tend to include larger sample sizes, this approach has been less successful at finding an association. This may be, as McCarthy et al. (2012a) postulate, because these disorders are likely attributable to various genetic variants, the organization of the circadian molecular system is quite complex and the susceptibility to psychiatric disorders as a result of genetic risk may be shared by multiple illness. However, in their survey of GWAS studies, it was found that there were associations between core clock genes and BD-spectrum illnesses and lithium responsiveness. In addition, Terraciano et al. (2010) did a GWAS and found RORA to be associated with depressive personality traits.

Human postmortem gene studies have also found differences between controls and individuals with histories of depressive mood disorders in relation to circadian genetics. For example, Li et al. (2013) compared the expression of cyclic genes in the postmortem brains of 55 controls without a psychiatric history to 34 with a history of MDD. This was carried out in various brain regions associated with depression. They compared the transcripts that they found to be most rhythmic and found that the rhythmicity of these genes in the MDD patients were weaker. Recently, in a microarray study carried out by Bunney et al. (2015), cyclic genes in six brain regions of postmortem controls and individuals with histories of MDD were also identified.

Subsequently, the expressions of these cyclic genes and their sinusoidal rhythms were, again, compared between the two groups. It was found that rhythms were particularly disrupted in genes such as ARNTL, PER1, 2 and 3, NR1D1 and DBP in individuals with MDD as compared to significant sinusoidal rhythms of these genes in controls, supporting Li et al.'s (2013) findings. Furthermore, another microarray study in postmortem brains of individuals who committed suicide compared to controls, found PER1 to also be downregulated in the brains of suicides, among other genes (Sequeira et al. 2012). Collectively, these genetic approach studies have offered some merit to the hypothesis that the disruption of the circadian system is associated with the etiology of psychiatric disorders.

Circadian Rhythm Disruptions in Major Depressive Disorder

According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5; APA 2013), Major Depressive Disorder (MDD) is characterized by two weeks of either depressed mood or loss of interest or pleasure, in addition to five other symptoms. These other symptoms include features such as changes in sleep (including insomnia, hypersomnia and sleep fragmentation nearly every day), changes in weight and appetite (either increase or decrease), and feelings of worthlessness or guilt. The majority of these symptoms are associated with circadian rhythmicity. Mood, sleep, and appetite, as discussed above, all follow daily rhythms. Not surprisingly, individuals with MDD show disruptions in these domains during episodes of depression. Their rhythms, however, also differ from individuals without a history of psychiatric disorder during euthymic periods as well.

For example, sleep disturbances have long been described in individuals with MDD, as compared to controls (Hawkins & Mendels 1966; Peterson & Benca 2008; Arfken et al. 2014;

Benca et al. 1992; Olbrich & Arns 2013). MDD is highly associated with symptoms such as hypersomnia and insomnia (Kaplan & Harvey 2009; McCall et al. 2010; Soehner, Kaplan & Harvey 2014; Yates et al. 2004). Some studies have found that women complain of hypersomnia more than insomnia, as compared to depressed males and that it is more prevalent in older individuals (Kaplan & Harvey 2009; Khan et al. 2002). Sleep is also disturbed during periods of remission, negatively impacting the risk of relapse (Zajecka 2013). Some studies have even shown that sleep disturbances precede depressive episodes (Cairns et al. 1980; Baglioni et al. 2011). Differences in REM sleep architecture, such as shortened REM sleep latency, have also been described in relation to MDD (Olbrich & Arns 2013; Rotenberg et al. 2002; Roberts et al. 2000).

Studies observing circadian disturbances in individuals with MDD have also measured hormonal dysregulation. Particular focus has been given to melatonin and cortisol because the cycles of these hormones are well established. Many studies have found differences in hormonal levels between depressed and non-depressed individuals. For instance, in regards to melatonin, a recent and well-designed longitudinal cohort study sampled melatonin via saliva samples three times a day for 30 days in depressed and non-depressed participants (Bouwmans et al. 2015). The results indicated that depressed individuals showed increased variability in their melatonin profiles, as well as overall higher melatonin levels. Moreover, an EEG study which found enhanced frontal low-frequency EEG activity during extended wakefulness particularly during the night in depressed women as compared to controls, also found their melatonin levels during the night to be attenuated (Birchler-Pedross et al. 2011). These findings mirror the results of prior work comparing melatonin levels in these groups (Mendlewicz et al. 1979). However, an older study found melatonin levels to be higher in depressed individuals

compared to controls (Thompson et al. 1988). In addition to different levels of melatonin, studies have also shown phase shifts in the melatonin rhythms in individuals with MDD (Crasson et al. 2004; Nair et al. 1984). A postmortem study by Wu et al. (2013) also found melatonin receptor 1 to be increased in the SCN of depressed individuals as compared to controls by using immunocytochemistry.

Similar findings of hormonal rhythm disruption have been shown in regards to cortisol. For example, in a recent study Rhebergen (2015) found higher morning cortisol levels in older depressed individuals as compared to those without a history of a psychiatric disorder. Many studies have reported differences in cortisol patterns between depressed individuals and healthy controls using salivary cortisol collection at different time points (Hsiao et al. 2010; Hinkelmann et al. 2009). Moreover, in an interesting study observing the coupling between daily activities as social zeitgebers of cortisol secretion, Stetler, Dickerson and Miller (2004) found that the two were coupled in healthy individuals but unrelated in individuals with depression. MDD has also been associated with differences in the cortisol awakening response, during which cortisol normally steeply peaks 30-45 minutes after awakenings and then returns to baseline 60 minutes after wakening as reviewed by Dedovic & Ngiam (2015). This awakening response has also been found to predict depressive episodes (Vrshek-Schallhorn et al. 2013; Halligan et al. 2007; Goodyer et al. 2010; Adam et al. 2010).

Body temperature also appears to follow a circadian rhythm, in that core body temperature decreases at night and rises during the early morning (Garry 1969). As a result, it may also be dysregulated. Such dysregulation has been observed in individuals with MDD. For instance, a study by Avery et al. (1982) found increased temperatures during the night and

overall lower temperature amplitudes in 9 depressed individuals (7 MDD and 2 BD) in comparison to 12 healthy controls. In a later study, Avery et al. (1999) again found the nocturnal temperature to be elevated in depressed individuals compared to controls. More recent studies have also shown discrepancies in temperature rhythms between individuals with MDD and without (Avila Moraes et al. 2013; Rausch et al. 2003). These are just some of the multitude of studies showing circadian rhythm disruptions in various domains as observed in MDD.

Circadian Rhythms Disruptions in Bipolar Disorder

Individuals with BD show either periods of mania and/or hypomania cycling with either melancholia and/or depression, as characterized by the DSM-5 (APA 2013). Mixed episodes may also occur. Mania is characterized by periods of elevated and irritable mood, with symptoms such as needing a lot less sleep, quick thoughts, and inflated self-esteem, among others. These symptoms generally last at least one week. Hypomania is similar, wherein the individual also experiences a greater drive with elevated and irritable mood, but symptoms are less severe, such that they do not impact social functioning or work/school and must last at least four consecutive days. Melancholia is a less severe form of depression. The literature associating circadian rhythm disruptions and mood episodes is even more extensive for BD (Gonzalez 2014; Milhiet et al. 2011; Murray and Harvey 2010).

For example, as with MDD, individuals with BD also show significant sleep disturbance during both episodes of depression and mania (Harvey 2008; Gruber et al. 2011; Ritter et al. 2012; Hudson et al. 1992). In addition, sleep disturbance is also present during interepisode periods (while in remission), as compared to healthy controls and is found to be prodromal of future episodes (Ng et al. 2015; Rocha, Neves & Correa 2013; Geoffrey et al. 2014; Sylvia et al.

2012; Duffy et al. 2010; Millar, Espie & Scott 2004). Sleep disturbance in BD has also been associated with severity of illness (Eidelman, Talbot & Gruber 2010).

Disruptions in the circadian hormonal profiles have been shown in BD as well. Although less work has been done for melatonin in BD, some studies have shown melatonin rhythm dysfunction in patients (Nurnberger et al. 2000). One study, by Kennedy et al. (1996), found lower melatonin serum levels in BD patients compared to controls, irrespective of mood state (depressed, manic or euthymic), suggesting its role as a trait and not state marker for BD. Some work has also been carried out in regards to cortisol rhythm disturbance in BD. For example, using area under the curve analysis, Cervantes et al. (2001) found increased cortisol secretion in depressed and manic BD patients compared to controls. Again, this finding suggested that cortisol rhythms are more so a trait rather than state marker. On the other hand, a more recent study of first time manic individuals with BD found decreased plasma cortisol levels compared to controls (Valiengo et al. 2012). This study also differentiated dysphoric mania from elated mania and showed higher cortisol levels in dysphoric patients. Studies have shown conflicting results in remitted patients, with some studies showing differences in cortisol (Havermans et al. 2011) and some showing normal cortisol levels compared to controls in remitted patients (Deshauer et al. 2006).

In regards to other circadian domains, such as body temperature, a few older studies have also found it to be dysregulated in individuals with BD (Souetre et al. 1988; Sothern, Slover & Morris 1993; Avery, Wildschiodtz & Rafaelsen 1982). In addition, although not discussed in the preceding section, social rhythms are also found to have a circadian pattern and are found to be perturbed in BD (Ashman et al. 1999; Malkoff-Schwartz et al. 1998). A recent study using a

circadian rhythms questionnaire with a social subdomain found a dose-dependent like association between degree of rhythm disturbance and depressive symptoms in individuals in a sample of BD patients and controls (Pinho et al. 2015). The aforementioned highlights a small portion of the extensive work that has been done showing circadian rhythm disruption in individuals with BD.

Subjective Sleep Disruption and Depression (pregnancy and postpartum)

Numerous studies have investigated subjective sleep across the perinatal period, using self-report questionnaires and rating scales, such as the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) and General Sleep Disturbance Scale (GSDS) (Lee 1992). Many have also studied the relationship between subjective sleep and changes in mood in the postpartum period. In healthy women, it has been shown that subjective sleep quality decreases from early to late pregnancy, with a distinct drop within the first few weeks postpartum and gradually improves in the months following delivery, as shown by Figure 1 (Gay, Lee & Lee 2004; Naud et al. 2010; Tsai et al. 2011; Park, Meltzer-Brody and Stickgold 2013). Studies in healthy pregnant women have also shown that their subjective sleep quality is worse than healthy non-pregnant controls (Okun & Coussons-Read 2007; Ko et al. 2010). Furthermore, even among differing sleep trajectories, it has been shown that such poor subjective sleep quality in healthy women during the perinatal period is associated with more anxiety and depressive symptoms in the postpartum (Tomfohr et al. 2015). This finding was supported by a previous study that found subjective sleep within two weeks postpartum to be associated with low mood in a study of 29 healthy women (Coo, Milgrom & Trinder 2014). Bei et al. (2010) also found such an association during the first week postpartum in healthy women at low risk for PPD (N=44).

Another study assessed sleep and depressive symptoms during the third trimester of pregnancy and later into the postpartum at two, three and four months (Goyal, Gay & Lee 2007). This was carried out in a sample of 124 women. History of a mood disorder was not reported. This study, too, found that subjective sleep disturbance was associated with depressive symptoms during late pregnancy and at four months postpartum. This group also conducted a study with a very similar design a few years later, but this time including fathers and other risk factors for PPD development, such as infant temperament and relationship satisfaction (Goyal, Gay & Lee 2009). It was again found that disturbed subjective sleep was associated with depressive symptoms in the postpartum period. Another group, Park, Meltzer-Brody and Stickgold (2013), also studied subjective sleep during the third trimester and at the 2nd, 6th, 10th, and 14th week postpartum. They found poor subjective sleep to be predictive of depressive symptoms at all weeks in 25 healthy, primiparous women. Finally, in a fairly recent study, Wu et al. (2014) found sleep quality in the third trimester of pregnancy to be predictive of PPD. This was found in a sample of 205 women, of which 21 developed PPD as determined by DSM-IV-TR Axis I disorder structured clinical interview - patient edition.

The preceding studies all used validated sleep scales to measure sleep quality and disturbance. Looking at group differences, one study of 38 healthy women using subjective sleep diaries found that those mothers who developed clinically significant depressive symptoms at 2-4 weeks postpartum also had more disturbed sleep during the third trimester of pregnancy compared to mothers that did not (Wolfson et al. 2003). Some studies have focused on the relationship between sleep quality and the recurrence of PPD in women with a history of this mood disorder. For example, in a sample of 51 women, sleep quality was compared

between those who recurred and those who did not. It was found that those who recurred after 4 weeks postpartum (44%) showed poor subjective sleep quality in comparison to those that did not (Okun et al. 2009). In a later longitudinal study, Okun et al. (2011) again studied the association between subjective sleep and PPD recurrence in 56 women with histories of either MDD or PDD, while also studying the impact of cytokine and hormone (estradiol, prolactin, and cortisol) changes. These women were euthymic and studied up to 17 weeks postpartum. It was found that only poor subjective sleep quality, and not cytokine or hormone level, was significantly associated with PPD recurrence, even when medication was controlled for. In fact, they found that a one point increase in a PSQI score was related to a 23.9% increase in risk of recurrence.

At a large scale, a cross-sectional, population based study of 2830 women at postpartum week 7 found more than half of the sample experienced poor sleep quality at this time point (Dorheim et al. 2009). In addition, the study found depressive symptoms were associated with poor sleep quality at this time point, even when other factors associated with depression were controlled for. In a similar type of cross-sectional study of 2816 women, Dorheim et al. (2012) found a 61.9% prevalence of insomnia at gestational week 32. They also found this to be strongly associated with poor subjective sleep quality. In a smaller cross-sectional study with a sample of 143 postpartum women, Swanson et al. (2011) also found that depressive symptoms in the postpartum were correlated with higher reported levels of insomnia.

