BIOLOGICAL RHYTHMS AND SLEEP IN MOOD AND ANXIETY

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Lay Abstract

Sleep and biological rhythms are often disrupted in individuals with depression and bipolar disorder. In this thesis, we aimed to compare sleep and biological rhythms in individuals with depression or bipolar disorder, against individuals without these disorders. We investigated whether sleep and biological rhythms contribute to functioning and quality of life in these individuals. As sleep and biological rhythms are disrupted in pregnancy and following childbirth, we assessed whether sleep and biological rhythms during pregnancy can be used to predict postpartum depression and anxiety severity. Finally, we investigated changes in sleep, biological rhythms and light exposure from pregnancy to postpartum. Results indicate that disruptions in sleep, biological rhythms, and changes in light exposure are widespread in mood disorders. These disruptions are linked to worse quality of life and functioning. Sleep and biological rhythms change from pregnancy to postpartum, and can be used to predict severity of postpartum depression and anxiety.

Abstract

Introduction:

In Major Depressive (MDD) and Bipolar Disorders (BD), there are well-documented changes in sleep and biological rhythms. However, how sleep and biological rhythm disruptions impact functioning and quality of life (QOL) in these populations, and how these disruptions affect perinatal mood and anxiety remains little-known. In this thesis, we aimed to compare sleep and biological rhythms in individuals with and without mood disorders, and to investigate whether these measures can account for worsened functional impairment and QOL in these populations. We investigated whether clinical variables combined with sleep and biological rhythms during pregnancy can be used to predict depressive and anxiety symptom severity postpartum. Finally, we investigated longitudinal changes in sleep, and biological rhythms over the perinatal period.

Results:

Subjective and objective sleep and biological rhythm disruptions, and light exposure differences are wide-spread in MDD and BD. Regression analyses showed that subjective and objective sleep and biological rhythm disruptions can explain 43% of variance in QOL scores, and 52% of variance in functional impairment in MDD, BD and healthy controls.

Clinical and demographic variables, objective and subjective sleep and biological rhythm measures collected during pregnancy accounted for 50% of postpartum depression and 49% of postpartum anxiety symptom severity variance, in regression analyses. Numerous sleep and biological rhythm changes occurred across multiple domains from pregnancy to postpartum.

Conclusion:

Results suggest that sleep and biological rhythm disruptions occur across many domains in mood disorders, including sleep, light exposure, daily activity rhythms and melatonin. These disruptions are associated with worse QOL and functioning in BD, MDD and healthy controls. Biological rhythms and sleep changes across the perinatal period can be used to predict severity of postpartum depressive and anxiety symptoms. This work highlights the importance of sleep and biological rhythms as intervention targets across different outcomes, and across different mood diagnoses.

Key words: biological rhythms, actigraphy, postpartum depression, postpartum anxiety, mood disorders

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List of Abbreviations

6-SM	6-sulfatoxymelatonin
ANOVA	Analysis of Variance
BD	Bipolar Disorder
BFI	Big Five Inventory
BRIAN	Biological Rhythms Interview for Assessment in Neuropsychiatry
CART	Classification and Regression Trees
CQ	Circadian Quotient
CRY	Cryptochrome
DERS	Difficulties in Emotion Regulation Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPDS	Edinburgh Postnatal Depression Scale
ESS	Epworth Sleepiness Scale
FAST	Functioning Assessment Short Test
GAD-7	Generalized Anxiety Disorder – 7
GAD	Generalized Anxiety Disorder
IS	Interdaily Stability
IV	Intradaily Variability
L5	5 Consecutive Hours with Lowest Activity
M10	10 Consecutive Hours with Highest Activity
MADRS	Montgomery-Åsberg Depression Rating Scale
MAE	Mean Absolute Error
MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
ML	Machine Learning
MLiT	Mean Light Timing Above Threshold
mRMR	minimum Redundancy Maximum Relevance
NRMSE	Normalized Root Mean Squared Error
OCD	Obsessive-Compulsive Disorder
pAR	Probability of Transitioning from Active to Rest State
PCR	Principal Component Regression
PDPI-R	Postpartum Depression Predictors Inventory – Revised
PER	Period
PLS	Partial Least Squares
PPA	Postpartum Anxiety
PPD	Postpartum Depression
pRA	Probability of Transitioning from Rest to Active State
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
QOL	Quality of Life
RA	Relative Amplitude

REM	Rapid Eye Movement
RF	Random Forest
RMSE	Root Mean Squared Error
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SE	Sleep Efficiency
SOL	Sleep Onset Latency
SPAQ	Seasonal Pattern Assessment Questionnaire
SWS	Slow Wave Sleep
TAT	Time Above Threshold
TST	Total Sleep Time
WASO	Wake After Sleep Onset
WHOQOL-BREF	The World Health Organization's Quality of Life Assessment - BREF
XGBoost	Extreme Gradient Boosting
YMRS	Young Mania Rating Scale
μR	Mean Activity During Rest Period
μA	Mean Activity During Active Period

Declaration of Academic Achievement

Chapter 2

A. Slyepchenko formulated research questions addressed in this manuscript, completed the statistical analyses presented in this manuscript, and composed the manuscript. She additionally completed several steps of actigraphy data pre-processing. O. Allega completed all data collection, and several steps of the pre-processing of the actigraphy data. She had completed previous versions of the group differences analyses, which were not included in this manuscript. X. Leng provided statistical guidance, and extracted transition probabilities from actigraphy data. L. Minuzzi provided statistical guidance, and assisted in manuscript composition. M.M. Eltayebani assisted in study recruitment, and manuscript composition. M. Skelly assisted in study recruitment, data organization and entry, and manuscript composition. R.B. Sassi, C.N. Soares, S.H. Kennedy, B.N. Frey contributed to project design, data analysis plan, formulation of the initial research questions, and manuscript composition. Marg Coote and Jodi Gilchrist completed laboratory analyses of the urinary 6-sulfatoxy melatonin samples

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A. Slyepchenko contributed to study design, completed participant recruitment and assessment, data collection, analysis, and composed the manuscript. E.M. Krawczak completed participant recruitment for the independent study, data collection for the independent study and preparation of the manuscript. L. Minuzzi and J.P. Reilly contributed to data analysis plan, and preparation of the manuscript. B.N. Frey contributed to formulation of initial research questions, initial study design, data analysis plan and preparation of the manuscript. M. Coote and J. Gilchrist completed laboratory analyses of the urinary 6-sulfatoxy melatonin samples.

This chapter, in its entirety has been ***submitted*** to the **Australian & New Zealand Journal of Psychiatry.**

Chapter 4

A. Slyepchenko contributed to study design, completed participant recruitment and assessment, data collection, analysis, and composed the manuscript. L. Minuzzi and J.P. Reilly contributed to data analysis plan, and preparation of the manuscript. B.N. Frey

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Chapter 5

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Chapter 1: Introduction

1.1 General Introduction

Disruptions in sleep and biological rhythms are present across many disorders, particularly in mental illness and disorders of the brain. In mood and anxiety disorders, disruptions in sleep and biological rhythms offer a potential transdiagnostic factor that can be addressed through targeted treatment through numerous approaches, like pharmacotherapies, psychotherapies, and light-based therapies. In spite of the potential of sleep and biological rhythm disruptions as biomarkers of mood and anxiety disorders, the pathophysiology of sleep and circadian systems within these disorders remains elusive.

The aims of the work detailed below were to (1) comprehensively characterize sleep and biological rhythm disruptions in adults with mood disorders, compared to their counterparts without mood disorders and (2) investigate the impact of these disruptions on the broad domains of quality of life and functioning in Chapter 2. Next, we (3) describe biological rhythm and sleep disruptions in women during pregnancy, and assess how these impact depressive symptoms (Chapter 3) and (4) anxiety symptoms (Chapter 4) in a longitudinal study during the postpartum period in Canadian women. Finally, in Chapter 5, we prospectively describe changes in sleep, biological rhythms and light exposure from pregnancy to two timepoints in the postpartum period in Canadian women.

Findings from this work highlight the potential of using light-based therapies and other strategies targeting sleep and biological rhythms to improve multiple domains of

well-being and symptom severity in adults with mood disorders, and women during the perinatal period at risk for perinatal mood and anxiety disorders.

1.2 Major Depressive and Bipolar Disorders, Functioning and Quality of Life

Mood disorders, such as Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are characterized by severe episodes of mood disturbance (American Psychiatric Association, 2013), and are associated with significant disability and functional impairment (Ratnaasingham et al., 2013). MDD is characterized by depressive episodes of at least 2 weeks, which are marked by depressed mood or decreased interest in pleasure occurring nearly every day. To be classified as depressive episodes, these periods must be accompanied by 5 of 9 symptoms, including depressed mood and reduced interest, somatic changes (e.g. loss/gain of appetite, sleep changes, changes in psychomotor agitation or slowing), cognitive changes (feelings of worthlessness/guilt, loss of energy or fatigue, inability to concentrate), and suicidality (American Psychiatric Association, 2013). In turn, BD type I disorder is characterized by presence of at least one manic episode, which lasts at least 1 week, or is severe enough to require hospitalization. During this episode, mood must be abnormally elevated, irritated, or expansive, accompanied by activation, that is, increased energy or activity. In addition to mood and activity/energy changes, individuals may experience a reduced need for sleep, increased self-esteem/grandiosity, racing thoughts, distractibility, talkativeness, higher goal-directed activity, and excessive risk-taking. Individuals with BD I may also experience depressive episodes, or hypomanic episodes. Hypomanic episodes consist of at least 4 days of

elevated, irritated or expansive mood, in addition to increased energy/activity, and the criteria described above (American Psychiatric Association, 2013). To be diagnosed with BD type II disorder, an individual must have experienced at least one hypomanic episode and at least one depressive episode, but not a full manic episode (American Psychiatric Association, 2013). Mood episodes must be accompanied by clinically significant distress or impairment, in social and/or occupational domains (American Psychiatric Association, 2013).

1.2.1 Epidemiology of Major Depressive and Bipolar Disorders

In Canada, MDD has a lifetime prevalence of 11.2%, according to the most recent Canadian Community Health Survey – Mental Health. Importantly, females are 1.8x more likely to experience MDD than males (Knoll & MacLennan, 2017), consistent with estimates of sex differences in MDD around the globe (Levinson, Ono, Posada-Villa, & Seedat, 2009). Females with MDD also experience longer episode duration (Eaton et al., 2008). In Canada, BD type I and II rates are 0.87% and 0.57%, respectively (McDonald et al., 2015). Though there are no sex differences in the prevalence of BD type I, there are several notable differences in the presentation of the disorder. BD type II has higher prevalence among women (Arnold, 2003). Additionally, a large proportion of women with BD report mood worsening during reproductive life events, such as the postpartum period, during the premenstrual period, and during perimenopause (Payne et al., 2007; Perich et al., 2017). Finally, women with BD more frequently present with mixed mania

episodes, rapid cycling, and depressive episodes, compared to men (Arnold, 2003; Christensen et al., 2003; Erol et al., 2015; Tondo & Baldessarini, 1998).

Age of onset for BD I disorder is approximately 18 years (American Psychiatric Association, 2013), while onset of BD II and MDD peaks in the 20s (American Psychiatric Association, 2013). Due to the early age of onset for these disorders, people with these disorders live with long periods of functional impairment (Ratnaasingham et al., 2013). Importantly, these disorders often span the period of reproductive life events like pregnancy and postpartum, and child-rearing years.

1.2.2 Functioning and Quality of Life in Major Depressive and Bipolar Disorders

Functioning is a complex concept that describes an individual's ability to conduct daily tasks, meaningfully engage in leisure and interpersonal relationships on a daily basis, cognitive and occupational functioning, capacity for autonomy and managing one's finances (Rosa et al., 2007). In turn, Quality of Life (QOL) accounts for an individual's understanding of their life in context of their environment and expectations, across broad domains of physical health, psychological, social well-being, and their environment (The WHOQOL Group, 1998). These two constructs are therefore important to understanding the disability, dysfunction and overall enjoyment of individuals affected by mood disorders.

Individuals with BD experience worse QOL and higher functional impairment, not only throughout the duration of mood episodes, but also during euthymia, compared to counterparts without BD (Martín-Subero et al., 2014; Pascual-Sanchez, Jenaro, &

Montes-Rodriguez, 2019). Symptom severity, particularly irritability and depressive symptoms, is linked to worse QOL and functional impairment in BD (Sylvia et al., 2017). Consequently, QOL and functioning tend to be at their lowest during depressive episodes, followed by mania, and euthymia (Martín-Subero et al., 2014; Rosa et al., 2010).

In MDD, functional impairment rates are high, with as many as 97% of individuals with MDD reporting some functional impairment, and with 60% reporting severe or very severe functional impairment (Kessler et al., 2003). Improvement in symptoms of MDD, however, does not necessarily achieve or indicate improvement in functioning, and functional impairment is a frequent residual symptom (Sheehan, Nakagome, Asami, Pappadopulos, & Boucher, 2017). Moreover, few individuals with current depression experience normal-range QOL (IsHak et al., 2015). According to a meta-analysis, QOL improves with psychological and pharmacological treatment of MDD (Hofmann, Curtiss, Carpenter, & Kind, 2017). However, symptomatic remission may not be indicative of return of QOL to its normal range (IsHak et al., 2015).

Considering the prevalence of functional impairment, and worsened quality of life in mood disorders, particularly as they extend beyond mood episodes, it is important to evaluate contributing factors, in order to develop targeted interventions to improve within-episode and between-episode functioning and quality of life in individuals with mood disorders.

1.3 Mood Disorders During the Postpartum Period

1.3.1 Definitions, Prevalence

The postpartum period is often defined as the 1st year following childbirth (Goyal, Gay, Torres, & Lee, 2018). The perinatal period, including pregnancy and postpartum, is a vulnerable period for women to develop mental illnesses: results from epidemiological research have indicated that depression and anxiety during the perinatal period are common (Dennis, Falah-Hassani, & Shiri, 2017; Gavin et al., 2005). Identifying these disorders prior to or early in their onset is important, as they impact mothers and their families well beyond the postpartum period.

In the Diagnostic and Statistical Manual of Mental Disorders (DSM)- 5, a diagnosis of peripartum depression is specified by the occurrence of a major depressive episode during pregnancy or within the first 4 weeks postpartum (American Psychiatric Association, 2013). However, this timeframe has been challenged, with numerous studies showing onset of postpartum depression (PPD) during later months in the postpartum period. A previous meta-regression has found that 2-3 months postpartum has the highest point prevalence of PPD, as compared to 4-12 months postpartum (Gavin et al., 2005).

As diagnostic criteria for PPD are equivalent to those for a major depressive episode with a different onset time, it may be difficult to discriminate between common pregnancy symptoms and depressive symptoms. For instance, changes in appetite, sleeping patterns and fatigue are expected during the perinatal period (Lee et al., 2007). This has led to development of tools such as the Edinburgh Postnatal Depression Scale (EPDS), which does not assess appetite changes, fatigue and other somatic complaints in

order to improve specificity of screening for depression during this time (D. Murray & Cox, 1990). It should be noted that during the perinatal period, women who report higher depressive symptoms according to the EPDS also report more somatic complaints (Apter et al., 2013).

Postpartum depression affects 7-13% of women (Gavin et al., 2005). By another estimate, postpartum depression affects 9-10% of women in high-income countries and 18-20% of women in low and middle-income countries (Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). Interestingly, during 1-3 weeks postpartum, 15-84% of women report postpartum blues – a transient disorder, marked by emotional lability, confusion, irritability, tearfulness, and mild elation. Postpartum blues appear to be a risk factor for developing PPD (Henshaw, 2003).

1.3.2 Outcomes Related to Postpartum Depression

Postpartum depression has been linked to a number of adverse effects on the well-being of mothers and their families. First, women with PPD consult more with general practitioners, and have worse QOL than their counterparts, have more relationship difficulties, and have lower social functioning (Weissman, 2018). PPD is linked to risk of difficulties in emotion regulation, social behaviour, internalizing disorders in children of mothers with PPD (Reviewed in (Stein et al., 2014)). Moreover, PPD is linked to depression in adolescence (Stein et al., 2014), as well as severity of attention deficit hyperactivity disorder and insecure attachment (Stein et al., 2014). Finally, PPD has been linked to deficits in cognitive outcomes in childhood, for instance, language development,

cognitive development, and exam achievement (Stein et al., 2014). A recent study found that children's total grey matter volume and fractional anisotropy at 10 years of age decreased in proportion to their mothers' PPD symptoms, though this was not true for antenatal depressive symptoms, or mothers' depressive symptoms during childhood (Zou et al., 2019).

1.3.3 Risk Factors for Postpartum Depression

A number of risk factors have been previously established for developing PPD. Psychosocial risk factors for PPD as assessed during pregnancy include demographics, such as lower income (Hutchens & Kearney, 2020) and older age (Silverman et al., 2017). Poor quality of social support, including lack of partner support, is linked to risk of PPD, as is intimate partner violence or interpersonal violence, and presence of chronic or life stress (Beck, 1996; Pilkington, Milne, Cairns, Lewis, & Whelan, 2015; Yim, Tanner Stapleton, Guardino, Hahn-Holbrook, & Dunkel Schetter, 2015). Other maternal characteristics that constitute risk for PPD include child care stress, less secure maternal attachment, infant temperament, whether the pregnancy was unplanned or unwanted, low self-esteem, negative attributional style, difficulties during pregnancy or birth, and neuroticism (Beck, 1996; Hutchens & Kearney, 2020; Yim et al., 2015). Gestational diabetes is also associated with PPD risk (Azami, Badfar, Solemani, & Rahmati, 2019; Silverman et al., 2017).