Figure 2 – Sleep Disturbance across the Perinatal Period in Healthy Women

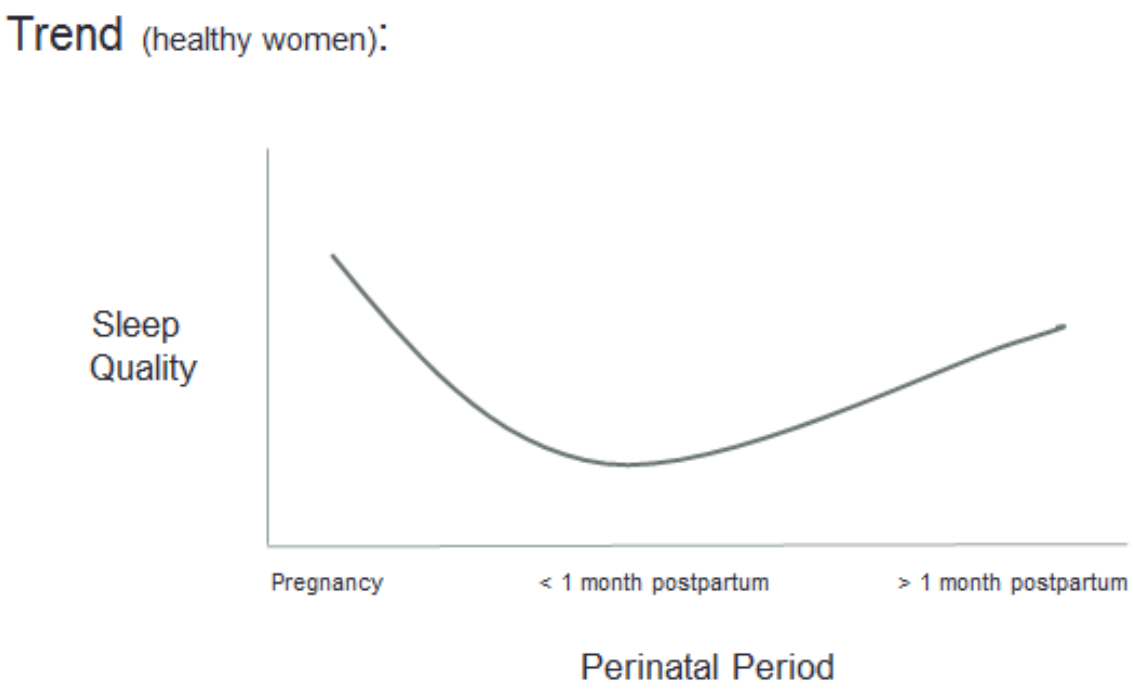

Figure legend: Collective findings on subjective and objective sleep research in healthy women show sleep quality drastically worsens in the first few weeks after delivery and gradually improves in the postpartum.

Objective Sleep Disruption and Depression (pregnancy and postpartum)

There are a few techniques available to study sleep objectively. For example, polysomnography, typically involving EEG, is a technique often used in a variety of sleep studies. The issue with this method is that they often result in studies with low sample sizes and often participants have to come to a sleep laboratory to participate, and so this may not be truly representative of the individual's sleep in his/her own environment. This being said, studies using these methods, such as one by Hertz et al. (1992) using polysomnography in pregnancy and an older study by Karacan et al. (1969) using EEG in pregnancy and postpartum, have shown that sleep is disrupted during the perinatal period compared to non-pregnant controls, with sleep being worst in the first month postpartum and gradually improving thereafter, particularly in healthy women.

Furthermore, a study using ambulatory polysomnography in a home setting across pregnancy (during each trimester) and at two postpartum time points (3-4 and 11-12 weeks post) found that sleep was more disrupted in the first month postpartum as compared to pregnancy in a sample of 31 women (Lee, McEnany & Zaffike 2000). It was noted that REM sleep was highly variable during pregnancy with total sleep time being stable. Moreover, this study found that while mood was stable during pregnancy, a time by group interaction was found when women were split into a positive and negative mood group during the postpartum. The negative mood group showed less REM and a shorter REM sleep latency. An older study using EEG also found sleep to be more disturbed in women with a history of an affective disorder (N=14) compared to women without one (N=20) (Coble et al. 1994). Sleep was monitored from 12 weeks pregnancy to 8 months postpartum. Sleep was found to be most disturbed for both

groups during the first few postpartum months and especially around the postpartum week four. Although there were significant differences between groups in relation to sleep parameters, these differences were not associated with changes in mood.

A more recent means of objectively studying sleep is through the use of actigraphy. An actigraph is watch-like device that collects data by recording an individual's movements (Sadeh & Acebo 2002; Ancoli-Israel et al. 2003). Actigraphy allows for the benefit of measuring sleep in a natural home setting and over a long period of time. In addition, actigraph obtained sleep parameters are found to be highly agreeable with those obtained from polysomnography (Jean-Louis et al. 2001; Signal, Gale & Gander 2005). This technique has been readily utilized by a multitude of studies to observe sleep measures such as total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), and sleep onset latency (SOL), among other measures. Moreover, actigraphy has been readily utilized to study sleep during the perinatal period and its relationship with numerous health outcomes, such as cardiometabolic risk (Haney et al. 2014). Actigraph studies support the changes in sleep across the perinatal period, as found in subjective studies and represented in figure 1 (Shinkoda, Matsumoto and Park 1999; Tsai et al. 2013; Montgomery-Downs et al. 2010; Park, Meltzer-Brody & Stickgold 2013; Matsumoto et al. 2003; Kang et al. 2002).

Studies have also used actigraphy to observe the association between sleep and mood changes in the postpartum period and across the perinatal period. Posmontier (2008) found women with PPD had worse sleep as measured by actigraphy compared to who did not at 6-26 weeks postpartum. They found women with PPD had lower SE and a higher WASO, suggesting greater sleep disruption. Moreover, the worsened sleep quality (sleep latency, WASO and SE)

also predicted PPD symptom severity. Tsai and Thomas (2012) also found sleep disturbances, such as objectively measure sleep variability, to be associated with depressive symptoms in 22 healthy women (none of which developed clinically significant PPD). One study, however, did not find an association between third trimester sleep and depressive symptoms within two weeks postpartum in 72 generally healthy women (Coo Calcagni et al. 2012).

A number of studies, however, have found that subjective sleep is more so associated with depressive symptoms in the postpartum than objective sleep (Park, Meltzer-Brody & Stickgold 2013; Coo, Milgrom & Trinder 2014; Bei et al. 2010). For example, in a study of 42 women in the postpartum, of which 21 were depressed, the depressed group showed more subjective sleep disturbances although objective measures did not differ between the two groups (Dorhiem et al. 2009). In fact, other studies have also shown that subjective and objective sleep parameters during the perinatal period tend not to correlate (Bei, Coo & Trinder 2015; Herring et al. 2013; Wilson et al. 2013; Van Ravesteyn et al. 2014; Tsai & Thomas 2012). In summary, the above-mentioned study of changes in sleep across the perinatal period and its impact on depressive mood has yielded mixed results and warrant further research. Moreover, a majority of the work has been done in healthy women without psychiatric history, which also needs to be addressed.

Circadian Rhythms Disruption and Depression (pregnancy and postpartum)

Literature on circadian rhythm disruption, apart from sleep, and its association with mood changes across the perinatal period is largely lacking. To date, only one study has prospectively examined changes in circadian rhythms from pregnancy to postpartum and their association with changes in mood in the postpartum. Sharkey et al. (2013) measured changes in

dim light melatonin onset (DLMO) phase from third trimester of pregnancy to six weeks postpartum in 12 euthymic women with history of a mood disorder. Nine women showed a phase shift in DLMO by at least 30 minutes. Moreover, the DLMO circadian measures were largely associated with depressive symptoms as captured by the Hamilton Depression Rating Scale (HAMD).

In another study, plasma melatonin levels were compared between women with a history of a mood disorder and healthy women in both pregnancy (n=25 [15 HC]) and postpartum (n=24 [11 HC]; Parry et al. 2008). Using analysis of covariance, in this study, depressed women showed lower levels of melatonin during pregnancy and higher levels during postpartum compared to their healthy counterparts, suggesting melatonin rhythm disruptions during these periods. Remaining studies have focused on sleep disruption and postpartum depressive symptoms, as already discussed above.

Chronotherapy and Postpartum Depression

Although studies exploring the impact of mood history on circadian rhythm disruption during the perinatal period, as well as the impact of circadian rhythm disruption during the perinatal period on postpartum depressive symptoms are limited, a few studies have aimed to determine the impact chronotherapy has on postpartum mood improvement. The results have been promising.

Sleep deprivation is one such non-pharmacological, chronotherapeutic intervention that has been used to successfully treat depression (Benedetti et al. 2007; Bunney & Bunney 2013; Voderholzer et al. 2003). One study assigned both early-night and late-night sleep deprivation to

9 women with either ante or postnatal depression (Parry et al. 2000). The postpartum patients responded better to the late-night sleep deprivation, in that this intervention decreased their depressive symptom scores. Although it has been shown that total sleep deprivation is better than partial sleep deprivation and that there might be a dose-dependent response (Giedke et al. 2003), many studies have shown that sleep deprivation offers rapid antidepressant effects that only last up to a couple of days, particularly in those who are unmedicated (Wu & Bunney 1990). Cognitive behavioural therapy for insomnia also targets sleep issues with the hopes of improving mood. Twelve postpartum women with concurrent depression and insomnia participated in a pilot study of this therapy, wherein they received individual sessions for five weeks (Swanson et al. 2013). Significant improvements in subjective mood and sleep quality were observed at the end of the therapy period.

Sleep disturbance has also been targeted pharmaceutically to improve depressive mood in the postpartum. For example, in a clinical trial, 54 pregnant women with insomnia were treated with diphenhydramine, trazodone or placebo (Khazaie et al. 2013). This treatment was started in the third trimester of pregnancy and was hoped to stabilize mood into the postpartum. Compared to placebo, both active treatments improved sleep and decreased depressive symptoms 2 to 6 weeks after delivery, suggesting preventative properties for the development of PPD.

Another chronotherapy that has been implicated in the treatment of depression is bright light therapy. Corral, Kuan and Kostaras (2000) found bright light therapy to substantially improve depressive symptoms in 2 women suffering from postpartum depression in an open trial. The women were treated for four weeks. Later, Corral et al. (2007) used this therapy once

more in a clinical trial at 10,000 lux to treat 10 outpatient women with PPD and assigned 5 women to dim red light at 600 lux for comparison. It was found that both groups showed significant symptom improvement over time. This therapy has also been efficacious at treating antenatal depression (Crowley & Youngstedt 2012). Another small pilot study also used bright light therapy to promote mood and sleep improvement in mothers of low birth weight infants in the neonatal intensive care unit (Lee, Aycock and Moloney 2013). Sixteen women were assigned to the bright light therapy and fourteen wore red light visors, acting as the control group. The intervention lasted three weeks. Although no significant effects were observed, most likely due to the small sample size, women's depressive symptoms and sleep quality improved in the treatment group compared to the controls.

Moreover, blue light has been found to suppress melatonin production. One study used this idea and gave women suffering from PPD glasses that blocked blue light (n=18) to ensure their melatonin rhythm was not being disrupted during night time awakenings, while the other participants received placebo glasses (n=9) (Bennett et al. 2009). They found that all of the women showed improvement, but the women in the first group appeared to recover faster than the women who were given placebo glasses. Collectively, this preliminary work in regards to treatment targeting circadian rhythm stabilization suggests an association between improving circadian rhythm stability, good mental health and the potential to even decrease the risk of postpartum episode onset.

Study Aims and Hypotheses

The goal of the work outlined in this thesis was to address the gap in the literature concerning the association between circadian rhythm disruption and postpartum depression

development. Longitudinal work looking at sleep and circadian rhythm disruption and maternal outcomes is needed (Chang et al. 2010). This was addressed by determining if circadian rhythm disruption was manifested across the perinatal period, through both subjective and objective measures. Moreover, it was determined if present circadian rhythm disruptions across the perinatal period is associated with postpartum mood worsening in women with and without a history of a depressive mood disorder. Sleep disruption was also measured because of its strong ties to circadian rhythmicity.

We first studied this association using subjective measures of circadian rhythm and sleep disruption. We hypothesized that women with a history of a mood disorder (MDD or BD) would show increased circadian rhythm and sleep disruptions during the third trimester of pregnancy and 6 to 12 weeks postpartum. We also hypothesized that greater disruptions in both domains would be predictive of PPD. This work is presented as a manuscript in Chapter 2, entitled "Do Changes in Sleep and Biological Rhythms Predict Worsening in Postpartum Depressive Symptoms? A Prospective Study Across the Perinatal Period" and is currently under review in the *Australian and New Zealand Journal of Psychiatry* since June of 2015.

Next, we continued our goal of investigating whether circadian rhythm disruptions occur during the perinatal period in women with and without a mood history and if this is associated with postpartum mood worsening using objective measures. We used actigraphy to measure both circadian rhythm and sleep disturbances during the same time period as outlined above. Again, it was hypothesized that objective measures of disruption would be greater for women with a mood history. It was also hypothesized that disruptions would be predictive of PPD. The findings of this study are presented in Chapter 3, as a subsequent manuscript entitled

"Association between Sleep, Circadian Rhythms and Postpartum Mood: A Longitudinal Study across the Perinatal Period" and submitted to the Journal of Clinical Psychiatry.

Finally, we carried out a small pilot study to determine if the circadian system is associated with postpartum depressive symptoms at a molecular level. We did this by obtaining blood samples and genotyping the 3111T/C single nucleotide polymorphism in the *Clock* gene, which has been previously associated with history of MDD or BD, as well as PPD development. It was hypothesized that more women with a history of MDD or BD would carry either the CT or CC polymorphism and that women who develop PPD would also carry the CT or CC polymorphisms. The rationale and methods for this study are summarized as a brief communication in Chapter 4 (unfortunately results are still pending).

CHAPTER 2

Do Changes in Sleep and Biological Rhythms Predict Worsening in Postpartum Depressive Symptoms? A Prospective Study Across the Perinatal Period

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Running title: Sleep, biological rhythms and depression in perinatal women

Abstract

Background: Abnormalities of sleep and biological rhythms have been widely implicated in the pathophysiology of Major Depressive Disorder (MDD) and Bipolar Disorder (BD). However, less is known about the influence of biological rhythm disruptions across the perinatal period on postpartum depression (PPD). The objective of this study was to prospectively evaluate the relationship between changes in both subjective sleep and biological rhythms and worsening of depressive symptoms from pregnancy to the postpartum period in women with and without mood disorders.

Methods: Eighty-three participants (38 euthymic women and 45 healthy controls) completed perinatal assessments of sleep and biological rhythms disturbances and depressive symptoms.

Results: Multivariate regression analysis showed that changes in biological rhythms across the perinatal period, but not changes in sleep, predicted worsening of depressive symptoms in both groups. This relationship was stronger in women with mood disorders. Moreover, women with a history of a mood disorder showed higher levels of sleep and circadian rhythm disruption during both pregnancy and the postpartum period.

Conclusion: These findings suggest that disruptions in biological rhythms, and not necessarily sleep, during the perinatal period increase the risk for postpartum mood worsening in all women, and that this effect is stronger in women with a diagnosis of a mood disorder.

Keywords: Bipolar Disorder; Biological Rhythms; Major Depressive Disorder; Mood; Postpartum; Pregnancy; Sleep

Introduction

Postpartum depression (PPD) is an ongoing societal health problem. Whereas between 7-15% of women in the general population develop PPD (Gavin et al., 2005; O'Hara and McCabe, 2013; Serhan et al., 2013), women with history of a mood disorder are at an even greater risk for its development (O'Hara and McCabe, 2013; Robertson et al. , 2004; Wisner, Parry and Piontek, 2002). PPD confers negative outcomes on mothers and their families, which are long lasting if left untreated. For instance, mothers suffering from PPD may experience undermined confidence in the care for their infant, a distorted sense of responsibility and, in more severe cases, infanticide ideation (Barr and Beck, 2008). Children of mothers who suffered from a depressive episode in the postpartum period are at greater risk for the development of subsequent affective, behavioural and cognitive problems (Sellers et al., 2013; Verbeek et al., 2012). PPD also places stress on marital relationships, which may result in greater family dysfunction (Faisal-Cury et al., 2013; Piteo et al., 2013). Notably, a number of studies have found increased risk for suicidal behaviour in this population, accounting for up to 20% of postpartum deaths (Kim et al., 2014; Lindahl, Pearson and Colpe, 2005; Pope et al., 2013; Tabb et al., 2013). Therefore, it is imperative that modifiable risk factors for PPD are properly identified and the underlying biological mechanisms are better understood.

A number of clinical features such as history of psychiatric disorders, high neuroticism, low-self-esteem and family history of mental health issues have been identified as risk factors for

development of PPD (Meltzer-Brody et al., 2013; O'Hara and McCabe, 2013; Robertson et al., 2004). In addition, psychosocial factors such as lower income, financial hardship and low perceived social support have also been implicated (Leahy-Warren and McCarthy, 2007; Razurel et al., 2013; Rich-Edwards et al., 2006; Xie et al., 2010). Despite a better understanding of the clinical and psychosocial risk factors for the development of PPD, little consensus has been reached about the biological mechanisms behind this disorder. Previous studies have investigated the role of the hypothalamic-pituitary-adrenal (HPA) axis (Brummelte and Galea, 2010; Glynn, Davis and Sandman, 2013; Kammerer, Taylor and Glover, 2006), sex hormones, thyroid-stimulating hormone (Klier et al., 2007; Okun et al., 2011), and inflammatory markers (Albacar et al., 2010; Sylven et al., 2013) as potential biological risk factor for PPD. However, the results from these biological studies are contradictory and the clinical utility of these biological markers remains elusive.

Work over the last few decades has linked sleep and biological rhythms disruptions, both physiological and behavioural, with a variety of depressive disorders. For example, individuals suffering from Major Depressive Disorder (MDD) and Bipolar Disorder (BD) show significant sleep and circadian rhythm disturbances during mood episodes (Gonzalez, 2014; Harvey, 2011; McClung, 2013; Palagini et al., 2013; Wirz-Justice, 2006). Perhaps more importantly, sleep and circadian disturbances are also present between episodes and *prior to* the development of mood episodes, acting as prodromes (Harvey, 2011; Ng et al., 2015; Scott, 2011). Throughout the perinatal period, women often experience a variety of somatic changes, which may influence the stability of biological rhythms and quality of sleep and be related to depressive symptom development (Williamson et al., 2015). For instance, the relationship between

changes in sleep measures during pregnancy and worsening of depressive symptoms during the postpartum period has been reported and replicated (Bei et al., 2010; Goyal, Gay and Lee, 2009; Okun et al., 2011; Park, Meltzer-Brody and Stickgold, 2013). In addition, preliminary work targeting sleep improvement and circadian stabilization as a treatment of depressive mood during the perinatal period has revealed encouraging results (Bennett et al., 2009; Corral et al., 2007; Epperson et al., 2004; Parry et al., 2000).

To our knowledge, only one small study (N=12) has examined the relationship between changes in parameters of biological rhythms and postpartum mood worsening longitudinally in women with mood disorders (Sharkey, Pearlstein and Carskadon, 2013). In this study, circadian phase shifts in salivary dim light melatonin onset from pregnancy to postpartum correlated with postpartum depressive symptoms in women with a history of MDD (Sharkey et al., 2013). Given the growing body of evidence relating biological rhythm disturbances to depression, we investigated whether changes in sleep and biological rhythms from pregnancy to the postpartum period are associated with worsening of depression. Because previous history of mood episodes is one of the strongest risk factors for development of PPD, we tested this hypothesis in women with and without mood disorders. We hypothesized that disturbances in sleep and biological rhythms will be associated with worsening of depressive symptoms at postpartum, and that this association will be stronger in women with a diagnosis of major depressive or bipolar disorder.

Method

Subjects and Study Design

This study was approved by the Hamilton Integrated Research Ethics Board and was in line with the principles of the Declaration of Helsinki as revised in 2013. All participants provided written informed consent before study entry. Subjects were recruited from the Women's Health Concerns Clinic at St. Joseph's Hamilton Healthcare and the Community Midwives of Hamilton. Data collection occurred between November 2011 and May 2015. Participants were screened over the phone for eligibility to participate in the study. Inclusion criteria were: 18 years of age or older, in the third trimester of pregnancy (≥26 weeks of gestation), being euthymic for at least two months, with or without a history of BD or MDD and being fluent in English. Participants were excluded if they suffered from sleep apnea, recently traveled across time zones or worked night shifts. Ninety-four women were enrolled in the study. One participant was excluded prior to the first visit for the reason that she was a surrogate. Two study participants were excluded because they met criteria for a current major depressive episode. Eight were lost in the follow-up, due to moving, failure to contact for follow-up or contact after the follow-up window had elapsed. Therefore, 83 women completed this prospective study. Study participation involved two visits. Mood, sleep and biological rhythm assessments were carried out longitudinally during the third trimester of pregnancy (≥26 weeks) and during the postpartum period (6-12 weeks). Subjects were divided into two groups: women with a diagnosis of a history of BD or MDD (mood group) and healthy controls.

Clinical Assessments

Psychiatric diagnosis was assessed using the structured diagnostic interview Mini International Neuropsychiatric Interview (M.I.N.I.) English Version 6.0.0 (Sheehan et al., 1998). Women who met criteria for a current mood episode were excluded from further study

participation. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure depressive symptoms during the third trimester of pregnancy and 6-12 weeks into the postpartum period (Cox, Holden and Sagovsky, 1987). This widely used instrument to assess depression has been validated for its use in both pregnancy and postpartum (Murray and Cox, 1990). The Major Depressive Disorder module A of the M.I.N.I. was re-administered during the postpartum visit conditional on a score of ≥12 on the EPDS to confirm a postpartum depressive episode.

Sleep was assessed using the validated Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a subjective scale, measuring sleep quality by means of 19 questions. The scale assesses domains of sleep quality such as sleep efficiency and fragmentation, as well as provides estimates of total sleep time and reasons for sleep disturbance. The total score is calculated based on 7 component scores, each of which is scored from 0 to 3. An overall score of above 4 on the scale indicates poor sleep quality.

The self-report Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), developed and validated by Giglio et al. for the clinical assessment of biological rhythm disturbance in bipolar disorder (Giglio et al., 2009; Giglio et al., 2010), was used to assess biological rhythm disturbances at both study visits. The BRIAN questionnaire is retrospective for the last 15 days and includes 18 items split into 4 biological rhythm domains: sleep (5 questions), activity (5 questions), social (4 questions), and eating pattern (4 questions). Each question is scored out of a possible 4 points, totalling an overall minimum score of 18 and maximum score of 72. A higher score indicates greater biological rhythm disruption. Chronotype is also captured by the scale, but was not used for analysis in this study. This was because although the mothers may have a preference for the timing of their daily activities, we predicted

that the infant's needs (i.e. feeding, cleaning, etc.) would mask this preference and therefore chronotype was not a sought outcome measure.

Statistical analysis

Statistical analyses were performed using R statistical software (version 3.0.1) (R Core Team, 2013). Normal distribution of the continuous variables was assessed using Shapiro-Wilk test. Bartlett test was used to evaluate the homogeneity of variances between groups. Group comparisons of changes in sleep (PSQI scores) and biological rhythms (BRIAN scores) from pregnancy to postpartum were done using two-way repeated measures ANOVA. In the situation that the data was not normally distributed, non-parametric Wilcoxon Rank-Sum tests were used. Specifically, pregnancy sleep (PSQI) and circadian rhythm (BRIAN) disturbances were compared to those in the postpartum for each group individually. To test for an interaction between group and perinatal timing using a non-parametric test, differences in questionnaire scores (ΔPSQI and ΔBRIAN) were obtained by subtracting pregnancy scores from the postpartum scores and compared for the two groups.

To answer our primary research question, the impact of changes in sleep and circadian rhythms on changes in depressive symptoms (ΔEPDS) from pregnancy to postpartum was analyzed by means of a general linear model. Specifically, analyses were performed using changes in continuous PSQI and BRIAN scores and group (mood group and healthy controls) as predictors and changes in continuous EPDS scores as the outcome variable in a stepwise multiple linear regression. Assumptions of multiple linear regression such as linearity, independence, normality, homoscedasticity and multicollinearity were tested for each model. The level of significance was set at α=0.05.

Results

Table 1 shows demographic and clinical characteristics for the healthy control and mood group. Thirty-eight women met criteria for lifetime mood disorder according to the M.I.N.I. (BD or MDD). The majority of women in our sample were married or partnered, and had an education surpassing high school. There was only a significant difference in socioeconomic status (SES) between groups, with a few woman in the mood group having a lower SES compared to the healthy controls ($p<0.05$). Age was not significantly different between groups ($p=0.79$). In the mood group, seven women were on psychotropic medication, while four were using over-the-counter sleep aids at the first visit. Four of the mood participants remained on psychotropics during the postpartum, while only one woman used a sleep aid during this period. Only four participants had scores of ≥12 on the EPDS at the postpartum period. Of these, only two woman met criteria for a current major depressive episode according to the M.I.N.I.

Group comparisons of biological rhythm and sleep disturbances across the perinatal period

Non-parametric analyses (Wilcoxon rank-sum test) were used to compare biological rhythm and sleep disruptions across the perinatal period between the two groups. Non-parametric tests were used because the assumptions of normality could not be met, despite transformations of the data. Women in the mood group showed significantly greater circadian rhythm and sleep disruption than healthy controls during the third trimester of pregnancy and during the postpartum period (both $p<0.001$). However, changes in circadian rhythms and sleep from pregnancy to the postpartum period (ΔBRIAN and ΔPSQI) were not different between groups ($p=0.26$ and $p=52$, respectively).

Changes in sleep and biological rhythms in the perinatal period as predictors of postpartum depressive symptom worsening

Stepwise multiple linear regression was used to evaluate whether changes in depressive symptoms (ΔEPDS) across the perinatal period were predicted by changes in sleep (ΔPSQI) and/or biological rhythms (ΔBRIAN). The first 11 women included in our study did not complete the PSQI, as it was added to the study protocol at a later time. As a result, the regressions were run with 40 women in the healthy control group and 32 women in the mood group. We ultimately wanted to use group as a predictor in the linear regression, however, such a model failed all assumptions of linearity, independence, normality, homoscedasticity and multicollinearity. Thus, we tested if the group factor acted as a moderator for the analysis. However, this too resulted in a failure to meet the necessary assumptions. We therefore used two separate linear models for each group. In healthy controls, changes in BRIAN (ΔBRIAN), but not PSQI scores (ΔPSQI), predicted changes in EPDS (ΔEPDS) scores from pregnancy to postpartum (Table 2a). In women with mood disorders, the results were much the same, with changes in BRIAN, but not PSQI scores, predicting changes in EPDS scores from pregnancy to postpartum (Table 2b). The model was more significant and explained more of the variance in depressive symptoms for women with a history of a mood disorder (Tables 2a-2b).

Discussion

The main finding of the present study was that self-reported changes in biological rhythms from pregnancy to the postpartum predicted changes in depressive symptoms in euthymic women with mood disorders, as well as in healthy controls. Consistent with our a priori hypothesis, the linear model was more significant and predicted a greater proportion of the variance in

depressive symptoms for women with a history of a mood disorder. Sleep quality did not predict depressive symptoms, suggesting that changes in biological rhythms beyond sleep have a strong link in mood worsening during late pregnancy to early postpartum. This association seems somewhat stronger in women with history of mood disorders. To the best of our knowledge, ours is the first study to prospectively determine if disturbances in biological rhythms predict mood worsening across the perinatal period. Our results are also consistent with the only study that investigated objective parameters of circadian rhythms in 12 euthymic women with diagnosis of MDD. In this study, phase shifts in salivary dim light melatonin onset from pregnancy to postpartum were associated with worsening of postpartum depressive symptoms in women with a history of MDD (Sharkey et al., 2013).

When measuring sleep parameters alone, some prospective studies have found that changes in subjective sleep are associated with worsening in postpartum depressive symptoms in similar populations. For instance, a recent study of 29 healthy women reported that worsened subjective sleep as measured by PSQI from late pregnancy to postpartum was associated with increased postpartum depressive symptoms, when compared to objective actigraphy measures of sleep (Coo, Milgrom and Trinder, 2014). This mirrored results from an earlier study (N=44) which also found that worsened subjective measures of sleep, such as less total sleep time and poorer sleep efficiency, during the postpartum were associated with a detriment in mood (Bei et al., 2010). Moreover, in relation to PPD reoccurrence, a study of 51 women with previous history of PPD who were euthymic during pregnancy found that subjective poor sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), was associated with timing of recurrence of PPD during the postpartum (Okun et al., 2009). More

specifically, this latter study found that poor sleep was related to late recurrence, defined as 5-28 weeks postpartum. In an extension of this same study assessing the influence of pregnancy-related hormones on PPD recurrence only PSQI scores, but not estradiol, prolactin, cortisol or interleukin-6, were associated with PPD recurrence, when medication status was controlled for (Okun et al., 2011). Another large sample, cross-sectional study of 4191 women during the postpartum which found that poor subjective sleep, as measured by the PSQI, was associated with depressive symptoms (Dorheim et al., 2009a). This is further supported by an older electroencephalographic (EEG) sleep study across the perinatal period which also found significant differences in various sleep parameters between euthymic women with mood disorders and healthy controls, even though the women with a mood history did not develop clinically significant symptoms (Coble et al., 1994). More specifically, women with mood disorders displayed reduced total sleep time and rapid eye movement latency as compared to healthy women. Whether these differences in circadian rhythm or EEG parameters are associated with an elevated risk for development of PPD remains to be determined.