There are several known clinical risk factors for PPD, including having prenatal anxiety and depression, having a history of depression overall, and substance use

disorders (Beck, 1996; Hutchens & Kearney, 2020; Yim et al., 2015). Moreover, postpartum blues constitute risk for later PPD (Hutchens & Kearney, 2020). Women with BD experience a high rate of depressive, manic and mixed episode recurrence during the postpartum period. (Di Florio et al., 2013). According to a population-based study, psychosocial risk factors for PPD differ according to whether women have a history of depression. In women who have been previously depressed, pre-gestational diabetes and mild preterm delivery increase the risk of PPD. In women without a lifetime history of depression, young age, C-sections, instruments used during delivery and moderate preterm delivery was linked to PPD (Silverman et al., 2017).

A number of biological risk factors for PPD have been previously investigated, including sleep disturbances, changes in hypothalamic-pituitary adrenal axis dysregulation, increased inflammation, and genetic risk factors (Hutchens & Kearney, 2020; Yim et al., 2015). Throughout late pregnancy, corticotropin-releasing hormone levels increase. Higher rise of this hormone during the 2nd and 3rd trimester of pregnancy has been linked to PPD symptoms (Yim et al., 2015). Levels of C-reactive protein, a systemic inflammation marker, during the 2nd postnatal day was not a predictor of postpartum PPD risk in a large (n=1,053) study (Albacar et al., 2010). Some findings from genetic studies have suggested that polymorphisms in candidate genes, including polymorphisms in catechol-O-methyltranferase, and monoamine oxidase-A (MAO-A), as well as polymorphisms in the estrogen receptor, corticotropin-releasing hormone receptor 1, the glucocorticoid receptor, and the oxytocin peptide may be linked to PPD risk. Additionally, some studies have reported that PPD may be linked to heightened

sensitivity to epigenetic modifications in genes related to estrogen signaling pathways (Yim et al., 2015). A recent population-based study found that polygenic risk scores associated with MDD, but not BD or schizophrenia was linked to higher risk of postpartum psychiatric disorders (Bauer et al., 2019).

Finally, the changes in reproductive hormones associated with the perinatal period have been extensively investigated in PPD. Absolute levels of estradiol or progestins do not seem to be the causal factor, and there are few lines of evidence pointing to hormone withdrawal as the causal factor for PPD (Yim et al., 2015). Recent findings have linked reduced levels of allopregnanolone during the 2nd trimester to higher risk of PPD, with every addition of 1 ng/mL a 63% decrease in risk of PPD. Allopregnanolone is a progesterone metabolite that is thought to be linked to the psychoactive properties of progesterone (Osborne et al., 2017). Some evidence also exists for low oxytocin levels in pregnancy as a predictor of PPD symptoms at 2 weeks postpartum (Yim et al., 2015).

While promising, findings from biological studies of risk factors of PPD have yet to yield a reliable predictor of PPD. Additionally, many studies have only investigated one potential biological marker, and have not consistently integrated their findings with known psychosocial risk factors. Integrating psychosocial and biological risk factors within research studies may lead to clarification of the processes that lead to development of this disorder (Yim et al., 2015).

1.4 Anxiety During the Postpartum Period

1.4.1 Anxiety Disorders

Anxiety disorders encompass a category of mental illness characterized by excessive anxiety in response to a future threat and worry in response to real or perceived threats (American Psychiatric Association, 2013). These disorders are characterized by excessive and persistent responses and can be differentiated from each other by the situations to which these cognitions and behaviours occur in response. Some of the most common anxiety disorders are: (1) Panic Disorder, characterized by unexpected and intense, recurrent panic attacks, where individuals experience acute physical and cognitive symptoms, and persistent worry about experiencing another attack. (2) Agoraphobia, a disorder where individuals have anxiety symptoms related to situations where escape or getting help might be difficult, such as in an open space, standing in a crowd, being away from home alone. (3) Social anxiety disorder, which is characterized by worry and anxiety that occur in the context of social and performance situations, with possible critical observation from other people. (4) Generalized Anxiety Disorder (GAD), which has the highest prevalence of any anxiety disorder, and is characterized by excessive worry and anxiety in response to a broad range of events (American Psychiatric Association, 2013). Two other common disorders closely related to anxiety – obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) – were previously described as anxiety disorders, but have now been categorized as obsessive-compulsive and related disorders and trauma- and stressor-related disorders, respectively. OCD is characterized by the presence of repeated and intrusive obsessions and compulsions.

Obsessions are cognitions, such as thoughts or images which are intrusive and distressing, while compulsions are behaviours or mental behaviours that an individual feels compelled to repeat as a reaction to the compulsion, and/or with rigid rules, in order to ameliorate the anxiety response. PTSD occurs following exposure to a serious trauma (death, serious injury, sexual violence), and is characterized by intrusive symptoms (e.g. distressing memories, reactions or dreams), avoidance of related memories or reminders, changes in mood and cognition related to the event, and changes in behaviour and arousal following the event. Anxiety and related disorders are differentiated from non-pathological conditions by the degree of mental distress and impairment in psychosocial functioning (American Psychiatric Association, 2013).

1.4.2 Postpartum Anxiety

During the postpartum period, anxiety is common, and is a strong contributor to postpartum distress. To date, less attention in clinical and research settings has been devoted to postpartum anxiety (PPA), compared to depression during this period (Miller, Pallant, & Negri, 2006). Unlike depression during this period, peripartum onset of anxiety is not acknowledged in the DSM-5 (American Psychiatric Association, 2013). It is important to understand the etiology of these disorders, their risk factors and prognosis, in order to identify and implement preventive and early treatment strategies.

A previous meta-analysis by Dennis and colleagues identified the prevalence of self-reported postpartum anxiety to be 18% at 1-4 weeks postpartum, 15% at 5-12 weeks postpartum, 15% at 1-24 weeks postpartum, and 15% at >24 weeks postpartum. In turn,

criteria for a clinical diagnosis of an anxiety disorder was met by 9.6% of women at 5-12 weeks postpartum, 9.9% at 1-24 weeks postpartum, and 9.3% at >24 weeks postpartum (Dennis et al., 2017). Postpartum anxiety was more common among low and middle-income countries, compared to high-income countries (Dennis et al., 2017).

In terms of specific anxiety disorders, GAD was found in 6.7% of women at 5-12 weeks postpartum, 5.7% at 1-24 weeks postpartum, and 4.2% at >24 weeks postpartum (Dennis et al., 2017). Interestingly, according to meta-analytic findings, women are at higher risk for OCD during the perinatal period than in the general population. Postpartum OCD prevalence in this study is 2.4% in postpartum women and 2.03% in pregnant women (Russell, Fawcett, & Mazmanian, 2013). Postpartum PTSD prevalence is approximately 1.8 - 3.1% (Goodman, Watson, & Stubbs, 2016; Grekin & O'Hara, 2014), prevalence of agoraphobia is 0.68%, social anxiety disorder is 1.28%, panic disorder is 1.7%, and any anxiety disorder is 8.6% (Goodman et al., 2016).

According to a meta-analysis, PPA linked to self-confidence issues, changes in stress response and worsened body acceptance in mothers (Goodman et al., 2016). PPA has also been linked to excessive crying in infants (Petzoldt et al., 2014), worse maternal self-confidence (Reck, Noe, Gerstenlauer, & Stehle, 2012), worse engagement of mothers and infants (Murray, Cooper, Creswell, Schofield, & Sack, 2007). There have been few longitudinal investigations of the outcomes of children of mothers with PPA (Goodman et al., 2016).

1.4.3 Risk Factors for Postpartum Anxiety

Investigations of risk factors for perinatal anxiety have been relatively few in number. According to a meta-analysis by Furtado and colleagues, there are a number of risk factors for anxiety worsening and new onset anxiety that have been established by multiple studies in the perinatal period. For anxiety worsening, these factors include having a comorbid psychiatric disorder, and possibly, maternal age. For new onset anxiety during pregnancy and the postpartum period, having lower levels of education, cohabitating with members of extended family, hyperemesis gravidarum, having a history of sleep disorders or a family history of mental illness were all deemed risks for developing perinatal anxiety. Administration of prenatal oxytocin was linked to both perinatal anxiety worsening and onset (Furtado, Chow, Owais, Frey, & Van Lieshout, 2018). In a population-based study, anxiety symptoms at 8 weeks postpartum were predicted by multiparity, history of psychiatric disorders, perceived stress, and stress related to care of children (Dennis, Falah-Hassani, Brown, & Vigod, 2016). Overall, few risk factors have been investigated for PPA, particularly in the domain of biological markers. In a longitudinal investigation, Furtado and colleagues found that intolerance of uncertainty, depressive symptoms and OCD symptoms during the 3rd trimester of pregnancy were predictors of PPA worsening. However, inflammatory markers measured in the 3rd trimester of pregnancy, including C-reactive protein, interleukin-6 and tumor necrosis factor-α were not significant predictors of PPA worsening (Furtado, Van Lieshout, Van Ameringen, Green, & Frey, 2019).

1.4.4 Comorbid Postpartum Mood and Anxiety

Depression and anxiety are often comorbid during the perinatal period. A prior population-based study found that 35% of women with anxiety during postpartum report depressive symptoms as well (Farr, Dietz, O'Hara, Burley, & Ko, 2014). Another study found that nearly 40% of women with postpartum depression had a comorbid anxiety disorder diagnosis (Austin et al., 2010). In a meta-analysis, Falah-Hassani and colleagues found that 9.5% of women report both symptoms of depression and anxiety in the postpartum period pregnancy, and 8.2% postpartum (Falah-Hassani, Shiri, & Dennis, 2017). Women with both disorders have a more complex clinical presentation, including worsened symptom severity, and worse outcomes than women with only a history of one of the disorders (Feldman et al., 2009). Furthermore, in the general population, individuals with comorbid depression and anxiety have worse functioning (Adams, Balbuena, Meng, & Asmundson, 2016), are at higher risk for suicide attempts (Sareen et al., 2005).

In a Canadian sample, Dennis and colleagues found that risk factors for comorbid anxiety and depression during the first 24 weeks postpartum include having a history of depression, having a history of postpartum depression, age of <26 years, having worse perceived support, as well as fatigue, stress related to acculturation, and impression that the infant is experiencing sleep problems (Dennis et al., 2018).

1.5 Sleep and Biological Rhythms in Mood and Anxiety

1.5.1 Sleep and Biological Rhythms: An Introduction

Two major processes are thought to be involved in the generation and timing of the sleep-wake cycle: (1) a homeostatic sleep process, where pressure to sleep builds over time, and is released once sleep is obtained; and (2) a circadian oscillator, with a natural oscillation period, which is entrained to the environmental light-dark cycle to a period of approximately 24 hours (Achermann & Borbély, 2003; Borbély & Achermann, 1999). The entrainment of the circadian oscillator by the light-dark cycle and other *zeitgebers* (time-keeping environmental signals) is centrally regulated by the circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN in essence ensures the timing of wakefulness to occur during the day and sleep during the night, where this rhythm interacts with the homeostatic component of sleep (Skeldon, Derks, & Dijk, 2016). Input to the SCN comes directly from the retina, including a specialized type of photosensitive retinal ganglion cell -- the intrinsically photoreceptive retinal ganglion cell -- characterized by presence of a photoreceptor pigment called melanopsin, via the retinohypothalamic tract (Zaki et al., 2018). The SCN also receives indirect input from the retina through the geniculohypothalamic tract and the intergeniculate leaflet, as well as serotonergic inputs from the raphe nuclei, among others (Rosenwasser, 2009).

The SCN projects to a number of brain regions, such as other hypothalamic nuclei, the preoptic area, basal forebrain and the thalamus (Rosenwasser, 2009). Importantly, the SCN projects to the pineal gland, where it regulates the secretion of melatonin. Melatonin secretion begins 2 to 3 hours prior to sleep onset, with maximum

secretion occurring at 3:00-4:00 in the morning. During the day, melatonin secretion remains low (Claustrat, Brun, & Chazot, 2005; Molina & Burgess, 2011). Melatonin can cross the blood-brain barrier and can access all tissues within the body. Urinary 6-sulfatoxymelatonin is the primary metabolite of melatonin in urine, and parallels melatonin patterns within the plasma. Exposure to light suppresses the production of melatonin, particularly at high light intensities (Claustrat et al., 2005). It is theorized that the main function of melatonin is to communicate the information of illuminance to the rest of the body, thereby synchronizing biological rhythms such as cortisol, body temperature, sleep-wake and activity rhythms (Claustrat et al., 2005).

The SCN drives the synchronicity of circadian rhythms within the body. It is thought that most cells in the body have endogenous rhythms, driven by the activity of clock genes within each cell. There is a complex network of clock genes which coordinates rhythmicity, regulated by several transcription translation feedback loops, which communicate environmental time to regulate biological rhythm activity (Geoffroy, 2018). The major transcription translation feedback loop consists of CLOCK and BMAL1, which are transcription factors that regulate the clock genes *PERIOD (PER)* and *CRYPTOCHROME (CRY)* expression, which feed back on to CLOCK and BMAL1 to control their own expression by entering the nucleus as a complex and impeding transcription by CLOCK and BMAL1 (Jagannath, Peirson, & Foster, 2013).

The broad concept of biological rhythms encompasses variations in behavioural and physiological processes. Biological rhythms with a period of approximately 24 hours

are referred to as circadian rhythms, whereas those that are longer or shorter than 24 hours are termed infradian and ultradian rhythms, respectively.

1.5.2 Sleep and Biological Rhythms in Mood Disorders

1.5.2.1 Subjective Sleep and Rhythms in Mood Disorders

Biological rhythms and sleep disruptions are common in mood disorders. Criteria for depressive and [hypo]manic episodes include sleep disruptions (American Psychiatric Association, 2013), and sleep disturbances are very common prodromes for manic and depressive episodes (Jackson, Cavanagh, & Scott, 2003; Van Meter, Burke, Youngstrom, Faedda, & Correll, 2016). Evidence suggests that subjective sleep disturbances in BD persist into euthymia, and are associated with worse functioning and QOL (De la Fuente-Tomas et al., 2018). Sleep disturbances also often persist into remission among individuals with MDD, and are linked to worse QOL (Li, Lam, Chan, Yu, & Wing, 2012). In a small (n=40) sample of individuals receiving treatment for MDD and healthy controls, those experiencing worse sleep according to a sleep log were more likely to report poor QOL. Individuals with MDD were more likely to report worse sleep quality and worse QOL, even though their sleep patterns were similar to healthy individuals, indicating possibility of worsened interpretation of sleep quality in individuals with MDD (Mayers, van Hooff, & Baldwin, 2003).

A number of previous studies have shown evidence of subjective biological rhythm disruption in BD and MDD. Duarte Faria and colleagues showed that young adults with current MDD, and current or euthymic BD had worse biological disruption

than the control group (Duarte Faria et al., 2015). Importantly, in BD, depressive symptom severity (Pinho et al., 2016), worsened functioning (Giglio, Magalhaes, Kapczinski, Walz, & Kapczinski, 2010; Pinho et al., 2016), and worsened QOL (Cudney, Frey, Streiner, Minuzzi, & Sassi, 2016) have been linked to subjective disturbances in biological rhythms. Another study found evening chronotype to be linked to worse QOL in individuals with BD in remission (Ng, Chung, Lee, Yeung, & Ho, 2016). Additionally, biological rhythm disturbances have been linked to higher lipid peroxidation in women with BD, but not the control group (Cudney et al., 2014).

Overall, these studies provide strong evidence that biological rhythms disruptions beyond sleep impact the well-being of individuals with mood disorders.

1.5.2.2 Polysomnographic Studies in Mood Disorders

Polysomnography (PSG) involves recordings of brain activity via an electroencephalogram (EEG), muscle activity via electromyography, and eye movements via electrooculography. PSG provides information regarding (1) sleep continuity, which refers to variables such as total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE), number of awakenings, and wake after sleep onset (WASO); and (2) sleep architecture, which refers to different sleep stages, including wake stages, rapid eye movement (REM) sleep and non-REM sleep (including stage 1, stage 2, slow wave sleep (SWS)). Non-REM and SWS are assessed as percentages of time spent in these stages during the night.

A prior meta-analysis of PSG found that compared a control group, individuals with MDD have worse sleep efficiency, increased REM sleep and density; shorter sleep periods, shorter latency to REM, and shorter SWS periods. In remission, sleep efficiency and REM latency were longer than during major depressive episodes, and SWS was shorter during remission (Pillai, Kalmbach, & Ciesla, 2011). A more recent meta-analysis of PSG studies in MDD found worsened sleep continuity, reduced sleep depth and higher REM pressure in this population, though no changes in SWS were found. Sleep continuity, depth and REM pressure differed from controls in males with MDD, but only sleep continuity was disturbed in females (Baglioni et al., 2016).