Studies comparing subjective and objective sleep have found that subjective sleep is more so associated with depressive mood than objective sleep (Bei et al. 2012; Coo et al., 2014). Moreover, two solely actigraphy-based sleep studies did not find an association between sleep and mood disturbance across the perinatal period (Coo Calcagni et al., 2012; Lee and Kimble, 2009). Taken together, prospective studies that evaluated subjective sleep and other parameters of circadian rhythms from pregnancy to the postpartum period are suggestive that disruption in these systems may be particularly detrimental to women with a history of mood

disorders and we believe that such vulnerability may be one of the reasons why the presence of a mood disorder is considered one of the strongest risk factors for development of PPD.

Another finding from our study was that, although women with mood disorders showed greater biological rhythm disturbances in late pregnancy and early postpartum period when compared to healthy controls, we found no interaction between perinatal timing and group status on biological rhythm disruption. This suggests that although perinatal timing does not appear to bear a significant effect on the *mean/average* levels of biological rhythm disturbance for either group, disruptions in biological rhythms are persistent in women with mood disorders across this period. This finding has major implications for preventative approaches and treatment alternatives for women during the perinatal period. Our results suggest that treatment approaches targeting stability of the circadian system in late pregnancy may protect women with mood disorders, as well as healthy women, against postpartum mood worsening. Moreover, these results indicate that treatment approaches addressing disturbances in sleep/circadian rhythms should be an integral part of the overall management of perinatal women with mood disorders.

One of the limitations of our study was that only one woman developed PPD and many had low depressive symptoms at the follow-up visit. This may be attributable to the fact that we did not exclude women using psychotropic agents, which may have stabilized biological rhythms, as well as depressive symptoms, in the mood patients. However, just a small number of participants were using psychotropics (N=7) or sleep aids (N=4) during the study. An alternative reason may have been related to the source of our recruitment. The participants were primarily recruited from the Women's Health Concerns Clinic, where they were being

monitored closely to prevent mood episodes during the perinatal period, as well as the Community Midwives of Hamilton. Midwife clinics are generally attended by women of high SES, as women of low SES often do not tend to seek out perinatal care (Johnson et al., 1994). Parity was not considered and this could have influenced our results. Previous studies have suggested that there may be differences in certain parameters of circadian rhythms between primiparae and multiparae (Di Florio et al., 2014; Kivlighan et al., 2008; Lee, Zaffke and McEnany, 2000). Finally, we used a subjective measure of biological rhythm disruption. The BRIAN has not yet been validated against objective measures of circadian rhythms. Moving forward, studies should collect objective measures of circadian parameters, such as actigraphy, melatonin or cortisol, prospectively across the perinatal period in women with and without mood disorders. As far as the strengths of this study, this is the first prospective study looking at biological rhythms in women at higher risk for postpartum mood worsening and in healthy women. Also, most of our sample were medication-free so there was little (if any) interference of psychotropic medications in our results. Finally, we only recruited women who were stable (euthymic) at study entry so our results were not affected by mood state.

In conclusion, we found that changes in biological rhythms from pregnancy to the postpartum period predict postpartum depressive symptom worsening in women with and without mood disorders, and that this effect was stronger in women with mood disorders. We also found that euthymic women with mood disorders show greater subjective sleep and biological rhythm disturbances than their healthy counterparts during the 3rd trimester of pregnancy and this disturbance persists at least until 6-12 weeks postpartum. Our results suggest that treatment strategies targeting stabilization of the circadian system should be high

priority in clinical management of this population. Future longitudinal studies employing objective measures of circadian rhythms across the perinatal period would help us in identifying which specific biological parameters of rhythmicity are particularly associated with risk for postpartum mood worsening.

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Contributors

Drs. Frey, Minuzzi and Hidalgo contributed to the study design; Ms. Krawczak participated in the recruitment, screening and clinical assessments of study participants, and writing of the first draft of the manuscript; Dr. Minuzzi and Ms. Krawczak conducted the statistical analyses; All authors contributed with the writing and approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest regarding the content of this manuscript.

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Table 1: Clinical and demographic data (N=83)

Measure	Healthy Controls (N = 45)	Mood Group (N = 38)	Total (N = 83)	Group Differences
Age	29.29 (4.24)	30.29 (5.23)	29.74 (4.71)	$p > 0.05$

Gest Week	31.78 (3.90)	32.58 (3.75)	32.17 (3.83)	p > 0.05
Post Week	8.33 (2.04)	8.97 (2.10)	8.59 (2.08)	p > 0.05
Marital status				
Married	45 (100%)	34 (89%)	79 (95%)	
Single	0 (0%)	4 (11%)	4 (5%)	P>0.05
SES				
High	45 (100%)	32 (84%)	77 (93%)	
Low	0 (0%)	6 (16%)	6 (7%)	P<0.05
preBRIAN	24.11 (4.89)	31.84 (9.02)	27.65 (8.03)	
postBRIAN	24.91 (5.69)	31.84 (8.87)	28.08 (8.06)	
deltaBRIAN	0.80 (5.62)	0.00 (8.53)	0.43 (7.07)	
prePSQI	4.90 (3.33)	8.03 (3.74)	6.29 (3.83)	
postPSQI	4.75 (1.81)	7.31 (3.26)	5.89 (2.84)	
deltaPSQI	-0.15 (3.12)	-0.72 (4.08)	-0.40 (3.56)	
preEPDS	1.51 (1.95)	4.6 (4.39)	2.94 (3.63)	
postEPDS	1.89 (2.07)	5.03 (4.39)	3.33 (3.67)	
deltaEPDS	0.38 (2.14)	0.39 (4.16)	0.39 (3.20)	

Table 2a. Linear regression model in healthy controls (N=40)

Predictors	**β coefficient (CI)**	**S. E.**	**t value**	**p value**

ΔBRIAN	0.50 (0.11, 0.90)	0.20	2.57	0.01
ΔPSQI	-0.15 (-0.55, 0.25)	0.20	-0.76	0.45

R^2=0.13, p=0.03; CI = Confidence Interval

Table 2b. Linear regression model in mood group (N=32)

Predictors	**β coefficient (CI)**	**S. E.**	**t value**	**p value**
ΔBRIAN	0.39 (0.03, 0.74)	0.17	2.25	0.03
ΔPSQI	0.22 (-0.13, 0.57)	0.17	1.27	0.21

R^2=0.21, p=0.01; CI = Confidence Interval

CHAPTER 3

Association between Sleep, Circadian Rhythms and Postpartum Mood: A Longitudinal Study across the Perinatal Period

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Running title: Sleep, Circadian Rhythms and Postpartum Mood

Abstract

Objective: Women with a diagnosis of mood disorders are at higher risk to develop postpartum depression. The primary objective of this longitudinal study was to determine if circadian rhythms and sleep parameters differ between women with and without a history of a mood disorder across the perinatal period. A secondary objective was to determine if changes in these parameters were associated with postpartum mood.

Method: 33 women were included in this study, 15 of which had a history of a mood disorder and 18 healthy controls. Sleep and circadian rhythms were assessed subjectively and objectively during the third trimester (≥26 weeks gestation) and at 6-12 weeks postpartum. Mood was also assessed at both time points.

Results: Women in the high-risk group showed greater subjective circadian rhythm and sleep disturbances across the perinatal period. Objective sleep efficiency was also significantly different between groups in the postpartum period. Changes in both subjective circadian rhythms and objective sleep efficiency were predictive of changes in depressive symptoms across the perinatal period. Certain subjective and objective parameters of sleep and circadian rhythmicity were associated with one another.

Conclusion: Findings suggest that preventative measures to ensure circadian rhythm and sleep stability across the perinatal period can decrease the risk of postpartum mood worsening, particularly in those with a history of a mood disorder.

Key Words: Objective, subjective, sleep, circadian rhythms, mood, postpartum

Introduction

Sleep disruption, and more recently, circadian rhythm disturbances, have been increasingly associated with onset and worsening of mood episodes[1-4]. This association has been extensively documented for Bipolar Disorder (BD) and Major Depressive Disorder (MDD) using a multitude of instruments. There is, however, a lack of prospective studies exploring the impact of disruption in circadian rhythms on postpartum mood symptoms.

Postpartum depression (PPD) remains a largely unexplained phenomenon, effecting 7-15% of women[5,6]. To date, little consensus has been reached in determining the biological underpinnings of this mental health condition. Studies seeking to determine risk factors of PPD have shown that psychosocial factors such as lower income, financial hardship and low perceived social support act as moderate risk factors[7-10]. Notably, various clinical features have been highly associated with PPD risk. A history of BD or MDD, high neuroticism, anxiety and/or depression during pregnancy have all been found to confer the largest risk for its development[5,11].

Previous studies suggest that sleep disturbance during the perinatal period is associated with postpartum mood worsening. For instance, studies comparing depressed and non-depressed women in the postpartum period have shown those with depression have worse subjective sleep[12,13]. Numerous longitudinal studies have also found subjective sleep disruption across the perinatal period to be associated with depressive symptom worsening in the postpartum[14-16]. On the other hand, studies using objective methods such as actigraphy have found inconsistent results when associating these measures with postpartum mood symptoms. For example, Park et al[17] found actigraph-measured sleep efficiency (SE_{acti}), wake after sleep

onset ($WASO_{acti}$) and sleep fragmentation to be significantly correlated with depressive symptoms in the postpartum. A study of women with and without PPD found that women with PPD displayed worse objectively measured sleep parameters[18]. Looking at day-to-day sleep variability over 7 days of actigraph monitoring, Tsai and Thompson[19] found increased variability to be associated with depressive symptom worsening in 22 healthy women. Dorhiem et al[20] on the other hand, found no significant differences in actigraphy parameters between depressed and non-depressed mothers at two months postpartum. Bei et al[21] also did not find any objective sleep predictors to be related to postpartum mood worsening. In a study of 29 healthy women with a similar study design to ours, Coo et al[22] found subjective perception of sleep to be more predictive of mood than objective sleep parameters. Other studies in this field also show that subjective sleep measures more often do not correlate with objective sleep measures during the perinatal period[23-25].

Circadian activity rhythms (CARs) can also be measured via actigraphy[26]. Few studies, however, have used actigraphy for this purpose. Of the few studies investigating CARs during the perinatal period, four have studied the mother-infant synchrony of CARs[30-33], whereas two other studies found lower amplitudes in the first few weeks postpartum in healthy mothers[34,35]. None of these studies have measured perinatal mood in relation to CARs or observed CARs in women at risk of PPD.

As highlighted above, based on the premise that the presence of mood disorders confers a high risk for PPD and that mood disorders are highly associated with disruption in circadian rhythms, we conducted a study to determine whether women with a history of a mood disorder showed greater circadian rhythm disruption across the perinatal period

compared to healthy controls. Moreover, we sought to determine if circadian rhythm disruption across the perinatal period increased risk for postpartum mood worsening.

Methods

Participants

This study was approved by the Hamilton Integrated Research Ethics Board. Women were recruited from the Women's Health Concerns Clinic and Community Midwives of Hamilton from August of 2013 to June 2015. This was a prospective cohort study that followed women with a high and low risk of developing PPD. Women with and without a history of a mood disorder were recruited to make up two groups: healthy control low risk (HC) and mood history high risk (MH) groups. Voluntary informed consent was obtained prior to study participation. The selection criteria were as follow: 18 years of age or older, fluent in English, third trimester of pregnancy (≥26 weeks gestation), not working shiftwork, not experiencing jet lag, and no history of a sleep disorder. Women with a history of a mood disorder (BD, MDD, or PPD) were required to be euthymic for a minimum of two months at the first study visit. In order to be consistent with the profile of women who are currently in clinical remission, we allowed women who were currently taking psychotropics and sleep aids. A total of 35 women were enrolled in this study.

Study Design and Procedures

The study was composed of two visits: one during the third trimester of pregnancy (T1; ≥26 weeks gestation) and another between 6-12 weeks postpartum (T2). The T1 visit took place at St. Joseph's Hamilton Healthcare, while the T2 visit took place either at the clinic or mother's home to ensure convenience for continued participation. At T1, diagnostic assessment and

clinical characterization was conducted using validated questionnaires (below). Sleep and circadian rhythmicity were measured both subjectively with clinical questionnaires and objectively via three weeks of actigraphy. Three weeks following each visit, a home visit was scheduled to collect the actigraphs.

Measurements

Clinical Assessment

The Mini International Neuropsychiatric Interview (MINI) English Version 6.0.0. was used to assess psychiatric history and determine group assignment[36]. The MINI is a semi-structured diagnostic interview covering 21 current and past mood modules. Women who met criteria for a current depressive, manic or hypomanic mood episode at T1 were excused from further study participation. We also used the Mood Disorder Questionnaire (MDQ) at T1 to screen for lifetime manic symptoms[37]. The MDQ has been shown to be an effective screening tool for BD during the perinatal period[38].

PPD Risk Assessment

The Postpartum Depression Predictors Inventory-Revised (PDPI-R) prenatal version was used to screen for well-established psychosocial risk factors of PPD[39,40]. This scale contains questions concerning 13 risk factors with a threshold score of 10.5 for PPD risk[40]. This scale was administered only at T1.

Mood Symptoms

The self-report Edinburgh Postnatal Depression Scale (EPDS) was used to measure severity of depressive symptoms at T1 and T2[41]. The EPDS is a well validated tool, with good sensitivity and specificity in pregnancy and postpartum[42]. The scale is retrospective for the previous week and contains 10 items. Each item offers 4 responses, each of which is scored out of a possible 3 points. A cut off score of ≥12 has been widely used as "positive" screening for perinatal depression. Women scoring ≥ 12 at T2 were further interviewed with the Major Depressive Episode portion (Module A) of the MINI to confirm a clinical diagnosis of PPD.

The Young Mania Rating Scale (YMRS) was used to measure severity of manic symptoms[43]. Women scoring ≥ 8 on the YMRS were further interviewed with the Manic and Hypomanic Episodes portion (Module C) of the MINI to confirm a current episode of Mania/Hypomania.