Fewer studies have investigated PSG characteristics of BD. A prior study described REM density is higher in euthymic BD compared to controls without bipolar disorder (Eidelman, Talbot, Gruber, Hairston, & Harvey, 2010). Individuals with hypomania have lower sleep efficiency, longer SOL, higher % of stage 1 and 2 sleep, lower stage 3 and 4 sleep, shorter REM latency and higher apnea index compared to healthy controls (Asaad, Sabry, Rabie, & El-Rassas, 2016). Mania is marked by decreased need for sleep in most individuals, longer SOL, as well as higher REM pressure. Depressive episodes, as in unipolar depression, are marked by insomnia or hypersomnia in most individuals, with longer SOL and higher sleep pressure (Harvey, Talbot, & Gershon, 2009). Overall, PSG studies have been limited by a lack of ecological validity, burden to participants, and their higher cost (Ancoli-Israel et al., 2003; Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Miller, Kyle, Melehan, & Bartlett, 2015).

1.5.2.3 Melatonin in Mood Disorders

Melatonin provides a reliable marker of the endogenous SCN rhythm (Claustrat et al., 2005). Melatonin profiles can be collected using several methods. Salivary sampling requires samples to be acquired every 30-60 minutes throughout a period that encompasses 1 hour before the rise in melatonin levels, and throughout this process. Salivary sampling requires individuals to avoid contamination of the samples by food, blood, food dye, and requires participants to be exposed to <30 lux of light throughout sample collection. A period of fasting for ~ 5 hours under dim light conditions is therefore necessary to avoid sample contamination. Melatonin can be also assessed through measurements in plasma, indicating the necessity of blood sampling every 20-30 minutes via intravenous catheter for optimal results from afternoon to overnight. The melatonin profile can also be assessed by analyzing levels of 6-sulfatoxymelatonin, its primary metabolite, excreted in urine. Overnight melatonin secretion can be calculated by controlling for creatinine in the first morning urine void, thereby not requiring sleep disruption or low light conditions (Molina & Burgess, 2011).

Prior studies have indicated changes in melatonin secretion in individuals with mood disorders since as early as 1979 (Mendlewicz et al., 1979). Findings regarding the relationship between melatonin levels and mood disorders have been heterogenous. Prior evidence has indicated that daytime melatonin levels during manic episodes are higher than in controls and in individuals with bipolar depression (Novakova, Prasko, Latalova, Sladek, & Sumova, 2015). Another investigation indicated later circadian phase, and lower melatonin secretion in the evening in individuals with BD (Melo, Abreu, Linhares

Neto, de Bruin, & de Bruin, 2017). One study found higher area under curve in salivary melatonin secretion in MDD compared to BD, and earlier melatonin secretion (Robillard et al., 2013).Yet another study found that levels of melatonin in cerebrospinal fluid during the morning are lower in individuals with BD, but not in MDD; and levels of serum melatonin were lower in MDD but not BD (Bumb et al., 2016).

In MDD, some investigations have found higher (Rubin, Heist, McGeoy, Hanada, & Lesser, 1992) or lower serum melatonin levels overnight, with higher levels of melatonin in the morning (Khaleghipour et al., 2012). Another study attributed differences in melatonin secretion between individuals with major depressive episodes and controls to a phase delay, where the peak melatonin secretion overnight occurred later for those with depression (Crasson et al., 2004).

1.5.2.4 Actigraphy in Mood Disorders

Actigraphy has been increasingly used to assess daily activity rhythms and sleep patterns in research settings, as it offers the advantage of ambulatory monitoring for extended periods of time. Methods of analysis of actigraphy data continue to be refined, with recent investigations using complex modeling of actigraphy data to, for instance, evaluate the probabilities of activity and rest state transitions, in addition to analysis of sleep, activity and daily activity rhythms (Ortiz, Bradler, Radu, Alda, & Rusak, 2016).

Prior investigations of actigraphy in BD have reported higher variability in daily activity rhythms, lower amplitude and changes in mean activity in this population. Biological rhythm disruptions are common to bipolar depression, indicated by lower

mean activity, higher variability of daily activity rhythms, and a shift to a later circadian phase (Melo et al., 2017). Individuals with BD are more likely to have an evening-type chronotype, and higher seasonality. However, results regarding the relationship between symptom severity and chronotype have been inconsistent (Melo et al., 2017).

Recent changes to criterion A necessary to the diagnosis of [hypo]mania include a marked rise in activity and energy in addition to mood changes. In bipolar disorder, the concept of activation has recently been proposed which includes objective change in motor activity and subjective changes in energy related to the objective changes, arising from a physiological phenomenon. According to Scott and colleagues' systematic review, compared to a depressive mood state in BD, but not compared to healthy controls, mania is characterized by higher mean activity levels. During depressive episodes and euthymia, individuals with bipolar disorder have lower mean activity levels compared to controls (Scott et al., 2017). Additionally, there appears to be a phase advance in acrophase in mixed and manic episodes (Salvatore et al., 2008). A study of euthymic individuals with BD has found that actigraphy-measured TST was longer in BD, as was SOL, worse SE, lower interdaily stability. Variability in measures such as time in bed, sleep duration, SE and fragmentation index were also higher in BD (Geoffroy et al., 2014).

Depressive episodes in mood disorders have been linked by meta-analysis to lower daytime activity, which increases throughout treatment (Burton et al., 2013). A prior investigation has found higher fragmentation index and lower motor activity throughout the day, in addition to higher activity and immobility during sleep in MDD (Volkers, 2003). Another study found lower total activity in depressive episodes, but no

significant differences in interdaily stability, intradaily variability or relative amplitude (Berle, Hauge, Oedegaard, Holsten, & Fasmer, 2010).

Findings from actigraphy indicate the presence of some markers of sleep and biological rhythm disturbance that are present for multiple psychiatric disorders. In an actigraphy study of group of young people aged 12-35, individuals with anxiety disorders, MDD and BD had later sleep onset and sleep offset compared to controls according to actigraphy. TST was longer in those with anxiety disorders and individuals with BD, while SE was lower in MDD. Later acrophase was found in individuals with anxiety disorders or BD. Additionally, there were various differences in variability of sleep parameters beyond mean values for these disorders (Robillard et al., 2015).

Some actigraph models have a built-in light sensor, allowing actigraphy to provide ambulatory information about light exposure throughout the day. To date, little is known about light exposure in MDD and BD. In a longitudinal study of elderly individuals who did not have baseline depressive symptoms, exposure to light at night of greater than 5 lux increased risk of presenting depressive symptoms after a 2 year follow-up (Obayashi, Saeki, & Kurumatani, 2018). Light-based therapies such as bright light therapy and blue-light blocking glasses have been increasingly used as adjunctive therapies in mood disorders. A recent meta-analysis demonstrated a significant effect of bright light therapy on reducing depressive symptoms in individuals with non-seasonal depression (Perera et al., 2016). In BD, bright light therapy has been shown to be an effective adjunctive treatment of depression by a recent randomized controlled trial (Sit et al., 2018).

Additionally, blue-light blocking glasses have shown a large effect in reducing manic symptoms as an adjunctive treatment for mania (Henriksen et al., 2016).

1.5.3 Sleep, Biological Rhythms and Anxiety

Sleep and biological rhythm disruptions are also present in anxiety disorders. Sleep problems are part of the diagnostic criteria for GAD and PTSD (American Psychiatric Association, 2013). A meta-analysis of polysomnographic studies found lower sleep depth and continuity, and higher sleep pressure in anxiety disorders, including shortened SWS and reduced REM latency (Baglioni et al., 2016). Disturbances in sleep may also predict the onset of anxiety disorders (Batterham, Glozier, & Christensen, 2012; Neckelmann, Mykletun, & Dahl, 2007).

Across different anxiety disorders, Biaggi and colleagues systematically reviewed objective and subjective sleep disturbances, finding evidence of changes in sleep profiles among different anxiety disorders. GAD is marked by lower TST, higher SOL and differences in non-REM sleep, while subjective sleep disturbances are predictive of the onset of GAD. OCD severity is associated with shorter TST, and potentially, delayed sleep phase. In panic disorder, there are subjective sleep disturbances, lower sleep efficiency, shorter TST, and higher SOL. Objective and subjective sleep disturbances are present in PTSD, including lower TST, higher SOL, and changes in REM. In social anxiety disorder, there are subjective sleep problems, though little research has been done on objective sleep disturbances (Biaggi, Conroy, Pawlby, & Pariante, 2016).

A number of studies point toward disruptions in biological rhythms in anxiety disorders. In an ecological momentary assessment study, Cox and colleagues found that in a sample of undergraduates and community members, sleep disturbance was predictive of medium increases in anxiety, and eveningness was a predictor of small increases in anxiety (Cox & Olatunji, 2019). Luik and colleagues found that clinically significant depressive symptoms and anxiety disorders were linked to intradaily variability, and subjective sleep quality; while depressive symptoms alone were linked to later dominant rest phase onset in middle-aged and older adults (Luik et al., 2015). Finally, Antypa and colleagues found that MDD, but not anxiety disorders were linked to eveningness in a large cohort in the Netherlands (n=1,944) (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2016).

1.5.4 Perinatal Sleep and Biological Rhythms, Mood and Anxiety

Sleep and biological rhythm disturbances are common in the perinatal period. Evidence suggests that poor sleep quality during pregnancy has negative effects on maternal health, including risk of gestational diabetes mellitus, suicidal ideation, and pre-term birth (Cai et al., 2017; Gelaye et al., 2015; Sedov, Cameron, Madigan, & Tomfohr-Madsen, 2018; Wang & Jin, 2020).

A number of studies have investigated the association of subjective and objective sleep quality with PPD. Wolfson and colleagues (2003) followed mothers from the 3rd trimester of pregnancy to several points up to 12-15 months postpartum. They found that women who had clinically significant symptoms of PPD 2-4 weeks postpartum had

higher TST, later wake up times, and a higher number of naps in the 3rd trimester of pregnancy, compared to those who did not have clinically high PPD symptoms (Wolfson, Crowley, Anwer, & Bassett, 2003). Park and colleagues (2013) found that subjective sleep is associated with PPD symptom severity from late pregnancy to 14 weeks postpartum. During the postpartum period, objective SE, sleep percentage, sleep fragmentation and WASO were associated with PPD symptom severity as well (Park, Meltzer-Brody, & Stickgold, 2013).

Some longitudinal studies have also investigated sleep during pregnancy as predictors of postpartum mood. For instance, McEvoy et al. found that subjective sleep quality at 1 month postpartum but not during the 3rd trimester of pregnancy was linked to PPD symptom severity at 3 months postpartum (McEvoy et al., 2019). According to a prior study by Coo Calcagni and colleagues, neither subjective nor objective 3rd trimester sleep were predictors of mood during 2 weeks postpartum (Coo Calcagni, Bei, Milgrom, & Trinder, 2012). Interestingly, women who have a history of manic episodes triggered by sleep loss have 2x the risk of postpartum psychosis, that is manic or mixed episodes, or depression with psychotic symptoms within the first 2 weeks following childbirth (Heron, Blackmore, McGuinness, Craddock, & Jones, 2007; Lewis et al., 2018).

Several studies have investigated the influence of subjective sleep during pregnancy on both depressive and anxiety symptoms postpartum, with somewhat heterogenous findings. Bei and colleagues found that subjective, but not objective sleep during the 3rd trimester was associated with PPD symptom severity at 1 week postpartum. Additionally, subjective sleep dysfunction, during the 3rd trimester was linked to

postpartum anxiety symptoms (Bei, Milgrom, Ericksen, & Trinder, 2010). Tham and colleagues in a prior investigation of 313 women found 3rd trimester subjective sleep quality to be associated with severity of PPD symptoms, but not anxiety at 3 months postpartum (Tham et al., 2016). However, Osnes and colleagues, in a large sample (n=1,563) found that women who had insomnia symptoms during the 3rd trimester of pregnancy had higher depressive and anxiety symptoms at 8 weeks postpartum, and were more likely to have anxiety disorders during this time (Osnes, Roaldset, Follestad, & Eberhard-Gran, 2019). Menke and colleagues have also reported perinatal depression and anxiety symptoms to be linked to subjective sleep quality (Menke et al., 2019).

Few investigations have focused on biological rhythms and mood or anxiety symptoms during the postpartum period. A previous study from our group has found that worsening of subjective biological rhythm disturbances, but not subjective sleep quality, from the 3rd trimester of pregnancy to 6-12 weeks postpartum were associated with worsening of mood during these timepoints (Krawczak, Minuzzi, Hidalgo, & Frey, 2016). Additionally, in a subset of this sample, objective sleep efficiency worsening from pregnancy to postpartum and subjective biological rhythm disruption were associated with worsening of depressive symptoms (Krawczak, Minuzzi, Simpson, Hidalgo, & Frey, 2016).

Few studies have investigated melatonin levels and their association with mood or anxiety during the perinatal period. In a small study of 12 women with a history of MDD, Sharkey and colleagues found that from the 3rd trimester of pregnancy to 6 weeks postpartum, women experienced a phase delay, and the gap between sleep onset and dim

light melatonin onset was shorter in most women. PPD symptoms at 2 and 6 weeks postpartum in this sample were linked to dim light melatonin onset phase and phase angle (Sharkey, Pearlstein, & Carskadon, 2013). A cross-sectional investigation by Parry and colleagues found that morning melatonin levels were greater in women with (n=13) than without (n=11) PPD in the first year postpartum. In pregnant women, however, morning melatonin levels were lower in those with current depression (Parry et al., 2008).

Though prior literature indicates the presence of a link between sleep, biological rhythms, perinatal mood and anxiety, studies have been limited by small samples, cross-sectional design, lack of objective measures of sleep and biological rhythms, poor clinical characterization of study samples, and few studies overall have looked at the influence of biological rhythms during the perinatal period on mood or anxiety (Gallaher, Slyepchenko, Frey, Urstad, & Dorheim, 2018). Moreover, few studies have investigated sleep or biological rhythms as a predictor of postpartum anxiety.

1.6 Main Aims

Given the association of biological rhythms and sleep with depression and bipolar disorder, and previous findings of subjective biological rhythms to be associated with functional impairment, we first aimed to (1) compare biological rhythms and sleep variables across a broad range of measures in individuals with and without bipolar and major depressive disorders. (2) We aimed to investigate whether these measures can account for impairment in functioning and worsened quality of life in this population.

(3) Next, we aimed to investigate sleep and biological rhythms during pregnancy and determine whether sleep and biological rhythm variables collected during pregnancy can be used to predict symptom severity of mood and (4) anxiety postpartum. Finally, we aimed to investigate (5) the longitudinal trajectory of sleep, biological rhythms and light exposure across the perinatal period.

1.7 Specific Objectives

The specific objectives of this thesis are described below:

1. Investigate differences between individuals with BD, MDD and healthy controls in a broad range of measures of sleep and biological rhythms, including subjective questionnaires, various objective measures from actigraphy and 6-sulfatoxymelatonin levels;
2. Investigate whether sleep and biological rhythm variables can be used to model functioning and quality of life in individuals with BD, MDD and healthy controls;
3. Examine sleep and biological rhythms in women during pregnancy, across a broad range of measures including subjective questionnaires, measures from actigraphy and 6-sulfatoxymelatonin levels. We aimed to use sleep and biological rhythm measures in conjunction with clinical variables to predict postpartum mood and
4. Use sleep and biological rhythm measures collected during pregnancy, as described in (3), in conjunction with clinical variables to predict postpartum anxiety.

5. Describe the longitudinal changes in clinical variables, sleep, biological rhythms, and light exposure from the 3rd trimester of pregnancy, to 1-3 weeks, and 6-12 weeks postpartum.

1.8 Hypotheses

The hypotheses for each of the outlined objectives are as follows:

1. Given findings of differences in sleep and biological rhythms in mood disorders, we hypothesized that sleep and biological rhythms would be more disrupted in the MDD and BD groups, compared to HCs across subjective and objective measures.
2. As previous findings have reported subjective biological rhythm disruption to be linked to worsened functional impairment in mood disorders, we hypothesized that disrupted objective and subjective sleep and biological rhythms would be linked to functional impairment and worse quality of life.
3. In light of prior investigations of disrupted sleep and biological rhythms being linked to worsened mood in the perinatal period, we hypothesized that worsened sleep and biological rhythms during pregnancy would be predictive of mood disturbances postpartum.
4. Previous literature described a variety of sleep disturbances and potential biological rhythm disturbances in anxiety disorders, and perinatal sleep disturbances may be linked to perinatal anxiety. We therefore hypothesized that sleep and biological rhythm disturbances measured objectively and subjectively during pregnancy would predict postpartum anxiety.

5. Based on prior literature reporting sleep disruptions throughout the perinatal period, with particularly prominent sleep worsening during the first month postpartum, we hypothesized that biological rhythms would be most disturbed at 1-3 weeks postpartum, compared to the 3rd trimester of pregnancy and 6-12 weeks postpartum.

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Chapter 2: Association of Functioning and Quality of Life With Objective and Subjective Measures of Sleep and Biological Rhythms in Major Depressive and Bipolar Disorder

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Abstract

Objective: Disruptions in biological rhythms and sleep are a core aspect of mood disorders, with sleep and rhythm changes frequently occurring prior to and during mood episodes. Wrist-worn actigraphs are increasingly utilized to measure ambulatory activity rhythm and sleep patterns.

Methods: A comprehensive study using subjective and objective measures of sleep and biological rhythms was conducted in 111 participants (40 healthy volunteers [HC], 38 with major depressive disorder [MDD], 33 with bipolar disorder [BD]). Participants completed 15-day actigraphy and first-morning urine sample to measure 6-sulfatoxymelatonin levels. Sleep and biological rhythm questionnaires were administered: Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), Munich Chronotype Questionnaire (MCTQ), Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Actigraph data were analyzed for sleep and daily activity rhythms, light exposure, likelihood of transitioning between rest and activity states.

Results: Mood groups had worse subjective sleep quality (PSQI) and biological rhythm disruption (BRIAN), and higher objective mean nighttime activity than controls. Participants with BD had longer total sleep time, higher circadian quotient, lower 6-sulfatoxymelatonin levels than HC group. The MDD group had longer sleep onset latency, higher daytime probability of transitioning from rest to activity than HCs. Mood groups displayed later mean timing of light exposure. Multiple linear regression analysis with BRIAN scores, circadian quotient, mean nighttime activity during rest and daytime

probability of transitioning from activity to rest explained 43% of variance in quality of life scores. BRIAN scores, total sleep time, probability of transitioning from activity to rest explained 52% of variance in functioning (all $p<0.05$).

Conclusions: Disruption in biological rhythms is associated with poorer functioning and quality of life in bipolar and major depressive disorder. Investigating biological rhythms and sleep using actigraphy variables, urinary 6-sulfatoxymelatonin and subjective measures provides evidence of widespread sleep and circadian system disruptions in mood disorders.

Keywords: biological rhythms, quality of life, functioning, actigraphy, mood disorders

2.1 Introduction

Changes in biological rhythms and sleep occur during most major mood episodes, and are linked to clinical severity in both Major Depressive Disorder (MDD) and Bipolar Disorder (BD) (Malhi and Kuiper, 2013). Notably, sleep disturbances are frequently reported by patients prior to the onset of either depressive or (hypo)manic mood episodes (Van Meter et al., 2016; Jackson et al., 2003), indicating sleep and biological rhythm disturbances persist beyond mood episodes (Geoffroy et al., 2015; Mondin et al., 2017).

While polysomnography is the gold standard of measuring sleep, use of actigraphy to estimate sleep and daily activity rhythms offers the advantage of continuous, ambulatory monitoring. Though research using measurement of activity and sleep patterns in mood disorders has grown exponentially, methods of collection, aggregation and analysis of these data are still under development. Use of objective measures of activity and sleep can help in designing the mechanistic rationale for chronotherapeutic treatments of these disorders. In this context, a deeper investigation of patterns, rhythms, and variability of activity is becoming increasingly relevant in the context of mood disorders (Scott et al., 2017). For instance, the DSM-5 has revised the core diagnostic criteria for (hypo)mania to include increased energy or activity in addition to mood changes. This has led to a multidomain conceptualization of activation, as a combination of objectively observable motor activity and subjective experience of energy, caused by physiological underpinnings. While previous reports have shown that activity in bipolar depression is more variable and lower than that of healthy controls (HCs), manic episodes appear to differ in variability in activity patterns, and the

robustness of these patterns, rather than activity levels. Additionally, activity levels in bipolar euthymia are lower in comparison to HCs and MDD (Scott et al., 2017). Furthermore, a recent study found that individuals with BD had desynchronization of diurnal heart rate rhythms with sleep and activity rhythms, while ultradian rhythms in negative affect and irritable mood were more highly correlated with sleep and heart rate rhythms (Carr et al., 2018).

The circadian system is synchronized to the environment through the process of entrainment involving time-keeping factors called *zeitgebers,* which set the master clock located in the suprachiasmatic nucleus (SCN). The most robust of these factors is light, though physical activity, eating patterns and social activity also play an important role (Mistlberger and Antle, 2011). Social rhythms and light have served as targets for chronobiological interventions for mood disorders, such as bright light therapy, interpersonal and social rhythm therapy, and blue-blocking glasses (Frank et al., 2005; Henriksen et al., 2016; Al-Karawi and Jubair, 2016). However, levels of illuminance exposure have been under-investigated in mood disorders. Similarly, melatonin secretion may provide additional insight into biological rhythms in mood disorders, given its central role on entrainment. It has been shown that manic subjects display higher daytime melatonin secretion compared to depressed individuals and controls (Nováková et al., 2015).

Subjective disturbance in sleep and biological rhythms in mood disorders has been extensively investigated using clinical questionnaires. For instance, evening chronotype is more prevalent in BD (Wood et al., 2009), and is associated with worse depressive

symptom severity (Au and Reece, 2017). Patients with BD have displayed dysfunctional beliefs about sleep, which may lead to maintenance of sleep disturbances in this population (Harvey et al., 2005). Additionally, subjective biological rhythm disturbances have been found to predict quality of life (QOL) in BD (Cudney et al., 2016) and functional impairment in BD and HCs (Pinho et al., 2016; Giglio et al., 2010). However, prior studies investigating sleep and biological rhythm disturbances have been limited by sample size, inadequate duration of actigraphy data collection, and use of either subjective or objective measurements of sleep and activity. To our knowledge, no prior study has reported on differences in light exposure, or subjective and objective measures of biological rhythms and sleep, in both BD and MDD; neither are there reports on objective measurements of activity and sleep as predictors of functional impairment and QOL in mood disorders.

Here, we present a study where sleep and biological rhythm disruption was assessed through a variety of measures, including subjective questionnaires, actigraphy-measured activity, sleep patterns and light exposure, as well as nocturnal melatonin secretion in a well-characterized sample of individuals with MDD and BD. We hypothesize that sleep and biological rhythms will be more disrupted in the mood disorder groups compared to HCs, on both subjective and objective measures. We additionally hypothesize that impairment on measures of functional outcomes and QOL will be linked to worse subjective and objective markers of sleep and biological rhythms.

2.2 Methods and Materials

2.2.1 Participants

Participants were between the ages of 18 and 65, had a diagnosis of major depressive disorder (MDD) or bipolar disorder (BD), or had no history of a psychiatric diagnosis (healthy controls, HC). To determine clinical diagnosis, psychiatric history and current mood state, the Mini International Neuropsychiatric Interview (MINI) English Version 6.0.0. was administered to all participants (Sheehan et al., 1998).

Participants were excluded from the study if they (1) had a current or lifetime history of a sleep disorder, (2) had used melatonin within 2 months prior to commencing the study, (3) were employed in shiftwork, (4) were currently using prescribed sleep medications (e.g. trazodone, zopiclone, zolpidem) or sedative-hypnotic medications (e.g. benzodiazepines, barbiturates), (5) were currently using illicit substances as sleep aids or recreationally (e.g. marijuana), (6) currently used prescription analgesics with sedative effects, such as opioids or non-steroidal anti-inflammatory drugs, (7) met current criteria for current alcohol/substance abuse or dependence according to the MINI or (8) if they were currently experiencing jet lag from a recent trip outside of the Eastern Standard Time. Participants were recruited from two psychiatric outpatient clinics (the Mood Disorders Program and Women's Health Concerns Clinic) at St Joseph's Healthcare Hamilton, Ontario, and from online and local community advertisements. All study participants gave written informed consent to take part in the study, with accordance to

the Declaration of Helsinki, as approved by the Hamilton Integrated Research Ethics Board (Project #14-251).

2.2.2 Study Procedures

Participants made two visits to St Joseph's Healthcare Hamilton over the span of 15 days. During the first visit, written informed consent was obtained. Clinical diagnosis, psychiatric history and mood state were determined using the MINI. Participants were then fitted with a configured actigraph (Actiwatch 2, Philips Respironics Inc., Biolynx, Montreal, Canada), which they were instructed to wear throughout the 15-day duration of the study. A sleep log was given to participants in order to record periods of actigraph removal, morning wake-up times, naps, and bedtimes. Subjects were then given a urine sample container and were instructed to collect the first morning urine sample on day 15. On day 15, participants returned for a second and final visit, and were asked to return the actigraph, urine container and sleep log.

2.2.3 Clinical Assessments

Subjective disturbances in biological rhythms were assessed using the self-report Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009). The BRIAN is an 18-item self-report questionnaire, developed for use in mood disorder populations, which monitors biological rhythm disruption over the preceding 15 days, evaluating sleep, activity, eating patterns, and social patterns. The BRIAN questionnaire additionally included a previously unvalidated 3-item measure of chronotype.

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-report questionnaire developed to assess sleep quality in individuals with affective disorders (Buysse et al., 1989). The Munich Chronotype Questionnaire (MCTQ) was used to assess chronotype, based on the mean mid-sleep point, calculated from the self-reported sleep onset and offset on work-free days, corrected for sleep debt accumulated throughout the week (Roenneberg et al., 2003). Functioning was assessed using the Functioning Assessment Short Test (FAST), a self-report checklist developed for use in psychiatric patients, which assesses functioning in six domains: autonomy, occupational and cognitive functioning, financial issues, interpersonal relationships and leisure time (Rosa et al., 2007).

The World Health Organization's Quality of Life Assessment - BREF (WHOQOL-BREF), was administered to evaluate quality of life (World Health Organization, 1996). Daytime sleepiness was measured using the Epworth Sleepiness Scale (ESS) (Johns, 1991). The clinician-administered Young Mania Rating Scale (YMRS) was used to assess symptoms of mania (Young et al., 1978), and Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess depressive symptoms (Montgomery and Åsberg, 1979). Finally, a General Circadian Disorder Checklist, consisting of 3 clinician-administered items, was used to confirm that participants in the study did not have a current circadian disorder.

2.2.4 Urinary 6-sulfatoxymelatonin

A first morning urine sample was used to measure melatonin's primary urinary metabolite, 6-sulfatoxymelatonin (6-SM). Participants were instructed to refrigerate the urine sample prior to arrival to the laboratory on the day that it was collected. 6-sulfatoxymelatonin levels were normalized to creatinine concentration, expressed as ng/mg. Creatinine levels in the urine were analyzed by the Hamilton Regional Laboratory Medicine Program at St Joseph's Healthcare Hamilton (license#4037) using the Jaffe method (kinetic alkaline picrate) (Abbott Diagnostics, Santa Clara, California, USA). Samples were then analyzed for 6-SM using ELISA for 6-SM (Buhlmann Diagnostics Corporation, Amherst, New Hampshire, USA). Assay sensitivity was 0.14 ng/mL. The intra- and inter-assay coefficients of variation were 7.1% and 11.9%, respectively.

2.2.5 Actigraphy

Objective measures of sleep and daily activity rhythms were obtained using the Actiwatch 2 monitor. Actigraphy data were extracted by a specialized software, which distinguishes sleep from waking, and information collection regarding sleep and activity phases. These data were collected in one-minute epochs continuously for 15 days and retrieved for processing using the Philips Actiware software Version 6.0. Default sleep/wake thresholds were used to determine sleep and activity periods throughout the observation period. Sleep and illuminance measures were extracted and averaged to produce a single value for each measure, using Actiware software. Total sleep time (TST) - amount of hours spent asleep, excluding time spent awake in bed; sleep onset latency

(SOL) - number of minutes encompassing the transition from wakefulness to sleep; sleep efficiency (SE) - percentage of TST divided by time in bed, where lower SE is reflective of worse sleep quality; and wake after sleep onset (WASO) - number of minutes spent active from sleep onset to sleep offset. Mean Mid Sleep Time was calculated manually as the midpoint between sleep onset and get up time, adjusting for SOL. Any periods during which actigraphs were removed, as recorded using the sleep log, were excluded from the analysis. Additionally, visual inspection was used to identify and remove intervals ≥ 20 minutes where no movement was observed. Intervals with ≥4 excluded hours were identified, and the 24-hour period surrounding these intervals was removed from the analysis. Data were split into weekend and weekday data, of which only weekday data were used in the final analyses.

Illuminance variables extracted from Actiware , included the following variables for rest, active, and sleep periods: light exposure, average light, maximum light, time above light threshold (1000 lux), percent invalid light.

2.2.6 Statistical Analysis

Statistical analyses were performed using R (Version 3.2.2) *(Team, 2016)* and Python (Version 2.7.6).

2.2.6.1 Cosinor & non-parametric actigraphy

Cosinor analysis was employed to evaluate daily activity rhythms, using the R package “cosinor”. This analysis fits time-series data to a single cosine wave, giving

characteristics of the wave which include (1) MESOR – midline estimating statistic of the rhythm; (2) amplitude of the rhythm; (3) acrophase – a measure of the timing of peak activity; (4) circadian quotient – the ratio of amplitude to MESOR, which can be used as a measure of the strength of an individual rhythm. Individual circadian activity rhythm periods were calculated using non-linear regression, where a period was assigned through extracting a peak between T=23h and T=25h from the periodogram. This individual analysis allowed for more accurate representation of each participant's endogenous period.

Applicability of cosinor analysis can be limited by non-sinusoidality of time series data, and inability to detect fragmentation of rhythms, which has led to the introduction of non-parametric circadian rhythm analysis. This approach complements cosinor analysis by addressing rhythm fragmentation, stability, average levels and timing of activity (Thomas et al., 2015). Non-parametric circadian activity rhythm analysis was employed using the nparACT (v.0.8) package, which obtained the following measures: (1) Interdaily stability (IS) – a measure of the strength of coupling between the endogenous circadian activity rhythm and external zeitgebers. IS ranges from 0 to 1, with higher values indicating greater synchronization of circadian activity rhythm to the external environment. It is the normalized ratio of the variance of the mean rhythm over the total variance throughout the study duration. (2) Intradaily variability (IV) is a measure of circadian activity rhythm fragmentation, which is the ratio of the mean square difference between successive measurements to the overall variance of the data. IV ranges from 0 to 2, with higher values indicating higher fragmentation of the circadian rhythm. (3) 5

consecutive hours of lowest average activity amplitude (L5), (4) start time of L5, (5) 10 consecutive hours with highest amplitude values (M10), (6) M10 start time. (7) Relative amplitude (RA) of the rhythm, consisting of the difference between average M10 and L5, divided by sum of activity during these 15 hours. RA ranges from 0 to 1, with higher values representing higher amplitude.

We calculated nighttime activity mean -- the total of the activity counts measured every night during sleep intervals, averaged across the data collection period. Higher nighttime activity mean indicates higher sleep disturbance.

2.2.6.2 Light Exposure

Minute-by-minute illuminance levels, as obtained from actigraphy, were used to calculate whole-day time above light threshold (TAT) and mean timing above light threshold (MLiT) – a measure of the average time during which TAT occurs. Four different thresholds of illuminance were used to calculate TAT and MLiT: 10 lux (dim light), 100 lux, 500 lux (approximate illuminance of office lighting), 1000 lux (approximate illuminance of an overcast day).

2.2.6.3 Transition Probabilities

We estimated transition probabilities from actigraphy data based on methods described by Ortiz et al. (Ortiz et al., 2016) and a prior publication from our group (Allega et al., 2018). A transition series was created between two states (rest and activity), estimated from the probability of staying in each state for each of the individual minute-

by-minute activity records. The probability of transitioning from each state was then calculated, as the probability that after a series of minute-by-minute epochs of remaining in one state, the individual would switch to the other state or vice versa (Ortiz et al., 2016). This analysis was performed using the Hidden Markov Model (HMM) - a statistical model based on the theory that a time series of observed data is the outcome of a hidden state variable. The hidden state sequence, therefore is dependent on the current state. The hmmlearn package (Version 0.2.0) was used in Python to build the model and calculate its parameters, using the Baum-Welch algorithm. We separated data into nighttime and daytime periods, where the nighttime period was defined as the lowest 8 mean activity hours, and the other 16 hours were defined as the daytime period (Ortiz et al., 2016). The mean activity counts of rest and activity states (μ_R and μ_A), and the probability of transitioning between states ($P_{rest\text{-}active}$ [pRA] and $P_{active\text{-}rest}$ [pAR]) were calculated for day and night. Higher values of pRA are indicative of the individual staying in an active state.

2.2.6.4 Group Differences

Chi square tests were used to evaluate differences in categorical variables across groups. One-way ANOVAs and Kruskal-Wallis tests were used to compare continuous variables across groups. Next, we performed a multiple linear regression analysis to predict FAST and WHOQOL-BREF scores using variables obtained from actigraphy, the BRIAN questionnaire, and MCTQ chronotype. We tested whether assumptions were met for linear regression analysis, including normality, linearity, independence of variance,

multicollinearity and homoscedasticity. Variables were transformed to meet regression assumptions if they were not normally distributed.

2.3 Results

Of the total of 131 participants enrolled in the study, 20 withdrew for a variety of reasons (family emergency, work schedule, exams, failure to report current melatonin use). The final sample consisted of 111 subjects (MDD = 38; BD = 33; HC = 40) (See Table 1 for demographic and clinical characteristics of the sample). A larger proportion of the BD group was unemployed compared to the HCs, and participants in the HC group had more years of education ($p<0.05$). In terms of clinical variables, participants with BD had an earlier age of onset than those with MDD ($p<0.05$). Approximately 36% of both mood groups were currently in a major depressive episode. Expectedly, the MDD and BD groups had higher scores than controls on the MADRS, indicating worse depressive symptoms. The BD group had higher manic symptoms (YMRS) compared to HCs (all $p<0.001$), although no participants with bipolar disorder met criteria for a current (hypo)manic, or mixed episode. In addition, both the MDD and BD groups had worse functioning (FAST) and quality of life (WHOQOL-BREF) ($p<0.0001$) (Table 2).