Sleep

Sleep was assessed subjectively through the Pittsburgh Sleep Quality Index[44] (PSQI). The PSQI is a 19 item self-report questionnaire. The PSQI contains questions about various components of sleep, such as sleep efficiency, duration, and use of sleep aids over the last month. It has a maximum global score of 21, with poor sleep being defined as an overall score above 5. Objective sleep was measured through actigraphy. An actigraph is a battery-operated, wristwatch-like device, which records movement using a piezoelectric sensor. Actigraphy offers the benefits of being non-invasive, can be utilized in a real-life setting, and collects data over a long period of time[45]. Actiwatch 2 monitors were purchased from Philips Respironics Inc (Murrysville, PA, USA). Data was collected in one-minute epochs continuously for 3 weeks. Actigraph data was retrieved and processed using Philips Actiware Version 6.0. Total sleep time

(TST_{acti}), wake after sleep onset ($WASO_{acti}$), sleep efficiency (SE_{acti}), and sleep onset latency (SOL_{acti}) were generated by the Actiware software.

Circadian Rhythms

The self-report Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was used as a subjective measure of circadian rhythm disruption[46]. The BRIAN was developed to assess symptom domains of biological rhythms, encompassing aspects of other well validated tools such as the Pittsburgh Sleep Quality Index[44]. This scale was developed and validated for the assessment of circadian rhythm disruption in individuals with BD, discriminating euthymic BD individuals from healthy controls[46]. Moreover, we and others have found that the BRIAN predicts functioning in euthymic and depressed BD subjects[47,48]. The BRIAN is a scale consisting of 18 items split into the domains of sleep, activity, social behavior and eating pattern. Each item is score from 1 (no difficulties) to 4 (severe difficulties), with higher overall scores indicating worse circadian rhythm disturbances.

Objective measures of circadian activity rhythm were obtained via actigraphy. Although as little as two days has been shown to be sufficient for obtaining circadian activity rhythm parameters[32], a three-week time interval was selected to mitigate weekend to weekday effects. The following actiware measures were obtained for each of the 21 days for the analysis of the circadian parameters: Date, Time and Activity. All circadian parameters were then calculated using R statistical software (version 3.0.1) with the package "cosinor"[49]. As a result, the following circadian rhythm parameters were obtained: Mesor (MES), Amplitude (AMP), Acrophase (ACRO), Circadian Quotient (CQ). We also calculate Interdaily Stability (IS) and Intradaily Variability (IV). The circadian quotient is a ratio of amplitude to mesor (CQ = AMP/MES).

Normalizing the data, a larger CQ, one that is closer to 1.0 as seen in healthy individuals, indicates a stronger rhythm of circadian activity[50-52]. In regards to IS (stability of rhythm between the days), scores around 0.6 or higher indicate a stable activity rhythm[53,54]. For IV scores, they should fall between zero and two, with a lower value indicating less fragmentation[55]. IV values of around 0.8-0.9 have been found in healthy controls, indicating relatively low activity fragmentation[56,57].

Statistical Analysis:

R statistical software (version 3.0.1) was used for statistical analysis[49]. Prior to statistical analysis, all assumptions of respective analyses were checked. Where applicable and possible, appropriate data transformations were carried out to meet the respective assumptions. To determine the agreement between objective and subjective sleep measures, the objective sleep variables (TST_{acti}, $WASO_{acti}$, SE_{acti} and SOL_{acti}) were correlated with total PSQI scores. To determine the agreement between objective and subjective circadian rhythm measures, the objective variables MES, AMP, ACRO, CQ, IS and IV were correlated with total BRIAN scores. Pearson correlations were used for normal data, while spearman correlations were used for non-transformable, non-parametric data.

Group differences were analyzed using repeated-measures ANCOVA if assumptions of normality and homogeneity of variances were met. In the cases the assumptions were not met and transformations failed, Mann-Whitney U test was used to assess group differences in pregnancy and postpartum with Friedman Test used to assess differences in measures from pregnancy to postpartum (effect of time) independently for each group. Finally, regression models were used to determine whether group or changes in subjective and/or objective

measures of sleep and/or circadian rhythms across the perinatal period predicted postpartum depressive symptoms. To account for the prospective changes in all variables (mood, CARs and sleep), delta scores of all measures were calculated by subtracting pregnancy scores from postpartum scores. The delta scores of sleep and circadian rhythms parameters were correlated with changes in depressive scores (ΔEPDS) to determine which parameters should be used as predictors in the subsequent univariate regression model, in which ΔEPDS was the independent variable.

Results

Of the 35 women enrolled in the study, 33 (94%) completed full study participation. One participant was diagnosed with a current mood episode at T1 and was excused from further participation. The other participant was lost to follow-up on account of her moving. Detailed information was collected for all 33 women who completed the study.

Demographics

Circadian rhythms and sleep parameters were obtained from 33 women between 22 and 40 years old (mean age 31) in the third trimester of pregnancy. Table 3 shows the demographic characteristics of control-low risk and history of a mood disorder-high risk groups. The groups did not differ in age, gestational week at T1, or postpartum week at T2. As expected, there was a group difference in the PDPI-R with the high-risk group scoring higher implying a greater risk for PPD development. As a result, PDPI-R scores were used as a covariate in the regression analysis in order to control for other psychosocial risk factors for PPD. One of the healthy controls had a life time history of panic disorder. This being said, overall, our healthy

control group was quite healthy. In the mood group, 7 women screened for a comorbid disorder. Five women had histories of panic disorder (3 with limited symptoms and 2 with a lifetime history). One of the women with a lifetime history of Panic Disorder also had current Obsessive Compulsive Disorder. In addition, one mood participant had a comorbid lifetime Antisocial Personality Disorder and another had current Agoraphobia, Generalized Social Phobia and Generalized Anxiety Disorder. The vast majority of women in our sample had a high SES. Only one participant was taking psychotropics during T1 and two were taking psychotropics at T2. Almost half the women were primiparous (n=15). Parity was, therefore, controlled for in the regression analysis. Most of the participants chose to breastfeed their infants, with only four women (3 in the low-risk group) choosing to solely bottle feed. This did not differ between groups. Clinical characteristics are shown in table 4.

Perinatal Sleep

In regards to subjective sleep, significant differences in PSQI scores were found between groups during both pregnancy (W=38.5, p=0.0005) and postpartum (W=74.5, p=0.03). The high-risk group scored higher on the PSQI at both time points, having mean scores above the 5 point cut off. The only objective sleep parameter to significantly differ between groups was SE (W=189.5, p=0.05), with the high-risk group showing a lower SE_{acti} in the postpartum period. No significant differences in SE_{acti} were found during pregnancy. $WASO_{acti}$ showed a trend towards a group difference (p=0.06), with the high-risk group showing increased WASO at both T1 and T2.

Perinatal Circadian Rhythmicity

Subjective BRIAN scores were significantly different between groups during both pregnancy (W=34.0, p=0.0003) and postpartum (W=42.5, p=0.0009). The high-risk group reported higher BRIAN scores at both time points. No significant differences were found in any objective parameters of circadian activity rhythms. However, repeated measures ANOVA showed a significant group X time interaction of for amplitude (p=0.02). Overall, women showed a high CQ in pregnancy (mean CQ 0.79) and postpartum (mean CQ 0.85). In addition, the women in this study collectively showed poor pregnancy IS (mean IS 0.50, n=33) and good pregnancy IV (mean IV 0.79, n=33), as well as poor postpartum IS (mean IS 0.53, n=33) and good postpartum IV (mean IV 0.69, n=33).

Perinatal Mood

There were significant group differences in EPDS scores during both pregnancy (W=70, p=0.02) and postpartum (W=62.5, p=0.009), with women in the high-risk group scoring higher overall at both time points. No women developed a manic or hypomanic episode at T2 and so YMRS scores were omitted from any further analyses. Two participants scored ≥ 12 on the EPDS, one of which met criteria for a PPD episode according to the MINI.

Relationship between Circadian Rhythmicity, Sleep and Mood

Changes in depressive symptoms (ΔEPDS) were correlated with all sleep and circadian rhythm parameters to determine which should be used as predictors in regression modeling. Off all the parameters chosen *a priori*, only changes in subjective circadian rhythms (ΔBRIAN; r=0.50, p=0.01), changes in SE_{acti} (ΔSE; r=-0.39, p=0.04) and changes in IS (ΔIS; r= -0.36, p=0.05), where significantly correlated with ΔEPDS. An univariate regression analysis, as seen in table 5,

revealed that a model containing group, parity, PDPI-R, ΔIS, ΔBRIAN and ΔSE_{acti} was significantly predicative of ΔEPDS, explaining 45% of the variance in changes in EPDS scores (F=5.38, p=0.001). In this model, ΔBRIAN and ΔSE_{acti} were the only significant predictors of ΔEPDS (β=0.52, p=0.005 and β=0.32, p=0.04, respectively).

Correlations between Subjective and Objective Parameters of Sleep and Circadian Rhythmicity

In regards to sleep, the pregnancy PSQI scores were found to correlate with pregnancy SOL_{acti} (r=0.40, p=0.02), whereas postpartum PSQI scores correlated with postpartum SOL_{acti} (r=0.38, p=0.03). $WASO_{acti}$ showed a trend of correlation with PSQI scores at both time points (p=0.06 for both). TST_{acti} also showed a correlation trend with PSQI scores at T2 (p=0.06). No other subjective and objective parameters of sleep were correlated across the perinatal period.

In our study, no objective measures of CARs correlated with the BRIAN scores in pregnancy. In the postpartum, BRIAN scores correlated with CQ (r=0.39, p=0.02) and IS (r=0.36, p=0.04).

Discussion

To our knowledge, this is the first prospective study exploring subjective and objective parameters of circadian rhythms across the perinatal period. This is also the first study to investigate their relation to postpartum mood in women at low and high risk for PPD. We found that changes in sleep efficiency, as measured objectively via actigraphy, and self-perceived biological rhythm worsening, as assessed with the BRIAN scale, were associated with postpartum depressive worsening. We also found that changes in IS, an objective measure of circadian rhythm stability[53,54], correlated with changes in mood symptoms from late pregnancy

to early postpartum. However, ΔIS no longer survived as predictor of perinatal mood changes in a model that included ΔSE_{Acti} and ΔBRIAN. As far as the association between changes in sleep and mood symptoms in the perinatal period, our results are in line with Posmontier[18] who reported that depressed postpartum women had worse sleep latency, wake after sleep onset and sleep efficiency compared to non-depressed counterparts. This study was carried out in 22 women who developed PPD and 22 women who remained healthy. Similarly, Goyal et al[58] found that mothers who slept < 4 h between midnight and 6 am and mothers who napped < 60 min during the day had more depressive symptoms at three months postpartum in a large sample of 112 healthy women. Dorhiem et al[20], on the other hand, found that women who were depressed at 2 months postpartum reported worse subjective sleep as assessed with the PSQI as compared to non-depressed postpartum women. However, no differences in objective sleep parameters as assessed with actigraphy were observed between the two groups. Finally, in the only study that investigated both subjective and objective sleep parameters longitudinally in a sample of 72 healthy women, Coo Calcagni et al[59] found that neither subjective nor objective sleep parameters were associated with postpartum depressive symptoms. While the demographic profile of women in the study of Coo Calcagni et al[59] were similar to our study population, differences in length of actigraphy assessment (3 weeks vs 1 week) may account for some of the discrepancies in the findings.

Although changes in IS were not significant predictors of changes in depressive symptoms across the perinatal period, but did contribute to the overall regression model, changes in IS did correlate with changes in perinatal depressive symptoms. In our study, a decrease in IS was correlated with an increase in EPDS scores. To the best of our knowledge,

only one study has investigated the association between circadian rhythms and mood during the perinatal period: In a prospective study of 12 women, Sharkey et al[60] measured changes in circadian phase and phase angle through salivary dim light melatonin onset (DLMO) during the third trimester of pregnancy and again at 6 weeks postpartum. They found that postpartum depressive symptoms as measured with Hamilton Depression Rating Scale at 6 weeks postpartum were associated with changes in phase angle from 3rd trimester of pregnancy to 6 weeks postpartum (r=0.556). In addition, we found that on average low- and high-risk women showed low IS and normal IV, which suggest that the late pregnancy and early postpartum are associated with poor stability but no fragmentation of CARs[61,62]. Although we are not aware of any previous study that investigated IS and IV in relation to mood in the perinatal period, Jones et al[62] found that euthymic individuals with BD displayed lower IS and higher IV scores compared to healthy controls.

Another finding from our study was that women with a diagnosis of a mood disorder, although clinically stable, scored worse in all of the self-reported questionnaires that assessed mood, sleep and biological rhythms in both assessment times compared to healthy women. This suggests a persistent perception of poorer mood, sleep and biological rhythms in the transition from pregnancy to the postpartum period. Notably, while the average PSQI scores fell over the threshold for poor sleep quality, the average EPDS scores fell below the threshold for possible depression. This finding of overall subjective disrupted sleep quality, particularly during the postpartum period, reflects the findings of previous studies[64,65]. Studies of euthymic individuals with mood disorders have also shown higher levels of subjective sleep and circadian dysfunction in comparison to healthy controls[46,62,66]. We found that the only objective parameter to be

significantly different between groups was SE_{acti} during the postpartum period. Notably, postpartum women in the high-risk group showed average SE_{acti} lower than 85%, which indicates poor sleep efficiency[67]. Poor sleep efficiency of less than 85%, as measured via actigraphy, has been previously reported in both healthy controls and depressed women at around two months postpartum[20].

One of the key questions when interpreting results from self-report questionnaires is how much they correlate with *objective* data. In our study, poorer subjective sleep quality as measured with PSQI was associated with SOL_{acti} at both T1 and T2. We believe that this finding is clinically meaningful, since in the clinical practice often times patients report high levels of psychological distress associated with difficulty getting to sleep. As previously mentioned, previous studies did not find significant correlations between subjective and objective sleep parameters[23-25]. It is possible that this discrepancy may be related to the actigraphy recording time, because most studies use actigraphy from two to seven days, while we used a 3-week protocol. This discrepancy may also reflect the study population, since previous studies were conducted in healthy women while in our study we also studied individuals with mood disorders. We also found that subjective biological rhythms as measured with the BRIAN correlated with objective CQ and IS, which are measures of circadian rhythm strength and stability. Unfortunately, we are unaware of any previous study that correlated subjective and objective parameters of circadian rhythms.

When interpreting the results from our study, certain limitations need to be recognized. Foremost, while our sample size (N=33) is comparable with most studies conducted in mood disorders[68-70], it is possible that more subjective and objective sleep and circadian parameters

would have correlated if the sample size was larger, as seen with the correlation trends for $WASO_{acti}$. In addition, only one participant met DSM-IV criteria for PPD. We expected that depressed women would have shown greater changes in sleep and CARs across the perinatal period. Because the majority of our study population were being followed by health professionals, It is likely that women enrolled in this study were more aware of the association between sleep disturbance and mood worsening and, as a result, were likely proactive in ensuring proper sleep hygiene.