2.3.1 Subjective Assessments of Sleep and Biological Rhythms

Both the MDD and BD groups had higher scores on the BRIAN questionnaire and its subdomains, excluding Chronotype, indicating higher disturbances in all 4 domains of biological rhythmicity (all $p\leq0.001$) (See Table 2). Sleep quality according to the PSQI

was also subjectively worse in both mood groups. No significant differences were found between the mood groups in subjective sleep quality (PSQI) or subjective biological rhythm disturbance (BRIAN). No differences were detected in daytime sleepiness (ESS), or chronotype (MCTQ, BRIAN; $p>0.05$) between the groups. It should be noted that as PSQI and ESS were added later in the study, data for 15 participants were missing for ESS, and data for 18 participants were missing for PSQI.

2.3.2 Objective Assessments of Sleep and Biological Rhythms

See Tables 3 and 4 for a summary of comparisons between BD, MDD and HC in objective measures of sleep, biological rhythms and light exposure.

2.3.2.1 Urinary 6-sulfatoxymelatonin

Levels of 6-sulfatoxymelatonin, adjusted for creatinine were lower in BD compared to the control group, indicating lower levels of overnight melatonin secretion in BD ($p<0.05$). Five subjects (n=2 HC, n=1 MDD, n=2 BD) did not complete urinary 6-SM sampling.

2.3.2.2 Actigraphy Variables

The BD group had a lower circadian quotient ($p=0.01$), longer TST ($p=0.03$), higher mean nighttime activity ($p=0.005$) and trended toward higher WASO ($p=0.09$) than HC. The MDD group had longer SOL ($p=0.03$), and higher mean nighttime activity ($p=0.01$) than HC. In terms of light exposure, the MDD group had a later peak of light

exposure above 500 lux (MLiT500) and 1000 lux (MLiT1000) than HC ($p<0.05$). The BD group had later peak of MLiT1000 than HC ($p<0.05$). No differences were observed between groups for any of the circadian cosinor variables or mean light exposure at rest, activity or sleep. Data from 1 HC, 3 MDD participants had to be removed from light analyses, due to a constant, high level of light exposure in these participants (>200,000 lux throughout 24h). Figures 1a and 1b provide a visualization of mean activity and light exposure patterns across 15 days for all participants.

2.3.2.3 Transition State Probabilities

The MDD group had higher pRA throughout the day compared to the HC group ($p<0.05$). Both the MDD and BD subjects had higher nighttime activity than HC ($p\leq0.01$).

2.3.2.4 Predicting Functioning and Quality of Life from Actigraphy, BRIAN Scores and Chronotype

Multiple linear regression analysis revealed that QOL (WHOQOL-BREF) was independently predicted by BRIAN scores (Std $\beta=-0.58$, $t=-7.39$, $p<0.001$), circadian quotient (Std $\beta=0.26$, $t=2.79$, $p=0.006$), nighttime μ_{rest} (Std $\beta=-0.19$, $t=-2.33$, $p=0.02$), and daytime pAR (Std $\beta=0.19$, $t=2.05$, $p=0.04$), explaining 43% of variance in QOL ($F_{13,97}=7.28$, Adj. $R^2=0.43$, $p<0.001$). Functioning, in turn, was independently predicted by BRIAN scores (Std $\beta=0.71$, $t=9.91$, $p<0.001$), total sleep time (Std $\beta=-0.28$, $t=-2.84$,

p=0.005), and daytime pAR (Std β=-0.19, t=-2.37, p=0.02), explaining 52% of variance in functioning ($F_{13,97}$=10.28, Adj. R^2=0.52, p=<0.001) (Table 5).

2.4 Discussion

In this comprehensive investigation of objective and subjective biological rhythms and sleep in BD and MDD, several key findings emerged: we found evidence of disturbances in subjective sleep quality and biological rhythms in both mood groups, though no differences were found in daytime sleepiness or chronotype. Both mood groups had higher mean nighttime activity than controls. Participants with BD had a sleep profile characterized by a longer TST, higher circadian quotient and lower urinary 6-SM levels than controls. The MDD group had longer SOL, and higher probability of transitioning from rest to activity during the day than controls, suggesting that MDD patients are more likely to stay active throughout the day, than healthy volunteers. Disruptions in the sleep and biological rhythm profiles of the two disorders were not restricted to any specific domain – rather, disruptions were widespread across each category of variables. We measured subjective disruptions, sleep variables, transition state probabilities, activity, light exposure, daily activity rhythms and urinary 6-sulfatoxymelatonin, finding at least one disturbance in each category of measurements.

An important, novel finding of our study is that we were able to predict QOL and functional impairment using subjective and objective measures of sleep and biological rhythms in individuals with mood disorders. Our results are consistent with prior reports of disturbances in subjective biological rhythms according to the BRIAN being predictive

of poor functioning (Pinho et al., 2016; Giglio et al., 2010) and worse QOL (Cudney et al., 2016) in BD. Specifically, we found that QOL scores were predicted by circadian quotient, mean activity count during nighttime rest, and probability of transitioning from activity to rest during the day. Functional impairment was predicted by shorter TST, and lower probability of transitioning from activity to rest during the day. To our knowledge, no prior study has investigated the link between QOL, functioning and objectively measured biological rhythms or sleep in a mood disorder population. However, several prior studies linked subjective reports of sleep disturbance to poorer functioning and quality of life in mood disorders and other populations. For instance, in a large study of individuals with BD, functioning and QOL were worse in those with longer or shorter self-reported sleep duration as compared to normal sleepers (Gruber et al., 2009). Elsewhere, BD individuals with delayed sleep phase had worse functioning (Steinan et al., 2016). Similarly, in a population-based study, individuals with self-reported non-restorative sleep and insomnia symptoms reported worse functioning than their counterparts (Zhang et al., 2013). Finally, greater disruptions in subjective and objective sleep measures were linked to worse functioning and health-related QOL in elderly individuals: sleep-related dysfunction was prospectively linked to health-related QOL, while daily functioning was prospectively linked to percentage of nighttime sleep after a 6-month follow-up (Martin et al., 2010).

In terms of profiles of light exposure, participants with MDD had later mean timing of light exposure over 500 and 1000 lux, although average time spent exposed to light levels above this threshold did not differ from controls. Similarly, BD subjects had

later mean timing of light exposure over 1000 lux. To the best of our knowledge, very little is known about light exposure in mood disorders, in spite of reports evaluating light exposure therapies in mood disorder patients, such as bright light therapy (Al-Karawi and Jubair, 2016), and blue-blocking glasses (Henriksen et al., 2016). A previous study suggested that higher early-life light exposure may influence earlier age of onset for patients with BD (Bauer et al., 2012). In healthy elderly individuals, levels of light exposure have been found to be negatively associated with depression scores (Ichimori et al., 2013). Light influences the circadian system directly through the SCN, where information about light intensity is transmitted through specialized intrinsically photosensitive retinal ganglion cells directly in the retina, which contain a photopigment called melanopsin, with peak sensitivity to blue light. These cells additionally signal to the ventro-lateral preoptic nucleus, which plays an important role in non-circadian sleep promotion. Light is therefore interlinked with the homeostatic and circadian processes of sleep, creating complex effects on mood, and alertness (Reviewed by (Stephenson et al., 2012)).

The BRIAN questionnaire has been suggested to be able to discriminate biological rhythm disturbances specifically between mood disorder groups, and across mood states, with the greatest disturbances seen in individuals with bipolar disorder in a current depressive episode (Mondin et al., 2017). Euthymic individuals with BD had a similar degree of disruption as currently depressed individuals with MDD, corroborating evidence that subsyndromal BD symptoms persist into remission (Mondin et al., 2017). Due to limited sample size, we were unable to compare depressed with euthymic patients.

However, an interesting finding was that worsening of biological rhythm disturbances in patients with BD and MDD was not accounted for by chronotype or daytime sleepiness. In addition to measuring disruptions in the rhythmicity of sleep and activity, one of the defining features of the BRIAN is that it includes measures of social rhythm disruption and eating pattern disruption. The two mood groups displayed worse disruption in all 4 BRIAN subdomains, including the social and eating subdomains. As mentioned previously, these factors also appear to play a role in the timekeeping mechanisms of mammals (Mistlberger and Antle, 2011). These findings are consistent with previous studies showing that disruption in social rhythms was associated with earlier onset of depressive and (hypo)manic episodes in BD (Shen et al., 2008), and depressive symptom severity in MDD (Szuba et al., 1992). Moreover, interpersonal and social rhythm therapy is a well-established treatment for BD (Frank et al., 2005).

We also found that levels of first morning urinary 6-SM were lower in individuals with BD, indicating lower overnight melatonin secretion in BD subjects. A prior study found morning melatonin levels to be lower in cerebrospinal fluid, but not in serum of patients with BD, and vice-versa for MDD (Bumb et al., 2016). Another study using salivary melatonin found that young mood disorder patients had delayed and reduced melatonin secretion, indicating a lower amplitude of secretion (Robillard et al., 2013). We did not find differences in morning urinary 6-SM levels between MDD and healthy volunteers. Investigations of melatonin levels in MDD have provided some inconsistencies, where some studies have found increased nocturnal serum melatonin in MDD patients (Rubin et al., 1992) others have found decreased nocturnal serum

melatonin and increased morning serum melatonin (Khaleghipour et al., 2012; Crasson et al., 2004). A study investigating serum and urinary 6-SM secretion found that there appears to be a phase shift in melatonin secretion for depressive patients, with higher melatonin secretion in the morning, as opposed to nighttime, and a delay of serum melatonin secretion (Crasson et al., 2004).

Activity patterns beyond sleep are an emerging topic in mood disorders. A systematic review of activity patterns in depression found heterogeneous results with regards to actigraphy-measured nighttime activity in patients with current depressive disorders, and hypothesized that nighttime activity is higher in depressive patients, though this is not reflected in measurements of sleep efficiency and sleep duration (Burton et al., 2013). This was in part consistent with our findings, as both MDD and BD groups had higher nighttime activity levels than controls, and no differences were found in sleep efficiency. Additionally, SOL was higher in the MDD group compared to healthy volunteers. In our sample, BD subjects had longer TST than HCs. This was consistent with findings from recent systematic reviews and meta-analyses, which found euthymic and depressed BD patients to have longer TST (De Crescenzo et al., 2017; Geoffroy et al., 2015). Mean nighttime activity, a variable which was highly correlated with WASO, was higher in BD than HCs.

A large-scale actigraphy study of (n=339) euthymic participants with BDI, BDII and MDD and HCs investigating timing, levels and variability of activity found participants with BDI and BDII to have higher variability in activity from day to day during the afternoon and evening respectively, compared to controls (Shou et al., 2017).

However, we did not find any differences between groups on measures of interdaily stability or intradaily variability. Circadian quotient, a measure of individual rhythm strength, was higher in bipolar disorder than the healthy volunteer group. Similarly, we did not find differences in chronotype between the groups, which is inconsistent with prior findings of BD being associated with eveningness (Melo et al., 2017).

Several limitations of our study must be noted. The cross-sectional nature of the study, does not allow us to explore the causal relationships between sleep and biological rhythm disturbances and mood in our samples. Our sample included individuals who were receiving treatment with various of psychotropic medications, which may have influenced patterns of melatonin secretion through effects on the circadian oscillator given prior reports that antipsychotics, lithium and sodium valproate influence sleep and circadian rhythms in BD (Geddes and Miklowitz, 2013). In addition, we were unable to study differences in biological rhythms and sleep in depressed and euthymic patients, as our sample size for each subgroup was insufficient to make meaningful comparisons. Future studies should additionally recruit participants in mixed states, as daily activity rhythms, transition state probabilities and light exposure profiles have been under-investigated in this mood state. Future investigations should consider tracking objective parameters of social and eating patterns in mood disorders. Finally, actigraphy, while having high concordance with polysomnography in healthy adults, has less accuracy in populations with worse sleep quality, where quiet wakefulness might be scored as sleep. However, longer recording periods (i.e. 7-14) nights improve sleep parameter stability (Van De Water et al., 2011). Strengths of our study include the use of 15-day actigraphy,

which allows for a representative analysis of sleep and daily activity rhythm patterns. Our methods of collecting data regarding both subjective and objective sleep and activity variables, along with light exposure and nocturnal 6-SM secretion, provide a comprehensive look at biological rhythms variables across BD and MDD. To our knowledge, this is the first investigation to examine objective actigraphy and melatonin profiles, in addition to subjective measures of sleep and biological rhythms in both BD and MDD.

2.5 Conclusions

We found that subjective and objective sleep and biological rhythm disturbances are strongly associated with quality of life and functioning in BD and MDD. Investigating sleep and biological rhythms in mood disorders is a complex, multidimensional process, which can involve a variety of subjective and objective measures. Subjective measures of sleep and biological rhythm disruptions consistently detect worsening in these variables for BD and MDD in a population with mixed current mood state. Measuring sleep, transition state probabilities, activity, light exposure, daily activity rhythms and urinary 6-sulfatoxymelatonin in addition to subjective measures may eventually become a clinically viable and useful tool to help provide diagnostic accuracy for clinicians. However, further longitudinal investigations must be conducted to analyze temporal relationships between sleep, biological rhythms and mood episodes.

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2.7 Declaration of Conflicting Interests

The Authors declare no conflict of interest with regard to the content of this manuscript.

2.8 Acknowledgements

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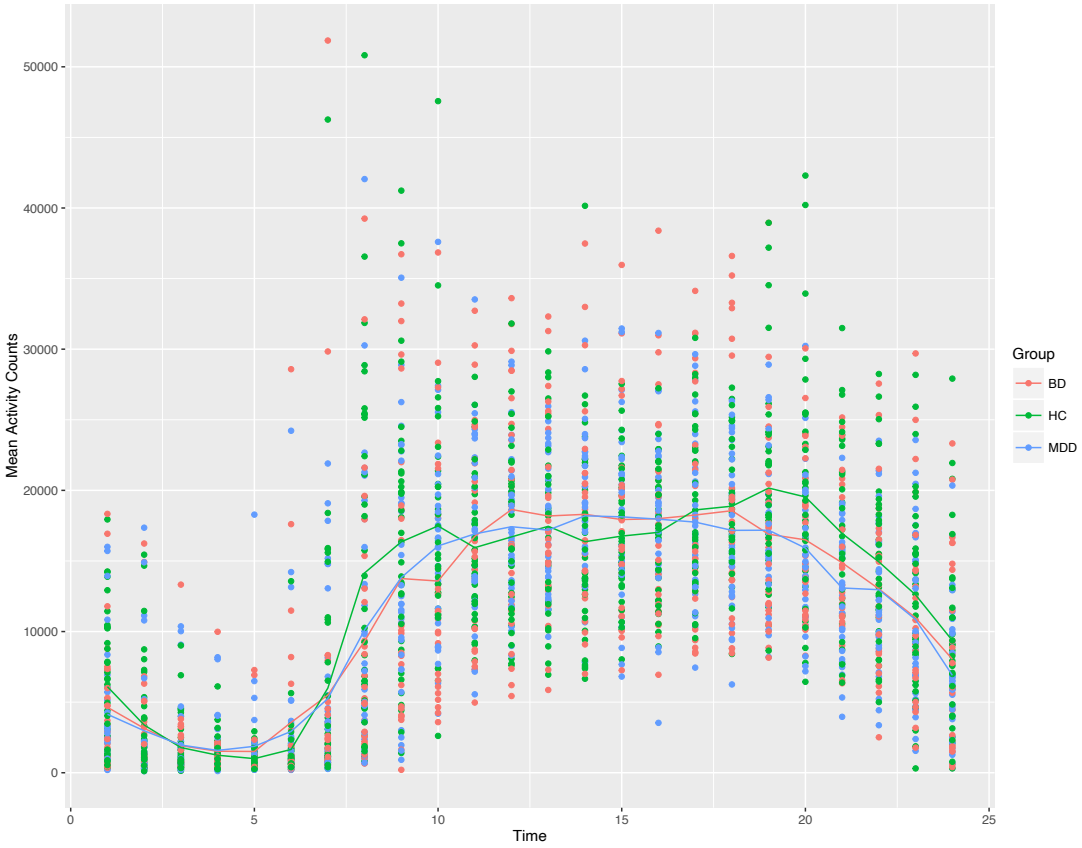

Figure 1a) Plot of mean hourly activity counts from 1 am to midnight for all participants. Coloured lines denote group means. Activity patterns show a circadian pattern.