In summary, this prospective study showed that changes in sleep efficiency, as objectively measured with actigraphy, and subjective changes in biological rhythms are associated with worsening of postpartum depressive symptoms. Because women with mood disorders displayed worse sleep efficiency and more self-report biological rhythm disturbances than healthy women across the perinatal period, we speculate whether these domains may be associated with their higher vulnerability to develop PPD. Taken together, these findings suggest that interventions targeting stabilization of sleep and circadian rhythms may prevent postpartum mood worsening and, possibly, prevent PPD. Future treatment studies of PPD should also include objective measures of sleep and circadian rhythms.

Conflicts of Interest

Dr. Luciano Minuzzi has received Grants/Research Support from Alternative Funding Plan Innovations Award, Brain & Behavioral Foundation, Canadian Institutes of Health Research, Hamilton Health Sciences Foundation, Ontario Brain Institute, and Ontario Mental Health Foundation, and Speakers Bureau/Honoraria from Bristol-Myers Squibb, Lundbeck, Canadian Psychiatric Association, and the Canadian Network for Mood and Anxiety Treatments.

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Table 3: Demographic profile of study participants

	Low Risk Group	**High Risk Group**	**Group Differences**

	(N = 18)	**(N = 15)**	
Age	30.61 (2.79)	31.80 (4.86)	n.s.
Gestational Week	30.72 (2.97)	31.07 (2.46)	n.s.
Postpartum Week	9.11 (1.78)	9.27 (1.94)	n.s.
PDPI-R	4.67 (7.71)	7.13 (9.78)	$p < 0.05$
History of mood disorder other than MDD, BD or PPD *Yes* *No*	 n = 1 n = 17	 n = 7 n = 8	$p < 0.05$
Marital status *Partnered* *Single*	 n =18 n = 0	 n = 14 n = 1	n.s.
Psychotropic Medication (pregnancy) *Yes*	 n = 0	 n = 1	n.s.

No	n = 0	n = 0	
Psychotropic Medication (postpartum)			
Yes	n = 0	n = 2	n.s.
No	n = 0	n = 0	
Parity			
Primiparous	n = 9	n = 6	n.s.
Multiparous	n = 9	n = 9	
Feeding			
Breast	n = 13	n = 8	
Bottle	n = 3	n = 1	n.s.
Mix	n = 2	n = 6	

PDPI-R= Postpartum Depression Predictors Inventory-Revised

Table 4: Subjective and objective parameters of sleep and circadian rhythms

Measure	Low Risk Group (N = 18)	High Risk Group (N = 15)	Group Differences
preBRIAN	22.50 (3.47)	31.20 (6.94)	$p < 0.05$
postBRIAN	23.78 (4.45)	33.13 (7.54)	$p < 0.05$
deltaBRIAN	1.23 (5.83)	1.93 (8.50)	n.s.
prePSQI	3.61 (1.97)	8.00 (3.63)	$p < 0.05$
postPSQI	4.39 (2.20)	7.93 (2.55)	$p < 0.05$
deltaPSQI	0.78 (2.76)	-0.07 (3.99)	n.s.
preEPDS	1.39 (1.33)	4.73 (4.18)	$p < 0.05$
postEPDS	2.11 (2.35)	6.13 (4.58)	$p <0.05$
deltaEPDS	0.72 (2.32)	1.40 (4.67)	n.s.
$preTST_{acti}$	428.79 (48.94)	441.41 (56.51)	n.s.
$postTST_{acti}$	420.46 (61.63)	430.42 (71.16)	n.s.
$deltaTST_{acti}$	-8.33 (57.90)	-10.99 (84.85)	n.s.

$preSE_{acti}$	85.93 (4.23)	83.97 (4.99)	n.s.
$postSE_{acti}$	85.39 (4.27)	82.96 (4.44)	$p < 0.05$
$deltaSE_{acti}$	-0.54 (3.37)	-1.01 (6.25)	n.s.
$preWASO_{acti}$	50.61 (18.83)	62.24 (24.07)	p=0.06
$postWASO_{acti}$	56.11 (15.93)	65.96 (13.78)	p=0.06
$deltaWASO_{acti}$	5.50 (16.95)	3.72 (21.29)	n.s.
$preSOL_{acti}$	9.19 (5.10)	11.23 (6.83)	n.s.
$postSOL_{acti}$	8.52 (6.17)	11.96 (8.74)	n.s.
$deltaSOL_{acti}$	-0.67 (6.01)	0.74 (5.85)	n.s.
preMES	221.19 (71.15)	196.78 (71.56)	n.s.
postMES	209.19 (54.32)	219.30 (71.29)	n.s.
deltaMES	-12.00 (64.79)	22.52 (25.04)	n.s.
preAMP	176.58 (64.61)	157.41 (66.63)	n.s.
postAMP	176.68 (45.08)	185.01 (58.31)	n.s.
deltaAMP	0.09 (51.36)	27.61 (31.23)	$p < 0.05$
preCQ	0.79 (0.08)	0.79 (0.10)	n.s.

postCQ	0.85 (0.09)	0.86 (0.12)	n.s.
deltaCQ	0.06 (0.11)	0.07 (0.14)	n.s.
preACRO	0.69 (0.25)	0.52 (0.60)	n.s.
postACRO	0.69 (0.27)	0.71 (0.37)	n.s.
deltaACRO	-0.01 (0.17)	0.19 (0.65)	n.s.
preIS	0.50 (0.13)	0.48 (0.13)	n.s.
postIS	0.50 (0.12)	0.57 (0.11)	n.s.
deltaIS	0.00 (0.16)	0.10 (0.13)	n.s.
preIV	0.79 (0.23)	0.79 (0.18)	n.s.
postIV	0.67 (0.30)	0.72 (0.22)	n.s.
deltaIV	0.07 (0.29)	-0.02 (0.17)	n.s.

Pre: Pregnancy; Post: Postpartum, Delta: changes in, BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry; PSQI: Pittsburgh Sleep Quality Index; EPDS: Edinburgh Postnatal Depression Scale; TST: Total Sleep Time; SE: Sleep Efficiency; WASO: Wake After Sleep Onset; SOL: Sleep Onset Latency; MES: Mesor; AMP: Amplitude; CQ: Circadian Quotient; ACRO: Acrophase; IS: Inter-daily Stability; IV: Intra-daily Variability

Table 5: Linear regression model of predictors of ΔEPDS (N=33)

Predictors	β coefficient (CI)	S. E.	t	*p*
ΔBRIAN	0.56 (0.22, 0.90)	0.13	3.41	0.0021
ΔSE_{Acti}	-0.32 (-0.63, -0.01)	0.15	-2.09	0.0047
ΔIS	0.012 (-0.33, 0.35)	0.17	0.072	0.94
Group	0.16 (-0.22, 0.55)	0.19	0.88	0.39
Parity	0.12 (-0.17, 0.40)	0.14	0.85	0.41
PDPI-R	-0.26 (-0.65, 0.12)	0.19	-1.41	0.17

R^2=0.44; p=0.001; CI=confidence interval

Figure 3: Actogram of one at low-risk participant during pregnancy (21 days)

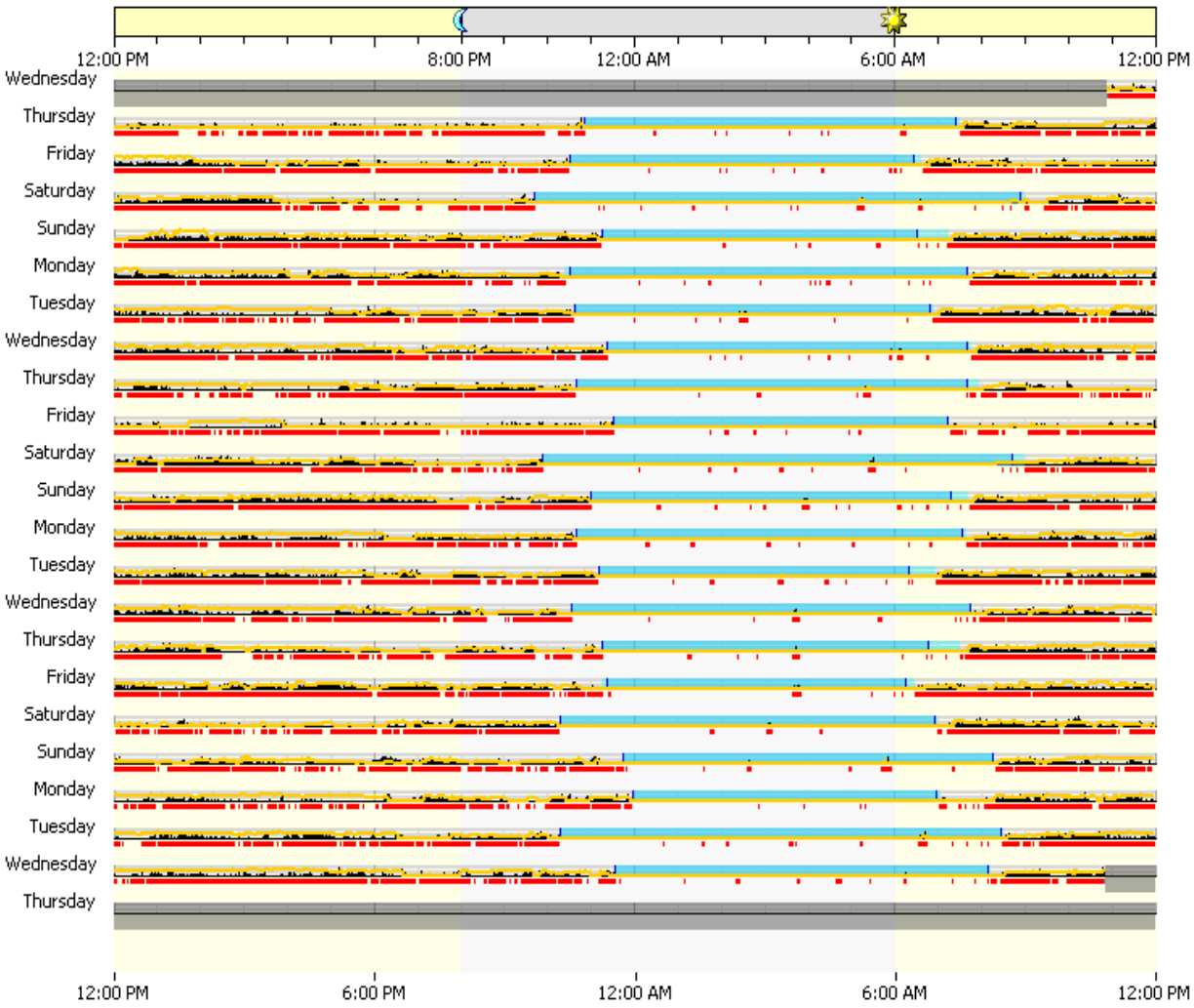
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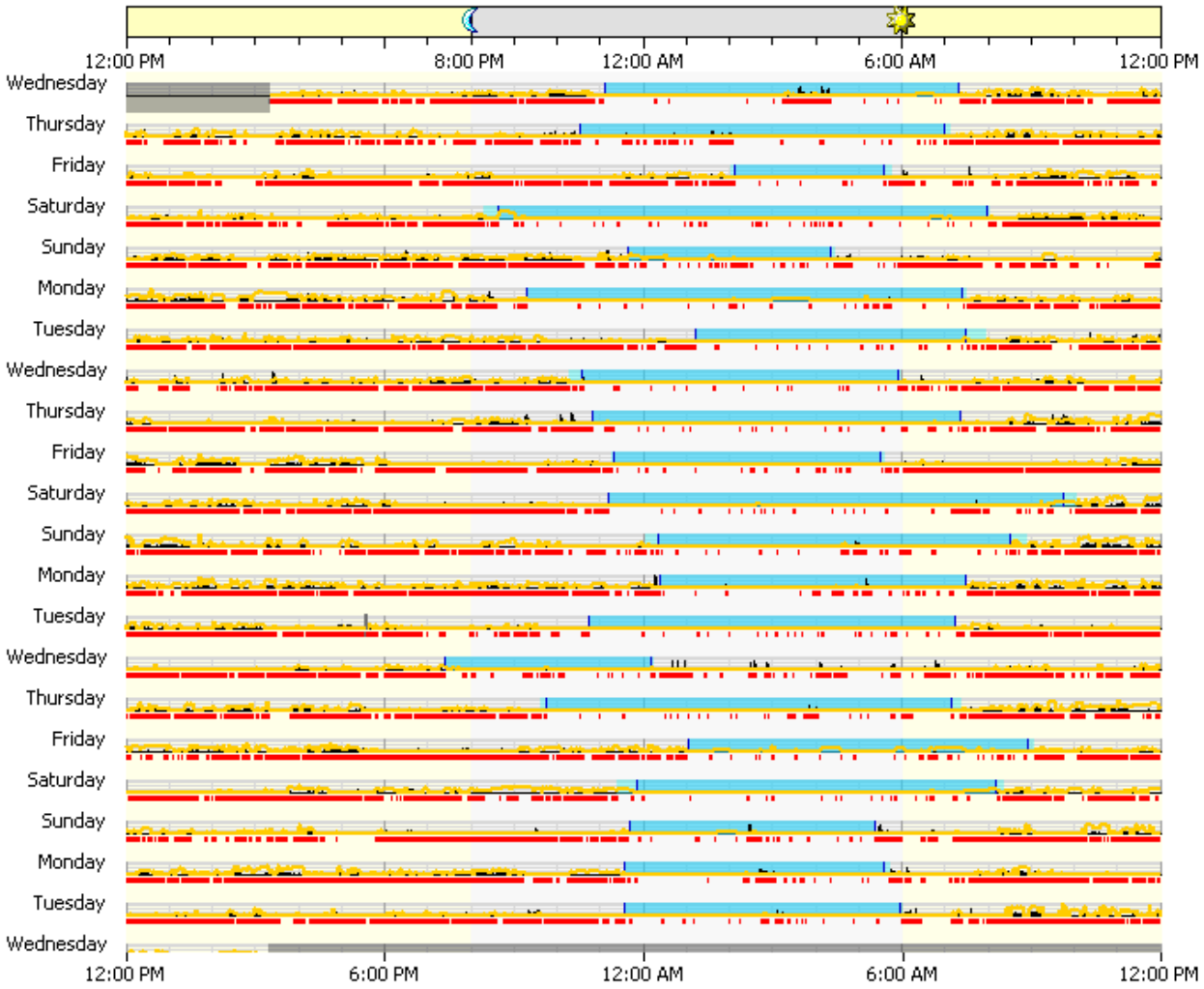
Figure 4: Actogram of one high-risk participant during the postpartum (21 days)



CHAPTER 4

Rationale and Methods for the genotyping of the Clock gene 3111T/C polymorphism in women with and without a history of a mood disorder to determine an association with mood history and postpartum depression development

There is a growing association between circadian rhythm dysfunction and mood disorders. In particular, work over the last few decades has shown polymorphisms in particular circadian genes to be associated with depressive mood disorders such bipolar disorder, seasonal affective disorder and major depressive disorder (Partonen 2012; Etain et al. 2011; Milhiet et al. 2011; McClung 2007; Johansson et al. 2003). The perinatal period is a unique time in which women are susceptible to various somatic disturbances and social changes that may impact circadian rhythm stability. This may be subsequently associated with changes in mood. The disruption of the sleep/wake cycle has already been thoroughly associated with changes in mood during the perinatal period (Dorheim et al. 2009; Posmontier 2008; Goyal, Gay & Lee 2007). In addition, depression has been associated with circadian rhythm disturbances in the postpartum, as measured by dim light melatonin onset (Sharkey et al. 2013).