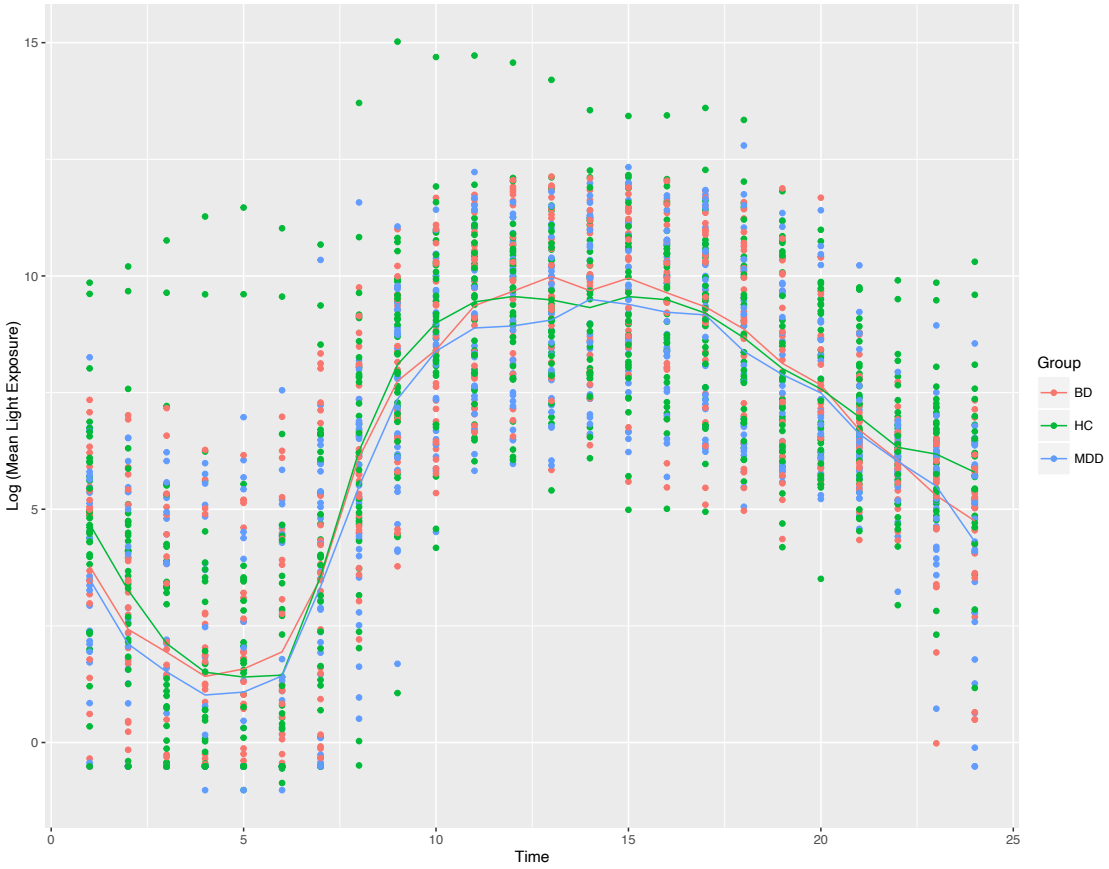

Figure 1b) Plot of log of mean light exposure (in lux) from 1 am to midnight for all participants. Coloured lines denote group means. Data from 4 participants were removed, as they displayed a constant, abnormally high level of light exposure (i.e. >200,000 lux) throughout the day. Mean light levels were log transformed in order to better visualize the circadian pattern throughout the day. (BD: Bipolar Disorder, HC: Healthy Control, MDD: Major Depressive Disorder)

Table 1: Demographics and Clinical Variables						
	HC (n=40) N(%) Mean±SD Median[IQR]	**MDD (n=38) N(%) Mean±SD Median[IQR]**	**BD (n=33) N(%) Mean±SD Median[IQR]**	**Statistic**	**p**	**Mult. Comp.**
Currently Euthymic	n/a	24 (63.2%)	21 (63.6%)	n/a	n/a	
Currently Depressed	n/a	14 (36.8%)	12 (36.4%)	n/a	n/a	
Age	30 [20]	39 [22.75]	37 [17]	χ^2=3.19	n.s.	
Sex						
Male	20 (50%)	13 (34.2%)	14 (42.4%)	χ^2=1.99	n.s.	
Female	20 (50%)	25 (65.8%)	19 (57.6%)			
Employed						
Unemployed	1 (2.5%)	11 (28.9%)	11 (33.3%)	χ^2=12.85	0.002	BD>HC
Employed or student	39 (97.5%)	27 (71.1%)	22 (66.7%)			
BMI[$]	24.7±4.1	26.7±5.4	27.2±5.2	F=2.52	0.08	
Years of Education[$]	17.5±3.3	16.0±2.6	15.7±3.4	F=3.57	0.03	HC>BD
Age of Onset	n/a	20.7±10.6	15.4±6.6	t=5.34	0.02	BD<MDD
Season Tested						
Summer	18 (45.0%)	17 (44.7%)	17 (51.5%)	χ^2=0.41	n.s.	
Winter	22 (55.0%)	21 (55.3%)	16 (48.5%)			
Psychiatric Medications						
Antidepressants		20 (52.6%)	20 (60.6%)			
Antipsychotics		7 (18.4%)	15 (45.5%)			
Mood Stabilizers		7 (18.4%)	15 (45.5%)			
Anxiolytics		3 (7.9%)	8 (24.2%)			

MADRS	2 [2.25]	8.5 [8.00]	11 [11.00]	χ^2=42.23	<0.0001	BD>HC, MDD>HC
YMRS	1 [2.00]	1 [2.00]	2 [3.00]	χ^2=9.04	0.01	BD>HC

[$]log transformed; [%]square root transformed, [x] squared transformed (BD: Bipolar Disorder, BMI: Body Mass Index, HC: Healthy Control, IQR: Interquartile range, MADRS: Montgomery Asberg Depression Rating Scale, MDD: Major Depressive Disorder, SD: Standard Deviation, YMRS: Young Mania Rating Scale)

Table 2: Group Differences in Measures of Subjective Biological Rhythms, Sleep, Functioning and Quality of Life

	HC (n=40) Mean ± SD Median [IQR]	MDD (n=38) Mean ± SD Median [IQR]	BD (n=33) Mean ± SD Median [IQR]	Statistic	p	Mult. Comp.
BRIAN	31 [9.00]	45 [19.50]	43 [17.00]	χ^2=31.30	<0.001	BD>HC MDD>HC
BRIAN – Sleep	10 [4.50]	14 [5.75]	14 [5.00]	χ^2=16.33	<0.001	BD>HC, MDD> HC
BRIAN – Activity	7.5 [3.00]	14 [6.00]	12 [7.00]	χ^2=33.54	<0.001	BD>HC, MDD>HC
BRIAN – Social	6 [2.25]	8 [4.75]	8 [5.00]	χ^2=13.60	0.001	BD>HC, MDD>HC
BRIAN – Eating Pattern	7 [3.00]	9 [7.00]	10 [4.00]	χ^2=14.64	<0.001	BD>HC, MDD>HC
ESS (n=32,34,36)	6 [7.00]	8 [5.50]	7.5 [5.25]	χ^2=0.26	n.s.	
MCTQ – Chronotype[$]	3.9±1.3	4.2±1.3	4.6±1.7	F=1.78	n.s.	
BRIAN – Chronotype	6 [2.00]	7 [2.75]	7 [3.00]	χ^2=5.05	0.08	
PSQI (n=32,32,29)	4 [3.00]	9 [5.25]	7 [7.00]	χ^2=14.86	<0.0001	BD>HC, MDD>HC
FAST[%]	9.2±8.9	23.1±15.2	26.1±15.0	F=21.03	<0.0001	BD>HC MDD>HC
WHOQOL-BREF[§]	308.1±40.5	247.5±71.6	245.0±57.9	F=15.12	<0.0001	BD<HC, MDD<HC

[$]log transformed; [%]square root transformed, [§]squared transformed

(BD: Bipolar Disorder, BRIAN: Biological Rhythm Interview of Assessment in Neuropsychiatry, ESS: Epworth Sleepiness Scale, FAST: Functioning Assessment Short Test, HC: Healthy Control, IQR: Interquartile range, MCTQ: Munich Chronotype Questionnaire, MDD: Major Depressive Disorder, PSQI: Pittsburgh Sleep Quality Index, SD: Standard Deviation, WHOQOL-BREF: The World Health Organization's Quality of Life Assessment – BREF)

Table 3: Group Differences for Objective Measures of Sleep and Biological Rhythms						
Urinary 6-Sulfatoxymelatonin						
	HC (n=38) Mean ± SD Median [IQR]	**MDD (n=37) Mean ± SD Median [IQR]**	**BD (n=31) Mean ± SD Median [IQR]**	**Statistic**	**p**	**Mult. Comp.**
Urinary 6-SM, adjusted for creatinine (ng/mg)	34.3 [22.5]	30.7 [30.6]	19.5 [27.8]	χ^2=7.74	0.02	BD<HC (p<0.05)
Absolute Urinary 6-SM levels (ng/L)	46.3 [34.4]	45.9 [35.4]	28.9 [71.5]	χ^2=3.68	n.s.	
Sleep Variables						
	HC (n=36) Mean ± SD Median [IQR]	**MDD (n=34) Mean ± SD Median [IQR]**	**BD (n=27) Mean ± SD Median [IQR]**			
TST	5.6±0.8	6.1±1.2	6.3±0.9	F=3.40	0.03	BD>HC (p=0.03)
Sleep Onset Latency[%]	11.5±10.4	16.0±9.8	12.1±7.7	F=3.21	0.04	MDD>HC (p-0.03)
Sleep Efficiency	0.8±0.06	0.8±0.08	0.8±0.07	F=1.02	n.s.	
WASO	41.4±18.9	50.5±20.2	51.9±19.0	F=2.85	0.06	BD>HC (p=0.09)
Awakenings	21.3±7.8	24.4±8.8	24.2±6.7	F=1.62	n.s.	
Mean Mid Sleep Time[S]	3.7±0.9	3.5±1.2	4.0±1.3	F=1.11	n.s.	
Cosinor Analysis						
Mesor[S]	212.7±52.5	198.9±51.1	201.1±71.2	F=0.84	n.s.	
Amplitude	142.8±49.7	147.4±49.9	159.0±58.9	F=0.75	n.s.	
Period	24 [0.67]	24 [0.13]	24 [0.06]	χ^2=3.44	n.s.	
Acrophase	10.8 [10.9]	12.1 [10.3]	11.1 [11.4]	χ^2=0.77	n.s.	
Non-parametric Circadian Rhythm Statistics						
IS	0.50±0.13	0.50±0.13	0.50±0.16	F=0.01	n.s.	
IV	0.86±0.20	0.78±0.21	0.75±0.22	F=2.35	n.s.	

CQ	0.68±0.19	0.75±0.19	0.81±0.21	F=4.24	0.01	BD>HC (p=0.01)
Relative Amplitude	0.90 [0.08]	0.88 [0.09]	0.91 [0.13]	χ^2=0.27	n.s.	
L5^{S}	25.8±28.7	25.5±23.1	26.6±25.5	F=0.09	n.s.	
L5 Start Time	1.59 [1.41]	2.14 [2.25]	1.98 [1.52]	χ^2=2.06	n.s.	
M10	322.2± 71.0	317.3± 80.8	329.5 ± 105.1	F=0.15	n.s.	
M10 Start Time	10.3±2.9	9.6±2.1	10.3± 2.7	F=0.87	n.s.	
Transition Probabilities						
pAR day	0.05±0.01	0.05±0.01	0.05±0.01	F=1.34	n.s.	
μ_A day^{S}	504.79± 131.26	455.49± 112.01	460.13± 142.34	F=1.69	n.s.	
pRA day^{S}	0.05± 0.01	0.06± 0.01	0.06±0.02	F=4.16	0.01	MDD > HC
μ_R day$^{\%}$	98.4± 48.9	76.6± 44.8	74.1 ± 57.1	F=2.96	0.05	
pAR night	0.09± 0.02	0.09 ± 0.03	0.09± 0.02	F=0.50	n.s.	
μ_A night^{S}	69.8 ± 40.0	58.6± 37.3	57.4 ± 47.5	F=2.40	0.09	
pRA night	0.10 ± 0.02	0.10± 0.03	0.10 ±0.02	F=0.23	n.s.	
μ_R night	0.00 [0.00]	0.00 [0.09]	0.00 [0.06]	χ^2=6.72	0.03	n.s.
Nighttime Activity Mean$^{\%}$	5201.2± 2371.6	6997.6± 2982.0	7472.6± 3072.8	F=6.30	0.002	BD>HC (p=0.005) MDD>HC (p=0.01)

^{S}log transformed; $^{\%}$square root transformed, §squared transformed

6SM: 6-sulfatoxymelatonin, CQ: Circadian Quotient, IS: Interdaily Stability, IV: Intradaily Variability, L5: mean activity during lowest 5 consecutive hours of activity, M10: mean activity during highest 10 consecutive hours of activity, pAR: Probability of transitioning from active to rest state, pRA: Probability of transitioning from rest to active state, TST: Total Sleep Time, WASO: Wake After Sleep Onset, μ_A: mean activity during active period, μ_R: mean activity during rest period

Table 4: Group Differences in Light Exposure Variables (4 abnormally high light exposure outliers removed (i.e. >200,000 lux exposure continuously throughout 24 hours))

	HC (n=35) Mean ± SD Median [IQR]	MDD (n=31) Mean ± SD Median [IQR]	BD (n=27) Mean ± SD Median [IQR]	Statistic	p	Mult. Comp.
Rest:						
Light Exposure – Rest[S]	2608.6± 12300.5	658.1±1147.6	1263.3± 3860.1	F=0.69	n.s.	
Light Average – Rest[S]	7.6±24.7	3.4±6.7	4.0±8.3	F=0.55	n.s.	
Light Max – Rest	13.0[26.4]	13.0[25.8]	13.1[24.1]	χ^2=0.46	n.s.	
TAT 1000 lux – Rest	0 [0]	0 [0]	0 [0]	χ^2=1.72	n.s.	
Light Percent Invalid – Rest	8.0[15.5]	6.1[8.7]	10.3[9.7]	χ^2=1.00	n.s.	
Active:						
Light Exposure – Active	158699.2 [399448.1]	115889.1 [263881.8]	161905.6 [244900.7]	χ^2=1.95	n.s.	
Light Average – Active	190.7[340.1]	162.0[403.6]	234.4[343.9]	χ^2=1.51	n.s.	
Light Max – Active	8765.8[19269.4]	8864.2[14215.4]	13383.2 [14685.1]	χ^2=2.35	n.s.	
TAT 1000 lux – Active	22.0 [70.5]	19.6 [43.0]	24.8 [40.1]	χ^2=1.90	n.s.	
Light Percent Invalid – Active	7.9 [10.4]	6.0 [8.8]	5.4 [10.8]	χ^2=1.03	n.s.	
Sleep:						
Light Exposure – Sleep[S]	395.0± 854.8	522.7± 1081.9	1172.7± 3846.8	F=1.54	n.s.	

Light Average – Sleep^{S}	5.4±22.9	2.2±3.5	3.8±8.4	F=0.97	n.s.	
Light Max – Sleep	9.1 [17.7]	9.0 [18.8]	12.4 [21.8]	χ^2=2.94	n.s.	
TAT 1000 lux – Sleep	0 [0]	0[0]	0[0]	χ^2=1.07	n.s.	
Light Percent Invalid – Sleep	7.4 [15.4]	6.6 [10.0]	11.2 [10.0]	χ^2=0.81	n.s.	
Time Above Light Threshold						
TAT: 10 lux	487.6± 172.4	436.2± 153.8	457.0± 166.3	F=0.81	n.s.	
TAT: 100 lux$^{\%}$	185.4± 129.2	146.5±109.3	155.0± 102.7	F=0.96	n.s.	
TAT: 500 lux	49.8 [111.4]	46.9 [90.2]	57.4 [79.7]	χ^2= 0.42	n.s.	
TAT: 1000 lux^{S}	71.4± 83.4	55.3± 59.3	64.0 ± 55.1	F=0.21	n.s.	
Mean Light Timing Above Threshold						
MLiT: 10 lux§	14.1±1.0	14.2±0.8	14.1±0.7	F-0.14	n.s.	
MLiT: 100 lux	13.8±1.0	13.9±1.1	13.8±0.9	F=1.25	n.s.	
MLiT: 500 lux	13.1±1.2	13.9±1.4	13.7±1.1	F=3.75	0.02	MDD > HC
MLiT: 1000 lux	13.4 [1.7]	14.0 [2.0]	13.8 [0.8]	χ^2=8.60	0.01	BD > HC, MDD > HC

^{S}log transformed; $^{\%}$square root transformed, §squared transformed

BD: Bipolar Disorder, HC: Healthy Control, IQR: Interquartile Range, MDD: Major Depressive Disorder, MLiT: Mean timing of above-threshold light exposure, TAT: Time above threshold

Table 5: Linear Regression Predicting Functioning and Quality of Life from BRIAN, MCTQ and Actigraphy Variables				
	WHOQOL-BREF Std. β	**P value**	**FAST Std. β**	**P value**
Intercept		<0.001		0.02
BRIAN	-0.58	<0.001	0.71	<0.001
MCTQ Chronotype	-0.01	n.s.	0.16	0.06
MLiT10	0.14	n.s.	-0.14	0.09
CQ	0.26	0.006	-0.13	n.s.
IV	0.12	n.s.	0.06	n.s.
IS	0.00	n.s.	0.07	n.s.
Number of Awakenings	-0.03	n.s.	0.10	n.s.
TST	0.04	n.s.	-0.28	0.005
SOL	-0.14	n.s.	0.06	n.s.
μR night	-0.19	0.02	-0.08	n.s.
pAR day	0.19	0.04	-0.19	0.02
pAR night	0.03	n.s.	0.17	0.07
Nighttime Activity Mean	-0.07	n.s.	0.03	n.s.
Adj .R^2	**0.43**		**Adj. R^2**	**0.52**
$F_{13, 97}$	**7.28**		**$F_{13, 97}$**	**10.28**
P	**<0.001**		**P**	**<0.001**

BD: Bipolar Disorder, BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, CQ: Circadian quotient, FAST: Functioning Assessment Short Test, L5: mean activity during lowest 5 consecutive hours of activity, MCTQ: Munich Chronotype Questionnaire, MLiT: Mean timing of above-threshold light exposure, pAR – probability of transitioning from activity to rest, SOL: sleep onset latency TST: Total sleep time, μ_R: mean activity during rest period, WHOQOL-BREF: World Health Organization's Quality of Life Assessment – BREF

Chapter 3: Longitudinal Prediction of Severity of Postpartum Depression using Objective and Subjective Sleep and Biological Rhythms

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Abstract

Objective:

The perinatal period is marked by numerous disturbances in sleep and biological rhythms. These disturbances may serve as good targets for prevention and intervention strategies aiming to reduce postpartum depression (PPD). This study aimed to use sleep and biological rhythms in conjunction with demographic and clinical factors to predict symptoms of PPD in a longitudinal cohort of women as they transition from pregnancy to the postpartum period.