To our knowledge, only one study has explored an association between a circadian gene and mood changes in the postpartum. Dallaspezia et al. (2011) genotyped the variable-number tandem-repeat polymorphism in the *Per3* gene in a sample of 67 patients. The polymorphism studied is found in the coding region of the gene, where a segment of 18 amino acids is repeated either four ($PER3^4$) or five times ($PER3^5$) (Ebisawa et al. 2001). This polymorphism has been found to be associated with diurnal preference, with the longer allele being associated with morningness (Archer et al. 2003). These patients were divided into three groups: women

with a postpartum onset of BD (n=17), women without a postpartum onset of BD (n=22), and men (n=28). They found that the $Per3^4$ polymorphism was associated with the postpartum onset of BD.

The *Clock* gene, like *Per3*, is another core component of the circadian molecular system, expressed in all body oscillators, including the brain's master clock; the Suprachiasmatic nucleus. Interacting with either NPAS2 or BMAL(ARNTL), CLOCK binds to E-box containing promoters on *per* and *cry* genes (Shearman et al. 2000; Hastings, Brancaccio & Maywood 2014). The heterodimer complex itself interacts with and is inhibited by the CRY and PER heterodimer complex. This feedback loop follows a 24-hour cycle, influencing the gene transcription of other necessary circadian components, establishing rhythmicity of various bodily functions. As a result of being a central component of the circadian molecular system, variability in the *clock* gene has garnered much attention in relation to both sleep and mood.

One particular CLOCK single nucleotide polymorphism (SNP) has garnered much attention. The CLOCK 3111T/C SNP (rs1801260) is located in the 3' flanking region of the gene and individuals carry either the 311T or 311C alleles, resulting in three genotypes (TT, TC or CC). This polymorphism was initially studied in relation to diurnal preference. Katzenberg et al. (1998) identified this SNP and subsequently found the 311C allele to be associated with an evening-type in a sample of 410 healthy adults, while controlling for confounding factors such as age and sex. These findings were replicated in a later study in a Japanese population. Mishima et al. (2005) also found the CC genotype to be associated with evening-preference in their sample of 421 individuals. In addition, they found homozygotes for the 311C allele to have delayed sleep onset, shorter total sleep time and increased sleepiness in the daytime. Once more, the

finding that evening types were carriers of the C allele was reproduced in a Korean sample of 180 individuals with BD (Lee et al. 2010). In regards to sleep, Serretti et al. (2003) also found this polymorphism to be associated with sleep dysregulations in 620 individuals with either MDD or BD. They found that homozygotes of the C variant showed a significant decrease in sleep need in BD, in addition to a similar finding of recurrence of insomnia in individuals with MDD.

In regards to mood disorders, there is some evidence that it is associated with the 311T/C CLOCK SNP. Lee et al. (2010) found significantly more individuals in a sample of 260 BD patients to be carriers of the C allele in comparison to 350 controls. In a recent study Dmitrzak-Weglarz (2015), also showed an association between the SNP and individuals with BD. Benedetti et al. (2007) found patients with BD who carried the C allele have increased activity in the evening, adding to the evidence discussed above. Antypa et al. (2012) did not find an association between the 311T/C polymorphism and depressive symptoms in a sample of 415 females, 12% of which were currently clinically depressed. This study, however, did find a gene-environment interaction, in that the polymorphism was associated with sleep disturbances in situations of previous stressful life experiences.

Although the above results suggest that the 3111T/C CLOCK polymorphism may increase vulnerability to mood or sleep disturbances through its underlying circadian function, some studies have not replicated the above and have not found such associations. In regards to mood, some studies have found no relationship between this SNP and mood disorders, particularly when studying MDD (Bailer et al. 2005; Desan et al. 2000; Kishi et al. 2011). Others have also tried to find an association between this CLOCK SNP and diurnal preference and haven not

replicated the finding of eveningness being prominent in carriers of the 311C allele. For example, Pedrazzoli et al. (2007) found no association between the SNP and diurnal preference.

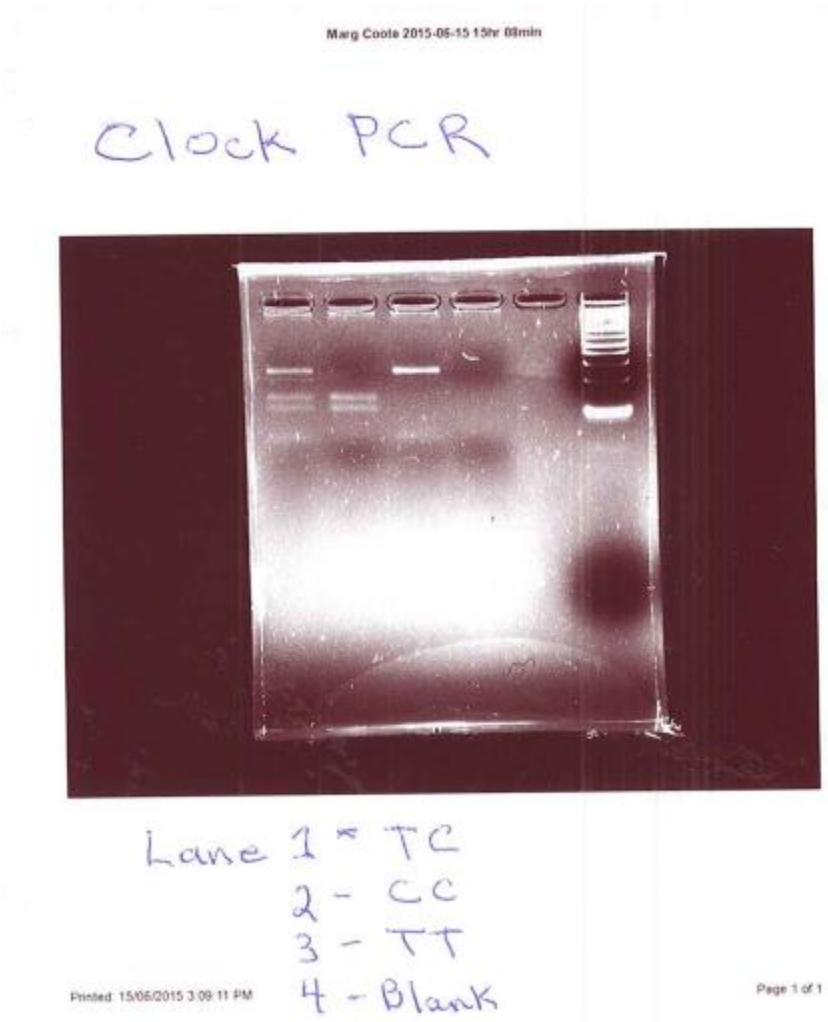
These considerations have led us to explore if the 3111T/C CLOCK polymorphism is associated with mood changes across the perinatal period in a sample of women with and without a history of a mood disorder (BD or MDD). In addition, we wanted to explore if the polymorphism is associated with increased circadian rhythm and sleep disturbances. We hypothesized that the 311C allele would be most prominent in a) women with a mood history, b) women showing increased sleep and circadian rhythm disturbances in the postpartum, and/or in c) women who developed significant depressive symptoms in the postpartum.

To test our hypothesis, we obtained blood samples from 44 consenting women between 26 weeks gestation and 12 weeks postpartum. Samples were stored in a -80^{o}C freezer until DNA extraction took place. DNA was extracted from whole blood samples according to the protocol in the Blood Mini Handbook 2012 obtained from the QIAmp DNA Mini kit. Samples were allowed to dethaw for at least two hours prior to DNA extraction. To improve the results of the subsequent genotyping, 200ml of distilled water was used in the last step, instead of Buffer AE.

Amplification of the target DNA of the gene was performed using PCR with the following primers: *clockforward*: 5'-TCCAGCAGTTTCATGAGATGC-3" and *clockreverse*: 5'-GAGGTCATTTCATAGCTGAGC-3' as previously reported by Katzenberg et al. (1998). The reaction was performed as described by Kissling et al. (2008) with the following modifications; a final volume of 50 ul consisting of 100 ng of genomic DNA in a premixed master solution containing *Taq* DNA Polymerase, dNTPs, $MgCl_2$, and reaction buffers (Promega, Mannheim, Germany). DNA was amplified in a (PTC DNA Engine Peltier Thermo Cycler (Bio Rad, USA), under

the following conditions: 2 min at 95^{o}C followed by 35 cycles at 94^{o}C 30 sec, 58^{o} C 35 sec, 72^{o}C 1 min, followed by 10 min at 72^{o}C. 10 ul of the final product was run on a 2% agarose gel stained with Cyber Safe to visualize the 221bp amplicon. The restriction enzyme digestion was performed on 10 ul of the PCR product, digested in a final volume of 20 ul with Bsp12861 (New England Biolabs, (Whitby, Ontario, Canada), at 37^{o}C for 3 hours. The digested samples were then run on a 4 % agarose gel stained with Cyber Safe in tris-borate electrophoresis buffer at 50 volts for 1 hour, to visualize the TT (221bp) , CT (221, 125, 96 bp) or CC (125, 96 bp) genotypes. **Results are still pending.

Figure 1 – *Clock* gene gel image showing successful genotyping of 3111T/C polymorphism



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CHAPTER 5

General Discussion

Changes in depressive symptoms across the perinatal period are influenced by subjective circadian rhythm disturbances, which are greater in women with a history of a mood disorder

The primary finding of this thesis was that subjective disruptions in circadian rhythms across the perinatal period, as measured by the BRIAN, predict changes in depressive symptoms. Surprisingly, although subjective sleep disturbances were greater in women with a history of a mood disorder, poor subjective sleep quality did not predict changes in depressive symptoms, when biological rhythms were added to the model. Objectively measured sleep efficiency, however, did predict symptoms of depression. These results are in line with previous findings, albeit in some differing samples of women. For example, Park et al. (2013) found that in a sample of 25 primiparous women, half of which had a history of a depressive mood disorder, both subjective and objective sleep parameters of percent sleep and sleep efficiency were correlated with depressive symptoms, as measured by the EPDS at the 2nd and 14th postpartum week. In addition, Posmontier et al. (2008) also measured objective sleep parameters using seven days of actigraphy in a sample of 44 participants (22 with and without PPD). This study found that women who developed PPD between 6 to 26 weeks postpartum had a larger WASO and lower SE than those who did not. Our work furthers this association, in that, as mentioned, we also found SE to differ between groups, with a trend in WASO.

Because only one other study has explored the association between circadian rhythm disruptions, albeit objectively through DLMO (as previously reviewed), and depressive

symptoms during the perinatal period, it is hard to comment on the validity of these results. Future work further exploring the relationship between both subjective and objective circadian rhythm dysfunction and its association with mood is warranted. In addition, a recent study found a dose dependent-like response between the BRIAN and depressive symptoms in healthy controls, euthymic BD patients, and BD patients experiencing a mood episode (Pinho et al. 2015). In fact, Pinho et al. 2015 also found that the BRIAN was associated with functioning when depressive symptoms were controlled for. In an earlier study, Cudney et al. (2014) also found the BRAIN to predictive of lipid peroxidation in female BD patients, while controlling for depressive symptoms. Thus, it remains imperative to determine what features of the BRIAN, a relatively novel scale, are associated with depressive symptoms, as this work has also revealed such an association. In addition, it would be interesting to determine the associations between the BRIAN and other domains outside of mood, as the studies highlighted above have found.

As noted above, the results of both chapters 2 and 3 also indicated that women with a mood history perceived worse sleep and circadian rhythm disturbance in both pregnancy and the postpartum. In a study with a somewhat similar design to the one outlined in chapter 2, subjective sleep/wake activity was compared across the perinatal period in women with and without a history of a mood disorder. Specifically, subjective sleep/wake activity, as determined by a seven-night sleep diary, was compared between women with BD (some with a history of postpartum psychosis; n=23) and controls (n=15; Bilszta, Meyer & Buist 2010). This study, however, found no differences in sleep/wake activity, contrasting our findings. This may be explained by the fact that 18 of the women with a history of BD in this sample were on mood stabilizers, none of which relapsed during the postpartum period. In fact, only three participants

relapsed within the first six months postpartum. We only found group differences in one objective parameter, SE in the postpartum, in addition to a group by time interaction for amplitude. These results, in that women did not differ on most objective parameters, most likely speaks to sample of participants recruited, as discussed below.

We also found agreeability between certain objective and subjective measures. Particularly in regards to sleep, SOL was significantly correlated with the global PSQI score with trends in WASO and TST as well. The postpartum correlations found between the BRIAN and two objective CARs parameters (IS and CQ) are less promising. The relationship of these associations was questionable because they were not in the expected direction. A better determination of what the BRIAN scale is measuring, whether it is truly circadian rhythmicity or more so functioning in these circadian domains, is warranted to appropriately validate this questionnaire objectively.

Finally, chapter 4 outlined the background and methods for an important circadian rhythms genetic study. There is quite a bit of literature on the 3111T/C CLOCK polymorphism and its association with chronotype, sleep and mood. This makes this SNP a promising candidate to focus on. Genetic work looking at the circadian system and its relationship to sleep and mood changes in the perinatal period is lacking, with only one study published to date and must be addressed.