Methods:

One hundred women in the 3rd trimester of pregnancy were enrolled and 79 completed the study. At baseline, demographic and clinical variables were collected through validated clinical questionnaires. Objective measures of sleep and biological rhythms were collected using clinical actigraphy and urinary 6-sulfatoxymelatonin. These variables were used to predict depressive symptom severity at 6-12 weeks postpartum through linear regressions and machine learning (ML) analyses. Then, we performed a second set of ML analyses on an externally collected data set (n=33) to further confirm/validate the accuracy of the predictive algorithm.

Results:

Light exposure, nighttime activity, and number of awakenings, in conjunction with clinical and demographic variables, accounted for 50% of variance in the severity of

postpartum depressive symptoms ($F_{10,68}$ =8.70, p<0.001). ML analyses confirmed that subjective biological rhythms, objective sleep light exposure, 6-sulfatoxymelatonin and clinical variables in pregnancy add to the prediction of postpartum depression severity.

Conclusions:

Subjective and objective sleep, light and rhythm markers collected during pregnancy can be used in conjunction with demographic and clinical variables to predict postpartum depressive symptom severity.

Keywords: postpartum depression, actigraphy, sleep, biological rhythms, mood disorders.

3.1 Introduction

Disruptions in sleep and biological rhythms are hallmarks of major depressive and bipolar disorders, which occur both before the onset of mood episodes (Jackson et al., 2003; Van Meter et al., 2016), and as part of their clinical presentation (Harvey, 2008; Germain and Kupfer, 2008). The perinatal period is marked by frequent disturbances in sleep and biological rhythms (Gallaher et al., 2018). Though the importance of these disturbances is often overlooked (Romero and Badr, 2014), there may be consequences to the mother including negative impact on health and quality of life (Cai et al., 2017; Da Costa et al., 2010), and disrupted sleep in infants (Field et al., 2007). Importantly, worsening of sleep and biological rhythms from pregnancy to postpartum have been linked with worsening in depressive symptoms during this period (Krawczak et al., 2016). Postpartum depression (PPD) is a debilitating disorder, which occurs in between 7-13% of women (Gavin et al., 2005). A better understanding of the specific risk factors for postpartum depressive worsening is crucial to inform effective preventive strategies for PPD. Although sleep and biological rhythm disturbances may serve as good targets for prevention and intervention strategies aiming to reduce PPD, previous investigations in this area have been limited by small sample size, poor clinical characterization, cross-sectional design, or use of only subjective or objective assessments of sleep and biological rhythms (Gallaher et al., 2018).

This study aims to characterize subjective and objective sleep and biological rhythms during pregnancy, and to use these variables along with well-established demographic and clinical factors to predict severity of postpartum depressive symptoms

in a cohort of women at high and low risk of PPD. We took advantage of objective ambulatory measures such as actigraphy, which permits the monitoring of sleep and biological rhythms in a naturalistic setting. We used both linear regression and machine learning models to predict depressive symptoms during the postpartum period and to test these models on an independently collected data set containing actigraphy and clinical variables. Unlike traditional statistical approaches, machine learning provides the ability to detect multivariate, complex patterns represented by multiple variables collected through high-throughput technologies such as actigraphy.

3.2 Method

3.2.1 Participants

From November 2015 to May 2018, 100 women with and without a history of mood disorders were enrolled in the study. Study participants were recruited from the Women's Health Concerns Clinic at St Joseph's Healthcare Hamilton, and from the community. Written informed consent to participate in the study was obtained from all subjects. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by the Hamilton Integrated Research Ethics Board (Project #0602). Participants were enrolled in the study if they: (1) were ≥ 16 years of age; (2) had no history of head trauma with loss of consciousness ≥5 minutes; (3) did not meet criteria for a current major depressive or hypo/manic episode; (4) were ≥ 27 weeks pregnant at

enrollment. Upon enrollment, mood state and diagnosis were established in all participants using the Mini International Neuropsychiatric Interview English Version 6.0.0 (Sheehan et al., 1998) according to Diagnostic and Statistical Manual-IV-TR criteria.

3.2.2 Clinical Assessments

Depressive symptom severity was assessed using the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report instrument validated for use in pregnancy and the postpartum period (Cox et al., 1987; Murray and Cox, 1990), and the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). A cut-off score of >12 on the EPDS is accepted as a significant risk of perinatal depression (Cox et al., 1987). Severity of manic symptoms were assessed using the 11-item Young Mania Rating Scale (YMRS) (Young et al., 1978). Anxiety symptoms were measured using the 7-item self-reported Generalized Anxiety Disorder – 7 (GAD-7) scale (Spitzer et al., 2006). Subjective disturbance in biological rhythms was measured using the 21-item Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN), a self-report questionnaire which can be subdivided into 5 domains: sleep, general activity, social, eating pattern and chronotype (Giglio et al., 2009). Seasonality was established using the self-administered Seasonal Pattern Assessment Questionnaire (SPAQ) (Raheja et al., 1996). The SPAQ provides a continuous global seasonality score. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Daytime sleepiness was assessed using the 8-item Epworth Sleepiness Scale

(ESS) (Johns, 1991). A prenatal version of the Postpartum Depression Predictors Inventory-Revised (PDPI-R) was administered to screen for psychosocial risk factors of PPD (Beck, 2003; Beck, 2002). The big five personality traits (Neuroticism, Openness to Experience, Agreeableness, Conscientiousness, and Extraversion) were assessed using the 44-item Big Five Inventory (BFI) (John and Srivastava, 1999). Finally, emotion regulation was assessed using the 36-item Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004).

3.2.3 Study Design

Participation in the study included visits to St Joseph's Healthcare Hamilton during the 3rd trimester of pregnancy, and 6-12 weeks postpartum. During the pregnancy visit, participants were interviewed using the MINI, MADRS, and YMRS and completed a series of questionnaires (PDPI-R, EPDS, PSQI, GAD-7, ESS, BRIAN, BFI, DERS, SPAQ). Participants were fitted with a configured actigraph (Actiwatch 2; Philips Respironics Inc, Biolynx, Montreal, QC, Canada), to be worn for 2 weeks. A sleep log was given to participants to record actigraph removal periods, morning wake-up times, naps, and bed times. Participants were given a package containing a urine sample container, and were instructed to collect the first morning urine sample on the last day of actigraphy data collection. Samples were returned to the lab for processing on the morning of urine sample collection. At 6-12 weeks postpartum, participants came in for a brief follow-up visit, where the EPDS was completed. The period of 6-12 weeks was selected based on meta-regression results from a previous systematic review showing

higher incidence of postpartum depression at 2 and 3 months compared to 4-12 months (Gavin et al., 2005).

3.2.4 Urinary 6-Sulfatoxymelatonin

First morning urine samples were used to measure levels of the major urinary metabolite of melatonin, 6-sulfatoxymelatonin (6-SM). On the morning of collection, participants were instructed to collect and refrigerate the sample until the sample was picked up or dropped off later that morning. Analysis of 6-SM levels was performed using enzyme-linked immunosorbent assay for 6-SM (Buhlmann Diagnostics Corporation, Amherst, NH, USA), with 0.14ng/mL assay sensitivity, intra-assay coefficient of variation of 7.1% and inter-assay coefficient of variation of 11.9%.

Urine creatinine levels were measured by the Hamilton Regional Laboratory Medicine Program at St Joseph's Healthcare Hamilton (license no. 4037) using the Jaffe method (kinetic alkaline picrate; Abbott Diagnostics, Santa Clara, CA, USA). The final 6-SM concentration was calculated as a ratio of 6-SM (ng) to creatinine (mg), to account for urine volume (Chang et al., 2016; Nowak et al., 1987; Sturgeon et al., 2014).

3.2.5 Actigraphy

Actigraphy data were extracted from Actiwatch 2 monitors using Philips Actiware software (v 6.0). Details regarding actigraphy data pre-processing and variable extraction are available in supplementary material and elsewhere (Slyepchenko et al., 2019). In brief, data were obtained in one-minute epochs continuously for 15 days. Variables

concerning sleep and illuminance were extracted from Actiware: total sleep time (TST, hours); sleep onset latency; sleep efficiency (SE); wake after sleep onset (WASO); number of awakenings; mean mid sleep time was calculated as the midpoint between sleep onset and offset. Rest, active, sleep and daily illuminance variables were extracted: light exposure, average light, maximum light, time above light threshold (TAT; 1000 lux), percent invalid light. Cosinor analysis was performed using the cosinor R package (Sachs, 2015) yielding: (1) MESOR; (2) amplitude; (3) acrophase; (4) circadian quotient. Non-parametric circadian activity rhythm analysis, conducted using the nparACT (v 0.8) package, obtained: (1) intradaily variability; (2) Interdaily stability; (3) L5 - 5 consecutive lowest-activity hours; (4) start of L5; (5) ten consecutive hours with highest activity (M10), and (6) start of M10; (7) relative amplitude of the rhythm. Nighttime activity mean and standard deviation (SD) were calculated. Raw data were used to evaluate TAT and mean timing above light threshold (MLiT) across the whole day, using different light thresholds: 10, 100, 500, 1000 lux. Transition probabilities were calculated using methods described by Ortiz et al (Ortiz et al., 2016), and in previous publications from our group (Allega et al., 2018; Slyepchenko et al., 2019), using the Python hmmlearn package (v 0.2.0). This yielded daytime and nighttime mean activity counts in each state, and probability of transitioning from rest to active (pRA) and active to rest (pAR) states.

3.2.6 Statistical Analysis

Statistical analyses were performed using R (Version 3.6.1) and Python (Version 2.7.6). Actigraphy data for 7 participants were not available, and 6-SM for 5 participants was not available.

3.2.6.1 Linear Regression

Multiple linear regression analysis was performed to model postpartum EPDS scores using variables from the pregnancy visit. Variables were selected using sequential replacement using the leaps package in R (v. 3.0). We tested whether assumptions were met for linear regression analysis, including independence of variance, normality, linearity, multicollinearity and homosceidasticity. Variables were transformed if they did not meet regression assumptions.

3.2.6.2 Machine Learning

Six machine learning (ML) methods were used to build predictive models using pregnancy variables to predict postpartum EPDS scores with the caret R package: principal component regression (PCR), partial least squares regression (PLS), elastic net regression, random forest (RF), bagged classification and regression trees (Bagged CART), and extreme gradient boosting (XGBoost) (Chen and Guestrin, 2016). PCR uses principal components of explanatory variables as variables in a linear regression model. PLS is a method of linear regression which extracts components that account for the largest possible correlation between predictive variables in the model and the outcome

variable. Elastic net regularization uses L1 and L2 regularization penalties to produce a regression model. Bagged CART is a tree-based ensemble method, which creates numerous regression trees, each with their own bootstrap sample of the training set, combining them to prevent overfitting of the ensemble in a process called bootstrap aggregation. Similarly, RF is another tree-based ensemble method which is used to reduce the variance of individual regression trees, by inducing numerous regression trees. RF uses a bootstrap sample of instances and a subset of variables to generate each tree. The final output is the mean regression of the trees. XGBoost is a highly optimized tree-based boosting ensemble method which uses a gradient descent algorithm to minimize error in models, regularization, and the weighted Quantile Sketch algorithm, among other methods to optimize model building (Chen and Guestrin, 2016).

The minimum Redundancy Maximum Relevance (mRMR) method was used to select model features. The mRMR feature selection method selects features with maximum relevance with respect to the outcome variable, while minimizing redundancy within the selected feature set of the model (Peng et al., 2005). Data were scaled and centered, and 5-nearest-neighbor imputation (Fix and Hodges Jr, 1951) was performed on missing data within completed pregnancy visits.

First, we split the data from the present project into a 75% training and 25% test set. Our second approach used the entire present data set as the training set, and an external, independently collected data set (Krawczak et al., 2016) as the test set. To select the optimal models, 10-fold cross-validation was performed, where hyperparameters were chosen in the context of mRMR-selected features.

The following metrics were used to evaluate the performance of the ML models: R^2, Spearman's Rho, Root Mean Squared Error (RMSE), normalized RMSE (NRMSE), Mean Absolute Error (MAE).

3.2.6.3 External Test Set

To test the performance of our machine learning approaches, we used a data set (thoroughly described in (Krawczak et al., 2016)) which was previously independently collected in the Frey lab using a majority of the measures that were used to collect the current data set. In brief, 33 study participants meeting the same criteria as outlined above participated in 2 study visits during the 3rd trimester of pregnancy and at 6-12 weeks postpartum. Actigraphy (21 days), clinical interviews (MINI, MADRS, YMRS) and questionnaires (PDPI-R, EPDS, PSQI, ESS, BRIAN) were collected in the same time points. Notably, participants did not complete urine sample collection.

3.3 Results

3.3.1 Demographics and Clinical Characteristics

Of 100 women who completed the pregnancy visit, 79 women returned for a follow-up at 6-12 weeks postpartum (see Table 1 for demographic and clinical characteristics of the sample). Of these women, 54.4% had a history of MDD or BD, and 48.1% met criteria for a current or lifetime anxiety disorder. Of the women enrolled in the study, 48.1% had a family member with a diagnosed psychiatric disorder. Women in the sample were on average 31.19 years old, with a Body Mass Index of 25.01. Participants

were enrolled at 31.85 weeks gestation, and had an average 17.11 years of education. A majority of the women were not taking psychotropic medication (84.8%), were taking prenatal vitamins (88.6%), and were not taking iron supplements (60.8%). Most women were partnered or married (94.9%), had a household income >$50,000 (81.0%), and had earned a University degree (60.8%).

3.3.2 Modeling Postpartum EPDS from Pregnancy Sleep, Biological Rhythms and Clinical Data

In a multiple linear regression analysis which used data from the pregnancy visit (See Table 2), PPD symptoms according to the EPDS were independently predicted by participants' age (Std. β=0.23, t=2.56,p=0.013); neuroticism (Std. β=0.44, t=4.19,p<0.001); number of awakenings (Std. β=-0.40, t=-2.75,p=0.008); timing of exposure to light levels over 100 lux (Std. β=0.49, t=3.52,p<0.001) and 500 lux (Std. β=-0.29, t=2.07, p=0.043); standard deviation of nighttime activity (Std. β=-0.24, t=-2.61,p=0.011); but not taking iron supplements (Std. β=0.31, t=1.83); PDPI-R total score (Std. β=0.12, t=1.16); BRIAN (Std. β=0.05, t=0.46); or pRA night (Std. β=0.25, t=1.82). This model explained 50% of the variance in EPDS scores ($F_{10,68}$ =8.70, Adj. R^2=0.50, p<0.001).

3.3.3 Machine Learning Analyses

Two sets of machine learning (ML) analyses were performed: the first based only on the newly collected sample (n=79), which had lengthier clinical characterization, and

offered additional variables such as anxiety symptom severity, personality trait and emotion regulation assessments, and melatonin metabolite sampling. The second analysis was performed using fewer predictor variables, using an external data set that was independently collected by our lab (n=33).

Prior to variable selection, 72 possible predictor variables were extracted from the available data set. We used mRMR to identify 13 most predictive features, according to training model performance. Results from the 6 machine learning models (Table 3) showed that the model with the lowest test NRMSE was bagged CART (0.61), followed by PLS (0.64), RF (0.67), XGBoost (0.78), elastic net (0.81), and PCR (0.87). For the best-performing algorithm (bagged CART), the variables were ranked according to their feature importance (Figure 1c): BRIAN, TST, Neuroticism, MLiT100, M10 start time, Percent Invalid Light Daily, GAD7, TAT1000, taking Iron supplements, 6SM levels, age, ESS, BRIAN Chronotype.

For analyses using the independent test set, a total of 51 predictor variables were available across both studies prior to variable selection. MRMR was used to identify the 9 most predictive features, according to training model performance. Results from the ML models show that the RF model had the lowest test NRMSE (0.84), followed by bagged CART (0.89), PLS (0.91), elastic net (096), PCR (0.98), and XGBoost (1.08). For the best-performing algorithm (bagged CART), the variables were ranked according to their feature importance (Figure 1f): BRIAN, comorbid anxiety, PDPI-R total score, MLiT100, TST, TAT1000, age, parity, nighttime activity SD.

3.4 Discussion

The present study found that objective sleep and biological rhythm markers collected during the 3rd trimester of pregnancy can be used in conjunction with demographic and clinical variables to predict 50% of the variance of depressive symptom severity at 6-12 weeks postpartum. Additionally, this study demonstrated the feasibility of using pregnancy assessments to identify the most useful predictors of postpartum depressive symptoms, using traditional linear regression and ML techniques. Using ML techniques, we were able to identify a set of variables which are together predictive of PPD symptoms, finding some novel predictors of PPD, and some which confirmed previous findings.