Socio-Economic Status and Good Mental Health influence the Stability of Circadian Rhythm and Sleep Disruption across the Perinatal Period

Mood, according to the EPDS, did significantly differ between the high and low risk group in both studies, in that women with a mood history scored higher on the EPDS at both visits. This being said, of the 83 women in chapter 2 and 33 in chapter 3 who completed full participation, collectively, only five women screened for PPD according to the EPDS (score ≥12). Of these five women, only two participants met requirements for clinically significant PPD according to the MINI. In addition, although women with a history of a mood disorder showed greater subjective sleep and circadian rhythm disruption than the healthy controls, the changes in these parameters were not significant from pregnancy to postpartum for either group. In addition, no appreciable differences were found in objective parameters of sleep and circadian rhythm disruptions. The majority of the at risk women with a mood history, therefore, managed to maintain the circadian rhythm and sleep parameters of their euthymia into the postpartum period. They also did not differ objectively compared to healthy women without a mood history. In so doing, the at-risk group maintained good mental health as well. This speaks to the uniqueness of the sample of women recruited to this study. These findings can potentially be explained by three phenomena.

First, many of the women in our sample had a high socio-economic status. Almost all of the women had a high level of social support, in that they were predominantly partnered and being closely looked after by a health professional (i.e. mental health care worker and/or midwife). A study by Banker and LaCoursiere (2014) found that a stress free relationship acts as a protective factor against PPD development. In fact, as discussed in the introduction, social support is an important strong to moderate risk factor for PPD development (O'Hara & Wisner 2014). Social support has also been specifically shown to be an important factor for PPD

development in Canadian cohorts of women (Davey et al. 2008; Lanes, Kuk and Tamim 2011). In addition, most of the women in our sample also had a high level of education. Again, a low education is also associated with PPD risk (Segre et al. 2007; O'Hara & McCabe 2013). Although research associating SES status and circadian rhythm stability is lacking, one study did investigated cortisol output in mother-infant dyads of high or low SES (Clearfield et al. 2014). It was found that infants and mothers of low SES showed less synchrony in cortisol output and showed a higher overall cortisol output compared to the high SES group. Overall, a high SES appeared to also contribute a protective role against PPD development in our sample of women. In addition, our results also suggest the idea that SES may mediate sleep and circadian rhythm stability across the perinatal period. This idea, however, requires future research.

The low level of PPD development may also be attributed to the type of locations that served as recruitment venues for the participants. Over 50% of the participants were recruited from a midwife clinic. Midwife care, over traditional family doctor or obstetrical care, has been shown to have a positive impact over several psychosocial outcomes, including mood (Shields et al. 1997; Fair & Morrison 2012). One study comparing different methods of care during pregnancy found that depressive mood was often discussed and screened for during midwife care, in contrast to shared care or hospital care, where questions about mood were less likely (Raymond 2009). The remaining participants were recruited from a mental health clinic wherein they were being monitored for the mental wellbeing over the course of the perinatal period.

Finally, we also did not exclude women who were on medication from participating. As a result, those women who may have been most at risk for PPD development had this risk mitigated by maintaining their treatment. In addition, a couple of participants were put on

mood stabilizers within the first few weeks postpartum, such that by the time they completed their second study visit, they were once more euthymic. Studies in MDD and BD have shown that some antidepressants, such agomelatine and citalopram, can enhance sleep quality in addition to improving mood (Corruble et al 2013; Shahsavand-Ananloo et al. 2013; Gorwood 2010; Wichniak, Wierzbicka & Jernajczyk 2012). Moreover, antidepressants such as low-dose ketamine, in addition to agomelatine, have been associated with the improvement of circadian rhythm stability in these mood disorders as well (Bunney et al. 2015; Gorwood 2010).

Overall, these results suggest that a higher SES, mental health geared care, particularly for women with a history of a mood disorder, as well as the maintenance of mood treatment throughout the perinatal period appear to be important factors in the mitigation of PPD development. Because sleep and the circadian system are closely related, our work suggests chronotherapies in addition to good sleep practices, apart from the above factors may offer protection against PPD development.

Implications for mothers

The findings from this study speak to the importance of mitigating circadian rhythm and sleep disruptions across the perinatal period in order to maintain good mental health and therefore decrease risk for PPD development. This can be done through the preventative approach of utilizing chronotherapy, as discussed in the introduction. The benefits of chronotherapeutics are that they are often options that are at a low cost and can easily be done at home (Terman & Terman 2005). In addition, they are non-pharmacological alternatives for those mothers who fear taking psychotropics during pregnancy.

In addition, our results also suggest that women, particularly those at risk for developing a mood episode during the perinatal period, should avoid any factors that may disrupt their circadian rhythm cycles. One such factor that has been shown to have detrimental consequences in this domain is shift work. There is evidence that women who work night shifts during pregnancy are more likely to have a spontaneous abortion, premature delivery or infants with a low birth weight (Zhu et al. 2004). Moreover, another study contrasting three different work schedules, including consistent daytime work, intermittent rotating shift works or persistent rotating shift works found that women with persistent rotating shifts showed decreased child bearing as well had infants with lower birth weights compared to the other groups (Lin et al. 2011). Women should, if possible, opt for an earlier maternity leave to decrease the risk of negative health consequences.

In our second study, outlined in chapter 3, we collected data on feeding choice (breastfeeding vs. formula). This was for the reason that breastfeeding has been associated with decreasing depressive symptom risk, particularly in multiparas (Sibolboro Mezzacappa & Endicott 2007). In addition, breastfeeding duration has been associated with PPD development in many studies (Dias & Figueiredo 2015). Mezzacappa and Katlin (2002) also found that mothers who breastfed, compared to those who were bottle feeding their babies, showed decreased negative mood within the first year postpartum. Most of the mothers in the sample were primiparous. Breastfed babies are also shown to have better sleep quality (Lucas & St James-Roberts 1998). This suggests that breastfeeding may allow a route for circadian rhythm synchronization between mother and infant. In fact, a study by Cubero et al. (2005) found that the tryptophan circadian rhythm in mothers was associated with 6-sulfatoxymelatonin

rhythm in a sample of eight breastfed infants. This was also associated with the promotion of nighttime sleep in the breastfed infants compared to bottle fed controls. In addition, breastfeeding may also decrease stress and thus mediate the cortisol rhythm, thus protecting against PPD development (Figueiredo et al. 2013; Mezzacappa & Katlin 2002). We did not find an association between feeding choice and depressive symptom development. This, however, may be attributable to our small sample size and the notion that most of the mothers in our sample did in fact choose to breastfeed, or breastfeed with formula supplementation. Only 4 of 33 women solely formula fed.

Implications for children

The results from this thesis and any future work implicating circadian rhythm disruption in postpartum depressive symptom development have important implications for not only mothers, but their children as well. Various aspects of fetal and child development appear to be contingent on circadian rhythm, sleep and mood stability in the mother. These factors include the proper development of physiology, including the circadian system in the fetus and infant, as well as the development of mood regulation and other cognitive functions in children (Stein et al. 2014).

Stable maternal circadian rhythms have been found to be important for the proper development of the child's own circadian system. Studies exploring the development of the circadian system of the fetus are still few, but it is known that fetal rhythm cues are generated by the mother's circadian system and not light (Brooks & Canal 2013). This being said, in a review by Reiter et al. (2014), the relationship between melatonin, which follows a strong circadian rhythm, in addition to overall circadian rhythms, and their impact on the developing

circadian system of the fetus was explored. A few conclusions resulted from this work, including the idea that the stability of the melatonin rhythm appears to be important for the programming of the developing fetal clock oscillators. One of the studies drawn up as evidence showed that a pinealectomy in rodents, thus eliminating the melatonin rhythm, disrupted certain circadian behaviours of the offspring, such as the drinking rhythm (Bellavia et al. 2006). Interestingly, this rhythm was restored in offspring of pinealectomized rats who received melatonin. In another, more recent study, melatonin rhythms were also manipulated by constant light exposure in the second half of gestation in rats to determine effects on the development of the fetus (Mendez et al. 2012). Again it was shown that that manipulating the melatonin rhythm had several negative repercussions to the fetus, such as growth retardation and changes in adrenal functioning. Interestingly, one study also found that circadian variation in diastolic blood pressure was associated with intrauterine growth retardation as well (Maggioni et al. 2005).

Furthermore, maternal circadian rhythms are also found to impact circadian entrainment in infants. In healthy babies, one recent study found that a variety of circadian rhythm parameters were found to stabilize to adult-like rhythms between 6 to18 weeks postpartum (Joseph et al. 2015). In an earlier study observing mother-infant synchrony via actigraphy, it was found that around 12 weeks postpartum, there was increased correspondence in actigraph parameters or circadian rhythmicity such as acrophase (Thomas et al. 2014). Other studies in healthy babies also support that circadian rhythm stability is apparent in various domains by around 3 months (Zornoza-Moreno et al. 2011; Guilleminault et al. 1996). Evidence also shows that this development is most likely supported by mother-infant

synchrony (Nishihara et al. 2002). Tsai et al. (2011) found that at around 7 weeks postpartum, there was strong synchrony in activity patterns between the infant and the mother.

In depressed mothers during the perinatal period, wherein there is evidence of associated circadian rhythm disturbance (as discussed in the introduction), proper circadian rhythm entrainment in children is shown to be compromised. For example, Field et al. (2007) found that women who were depressed during pregnancy showed disrupted sleep and cortisol levels compared to healthy pregnant controls. This was associated with greater sleep disruptions and more crying and fussing in the infants of the depressed mothers. Sleep disturbances are also found in infants of depressed mothers (Piteo et al. 2013). Armitage et al. (2009) used actigraphy to measure sleep disturbance in infants born to either depressed or non-depressed mothers. Measurements were taken at 2 and around 24 weeks postpartum. At both time points it was found that infants born to depressed mothers had worse objective sleep, such as lower sleep efficiency and had more fragmented sleep during the night, compared to the infants of healthy mothers.

The outlined relationship between maternal, fetal and infant circadian rhythmicity may be related to the development of future mood dysregulation in children of mothers with PPD. Numerous studies have found that infants of mothers with mood episodes in the postpartum are more likely to show problems with emotional regulation and cognitive impairment (Jones et al. 2013; Carvalho, Martinez & Linhares 2008). For example, Kaplan et al. (2014) found problems in the expressive communication of one-year-old infants to be associated with maternal depressive symptoms. In addition, children of depressed mothers are found to be more likely to

develop psychiatric conditions themselves (Apter-Levy et al. 2013; Letourneau, Tramonte & Willms 2013; Sellers et al. 2013; Verbeek et al. 2012).

Limitations and future directions

The largest limitations encountered were the resulting homogeneity of the two groups studied, resulting from the suspected reasons outline above, as well as the smaller sample size of the study in chapter 3. Although the groups still showed differences in subjective measures of sleep and circadian rhythm disturbances, they were alike in objective parameters and sociodemographic characteristics. In studies stemming from this work in the future, a more heterogeneous sample should be aimed for each group by recruiting from a variety of places. Increasing our sample size for the objective study would have contributed to more power for the detection of additional significant findings. I suspect that the global PSQI score would have been significantly correlated with $WASO_{acti}$ had this been the case. The relationship between these two parameters was close to significant in both pregnancy and postpartum ($p=0.06$ for both). We also found a few other trends, as discussed in chapter 3.

Apart from these main limitations, certain covariates should have been measured and accounted for in the analyses. For example, as in the second study outline in chapter 3, parity ought to have been accounted for in the first study outlined in chapter 2. Parity, however, was a measure that we started to collect at a later date. The relationship between parity, in that being a first time mother, has been shown to be associated with PPD development (Coo Calcagni et al. 2012; Lee, **Z**affke & McEnany 2000; Waters & Lee 1996). Even in a large population based study, primiparity was found to be predictive of higher EPDS scores (Dorheim, Bjorvatn & Eberhard-Gran 2014). In addition, primiparity has also been associated with increased risk for the

development of postpartum psychosis (Di Florio et al. 2014). It may be that the infant acts as a new zeitgeber that is introduced into a woman's life and where synchronization does not occur properly or at all, circadian rhythms are disturbed and mood episodes ensue. Then again, a recent study found no significant effect of parity between depressed and non-depressed women (Gaillard et al. 2014).

Seasonality is another factor that could have been considered in the analyses. Meliska et al. (2013) sought to determine the effects of seasonality on depressive mood during pregnancy by means of studying the circadian parameters of melatonin and cortisol obtained from blood samples. They found in depressed patients, and not healthy controls, depressive symptom scores were highly correlated with seasonally longer nights. In addition, depressed women also showed phase-advances in both the synthesis offset of melatonin and acrophase of cortisol. Another study found that carriers of specific polymorphisms in the serotonin transporter and BDNF genes were more likely to score high on the EPDS at six weeks postpartum and that this was mediated by season of delivery (Comasco et al. 2011). Other studies also found that delivery in the last few months of the year were associated with higher depressive symptoms (Sylven et al. 2011; Sit, Seltman & Wisner 2011). On the other hand, in an Italian cohort of women, no effects of seasonality were associated with PPD (Barbadoro et al. 2012). However, this may speak to the population of women studied and the relative climate. SAD, for example, is more prominent in countries of higher latitudes (Rosen et al. 1990).

The potential covariates outlined above may all contribute to circadian rhythmicity in one way or another. Future studies, therefore, should control for these variables when studying the association between circadian rhythm dysfunction and PPD development in women with

and without a history of a mood disorder. These factors may put women with a mood history at an increased risk for developing a depressive mood episode in the postpartum.

In addition, future studies could utilize alternative techniques for the measurements of circadian rhythmicity. A gold standard method is dim light melatonin onset (DLMO). Cortisol rhythms could also be measured. It is important that any studies of PPD include measures of circadian rhythmicity because the results from this work, as well as previous research, suggests that disruptions of this system act as moderator or even mediator of other risk factors, and should therefore be considered. It is suspected that circadian rhythm disturbances, if had been measured, may have explained various findings in regards to risk factors and PPD development. Finally, future research endeavours in this area should also ensure that participants with a mood history are not taking medication, as well as strive to recruit a less homogenous sample by recruiting from a multitude of locations.

Conclusion

The findings from the studies outlined in this thesis in chapters 2 and 3 show evidence for an association between circadian rhythm and sleep instability from day to day and depressive symptom development across the perinatal period. Moreover, this relationship is stronger for women with a mood history, who are at higher risk for PPD development. However, these results must be interpreted with the limitations outlined in mind. The results of the collective work have implications for mood episode, and even preventative, chronotherapeutic treatments. By targeting sleep and circadian rhythm stability during the perinatal period, and thereby reducing the vulnerability to PPD development, the negative repercussions associated

with PPD are minimized. This is true not only for the mother, but for the infant and overall family unit as well.

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