3.4.1 Subjective Biological Rhythms, Sleep and Sleepiness

Subjective biological rhythm disruption during pregnancy according to the BRIAN had the highest variable importance in predicting postpartum EPDS across both sets of ML models. However, BRIAN was not a significant independent predictor of EPDS according to the linear regression model. In prior analyses of the external test set in this study, changes in BRIAN from pregnancy to postpartum were predictive of changes in EPDS from pregnancy to postpartum (Krawczak et al., 2016).

Daytime sleepiness appeared in one of the ML models. A prior study found that high daytime sleepiness during the 3rd trimester of pregnancy was linked to symptoms of PPD, though this study did not investigate other sleep or circadian parameters (Sarberg et al., 2016).

Chronotype appeared with low variable importance in one of the ML models. Sharkey and colleagues have previously found that 3rd trimester eveningness preference was linked to higher depressive symptoms during the 2nd and 6th weeks postpartum (Sharkey et al., 2013).

Neither method of mRMR feature selection or sequential replacement model selection found subjective sleep quality according to the PSQI to be a significant predictor of postpartum EPDS. This is consistent with prior findings, which have shown that PSQI during the 3rd trimester of pregnancy was not a predictor of symptoms of depression at 3 months postpartum (McEvoy et al., 2019).

3.4.2 Light exposure

An interesting finding of our study is that several variables related to light exposure during pregnancy were linked to postpartum depressive severity. A measure which describes the timing of light exposure over 100 lux throughout the day (MLiT100) was a significant independent predictor of depressive severity in the linear regression model and had high variable importance in the ML models. In the linear regression model, earlier timing of light exposure over 500 lux (MLiT500) was also a significant predictor of higher EPDS, while in the ML models, time spent above the 1000 lux threshold (TAT1000) appeared in both ML models. Finally, daily percentage of invalid white light appeared in one of the ML models. To our knowledge, this is the first investigation to look at the effect of light exposure during pregnancy on severity of postpartum depressive symptoms. This finding may indicate not only a predictor for

future depressive severity, but may also indicate the opportunity for a preventive lifestyle modifications. Our study provides a rationale for future investigation on the use of light-based therapies, like bright light therapy, in pregnancy in order to prevent postpartum depressive worsening. Previous small studies that investigated bright light therapy (Swanson et al., 2018) and blue-light blocking glasses (Bennett et al., 2009) as treatment for PPD have found preliminary evidence for post-treatment improvements in depressive symptoms in response to both treatments.

3.4.3 Objective Sleep Variables

Several objective sleep parameters measured by actigraphy in pregnancy were predictive of severity of postpartum EPDS scores. Lower number of awakenings during pregnancy was a significant independent predictor of higher postpartum EPDS in the linear regression model. TST appeared in both ML models, being the second-to-highest variable importance in one of the models. These findings are, however, in contrast with a smaller longitudinal study (n=34), which found that neither objective sleep variables (TST, SE, WASO, sleep fragmentation, sleep disturbance or number of daytime naps) nor subjective sleep (according to the PSQI) obtained during the 3rd trimester were predictive of mood in the first 2 weeks postpartum (Coo Calcagni et al., 2012). It is possible that sleep variables are only effective predictors of postpartum EPDS in conjunction with other variables in our models.

3.4.4 Objective Biological Rhythms

Overnight melatonin secretion, obtained via morning 6-SM levels, was a predictor of EPDS symptoms in an ML model. A previous investigation by Sharkey and colleagues has found that later dim light melatonin onset phase and longer phase angle during the 3rd trimester of pregnancy were associated with higher depressive symptoms during the 2nd and 6th week postpartum in a small sample (n=12) (Sharkey et al., 2013). Start time of M10 was also a predictor of EPDS in one of the ML models, while lower variability of nighttime activity was a significant predictor of higher EPDS symptoms, according to the linear regression model. Variability of nighttime activity also appeared in one of the ML models but had relatively lower importance in the model. This emphasizes the importance of including variability measures while modeling circadian activity rhythms (Krane-Gartiser et al., 2019).

3.4.5 Clinical and Demographic Variables

Previously established clinical and demographic risk factors for PPD include having a psychiatric disorder diagnosis, particularly a previous depressive episode, and psychosocial risk factors such as marital discord, poor social support, presence of life stressors, gestational diabetes, depression during pregnancy, and higher neuroticism (Lee et al., 2000; O'hara and Swain, 1996; Silverman et al., 2017). Unsurprisingly, severity of anxiety and having comorbid diagnosis of anxiety were predictors of EPDS severity in the ML models. Anxiety during pregnancy is a well-known strong risk factor for PPD (Robertson et al., 2004). Neuroticism was a predictor of depressive symptom severity in

both the linear regression model and ML models. This is consistent with prior studies reporting that neuroticism is associated with higher risk for PPD and severity of postpartum depressive symptoms (Martin-Santos et al., 2012; Lee et al., 2000). Total score on the PDPI-R had high importance in one of the ML approaches. The PDPI-R assesses well-established risk factors for PPD, including social support, marital satisfaction, having a history of depression, self-esteem, socioeconomic status, marital status, and whether the pregnancy was unplanned or unwanted (Beck, 2002). However, in our study, linear regression analyses did not find PDPI-R to be a significant predictor of EPDS scores. In a prior analysis of the external test set used in this study, PDPI-R was also not found to be an independent predictor of EPDS scores in a linear regression model (Krawczak et al., 2016). We believe that this indicates that the risk factors assessed by PDPI-R may have been accounted for by the other variables.

Older age was a significant predictor of higher EPDS scores in the linear regression model and in both ML models. This is consistent with a prior population-based study showing that older age is a risk factor for PPD for women with a history of depression, while younger age is a risk factor for PPD in those without a history of depression (Silverman et al., 2017). Taking iron supplements appeared as a predictor in one of the ML analyses but was not an independent predictor of EPDS scores in the linear model. Prior investigations have had largely negative findings regarding the impact of iron supplementation during pregnancy on postpartum mood, though postpartum iron supplementation has been found effective in several studies (Reviewed in: (Wassef et al., 2019)). Parity was a variable included in one of the ML models. Prior studies have

indicated that there may be an influence of parity on sleep parameters during the perinatal period (Christian et al., 2019), though in a past meta-analysis, parity was not a significant risk for PPD development (O'hara and Swain, 1996).

3.4.6 Data Analytic Approach

Differences between results from the ML and regression approaches in this study highlight several limitations of using traditional statistical methods and ML in complex clinical samples. In this study, we used two sets of ML analyses, one of which used a 75-25% split for training and validation vs testing. The second used an external data set for testing the algorithm. In spite of the larger sample size in the analysis that used the external data set for testing (n=112, compared to n=79), model accuracy decreased in this set of analyses. This can be attributed to several factors: first, the external data set had a less thorough clinical characterization of the study participants and did not evaluate melatonin metabolite levels. Actigraphy assessments in this study lasted for 3 weeks, compared to 2 weeks in the original study dataset. This is reflective of real-world study and clinical conditions, where separate investigations or individual clinicians may use different clinical assessments and biological sampling methods, leading to discrepancies in variables that can be entered into the model. In the case of differences in available variables, it is not possible to adjust the original ML models. On the other hand, a benefit of ML models in this context is that they can be used to detect more subtle, complex, non-linear relationships between variables, represented across multiple variables obtained from actigraphy and clinical questionnaires. Linear regression models cannot account for

these, even if linear interactions are specified between variables. While applying results from a linear regression model, on the other hand, variables can be removed from the model if they are unavailable for the other data set. We argue, therefore, that using both of these types of analyses can be used as a practice to provide complementary information when modeling complex phenomena. Results from the traditional statistical modelling produced by this study can be used for the purpose of inference, while the ML methods may be used to attempt to improve prediction.

3.4.7 Strengths & Limitations

One limitation of this study is its modest sample size, particularly for ML analyses. However, our sample is the largest prospective study looking at objective sleep and biological rhythms in the perinatal period to date. Few of our study participants developed full-blown PPD, as they were being followed by clinicians throughout their pregnancy and postpartum period. However, the proportion of participants who did develop PPD is consistent with population-wide studies which have found 7-13% of women to have PPD (Gavin et al., 2005). In a prospective design, such as this, where women were clinically well upon enrolment, several hundreds of participants would need to be followed to collect a sample large enough to test prediction of actual diagnosis of PPD. Finally, we did not assess whether participants were currently following sleep hygiene guidelines or if they received psychotherapy during the study. These interventions may have influenced sleep, rhythms and mood within our sample.

Strengths of this study include a thorough clinical characterization of the study sample. We used well-validated clinical diagnostic interviews and self-reported questionnaires to assess mood and clinical history. In addition, multiple objective (actigraphy, melatonin collection) and subjective measures (BRIAN, PSQI, SPAQ, ESS) of sleep and rhythms were used within our sample. Another strength of our study is its prospective design, which allowed us to track the mood of women from the 3rd trimester of pregnancy to 6-12 weeks postpartum. Finally, we used a separately collected data set in order to evaluate the performance of our ML models.

Declaration of Interest

None.

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Table 1: Demographics and Clinical Characteristics										
Newly Collected Dataset						**External Data Set**				
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
Age	31.19	3.71	31	28	33.5	31.15	3.85	32	29	33
Body Mass Index	25.01	5.76	23.56	21.37	26.26	25.98	8.33	20.86	23.7	25.8
Years of Education	17.11	2.61	17	16	18					
Weeks Gestation	31.85	3.24	32	29	35	30.97	2.71	31	28	33
PDPI-R Total Score	4.76	4.75	3	2	6	3.39	4.49	2	1	5
DERS	90.86	23.48	78	60	97					
GSS	8.42	4.45	9	5	11.5					
Neuroticism	2.81	0.86	2.75	2.25	3.44					
Openness	3.221	0.5	3.2	2.9	3.6					
Conscientiousness	4	0.61	4.11	3.56	4.44					
Agreeableness	4.01	0.52	4	3.67	4.44					
Extraversion	3.38	0.82	3.38	2.62	3.88					
MADRS[$]	7.99	6.64	7	3	11	3.76	4.05	3	1	5
YMRS[$]	2	1	3	2.18	2.22	0.82	1.63	0	0	1
GAD7	4.38	4.86	3	1	6					
ESS	8.24	3.88	8	6	11					
PSQI	9.82	3.9	9	8	11	5.64	3.60	4	3	7
BRIAN	39.15	9.98	39	31.5	46.5	26.45	6.84	25	21	31
BRIAN Chronotype	6.11	1.83	6	5	7	5.21	1.08	5	4	6
EPDS – Pregnancy[$]	6.2	4.89	5	2	9.5	2.88	3.39	2	0	3
EPDS – 6-12 Weeks Postpartum	5.86	4.62	5	2.5	8.5	3.94	4.03	3	1	5
	N (%)					**N (%)**				
Marital Status										
Single	4 (5.1%)					1 (3.0%)				

Partnered	75 (94.9%)					32 (97.0%)				
Household Income										
> 50,000	64 (81.0%)					25 (75.8%)				
< 50,000	15 (19.0%)					8 (24.2%)				
Highest Level of Education										
Less than High School	1 (1.3%)					0 (0.0%)				
High School Diploma or Trade Certificate	2 (2.5%)					6 (18.2%)				
College certificate/ diploma	28 (35.4%)					7 (21.2%)				
University – bachelor's degree and higher	48 (60.8%)					20 (60.6%)				
Mood Disorder History										
No History of Mood Disorders	36 (45.6%)					18 (54.5%)				
History of Major Depressive or Bipolar Disorder	43 (54.4%)					15 (45.5%)				
Current or Past Anxiety Disorder										
Yes	38 (48.1%)					7 (21.2%)				
No	41 (51.9%)					26 (78.8%)				
Shift Worker										
Yes	7 (8.9%)									

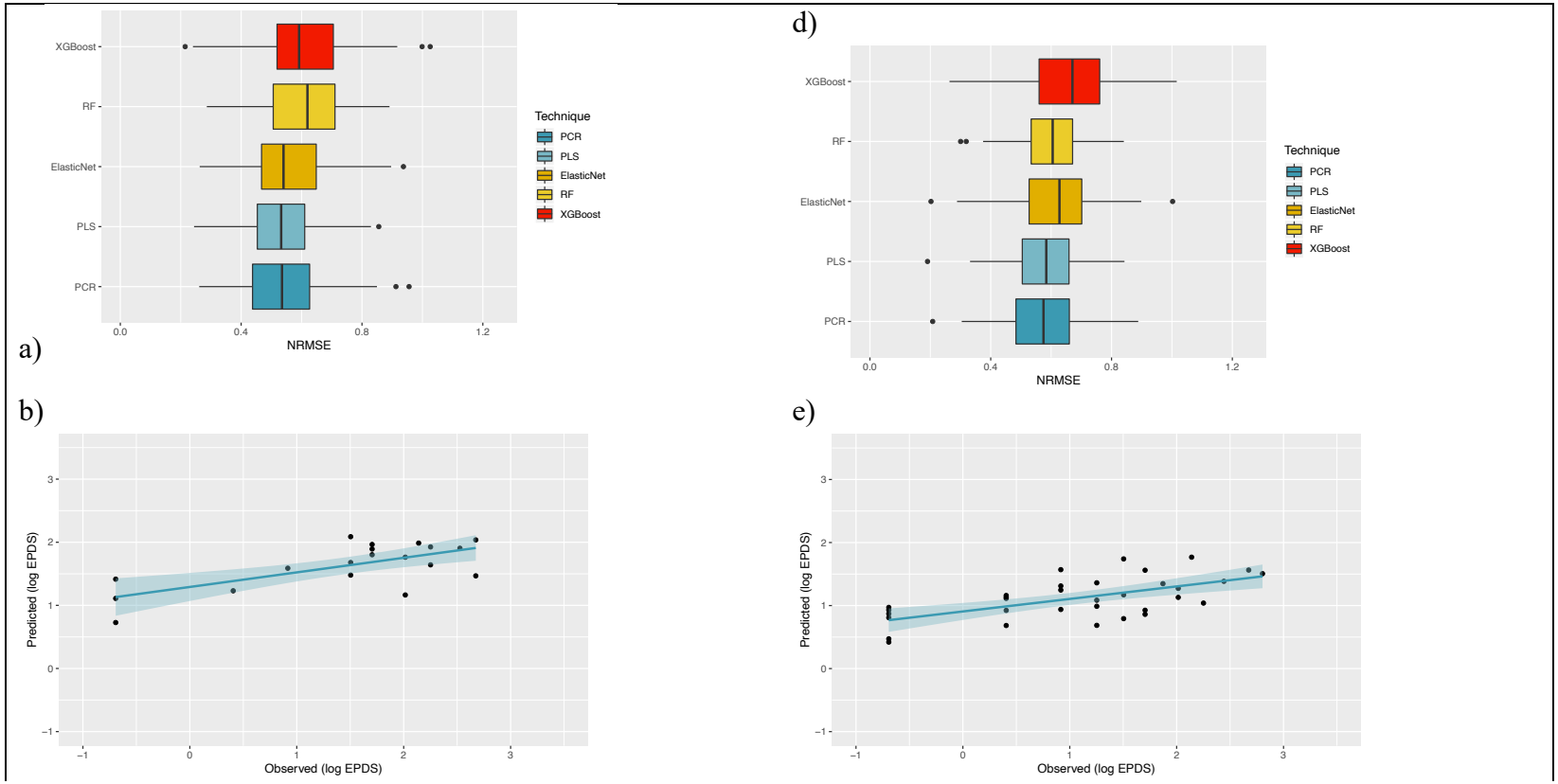
No	72 (91.1%)									
Prenatal Vitamins										
No	9 (11.4%)									
Yes	70 (88.6%)									
Iron										
Yes	31 (39.2%)									
No	48 (60.8%)									
Psychotropic Medication										
No	67 (84.8%)					31 (93.9%)				
Yes	12 (15.2%)					2 (6.1%)				
Current Smoker[$]										
Yes	2 (2.5%)									
No	77 (97.5%)									
Family Mood History										
Yes	38 (48.1%)					14 (53.8%)				
No	41 (51.9%)					12 (46.2%)				
Sleep Apnea										
Yes	1 (1.3%)									
No	(98.7%)									
Parity										

Nulliparous	32 (40.5%)					10 (38.5%)				
Multiparous	47 (59.5%)					16 (61.5%)				

Abbreviations: BRIAN - Biological Rhythms Interview of Assessment in Neuropsychiatry; DERS – Difficulties in Emotion Regulation; ESS – Epworth Sleepiness Scale; GAD7 - Generalized Anxiety Disorder -7;GSS – Global Seasonality Scale; MADRS – Montgomery Asberg Depression Rating Scale; PDPI-R - Postpartum Depression Predictors Inventory – Revised; PSQI – Pittsburgh Sleep Quality Index; YMRS – Young Mania Rating Scale

[$]not included in model selection

Table 2: Regression Model of Postpartum 3 log EPDS Using Data Collected During Pregnancy					
	Beta	**95%CI**	**Std. Beta**	**T**	**p**
Intercept	-5.51	(-8.49, -2.53)	-0.12	-3.69	<0.001
Age	0.066	(0.01, 0.12)	0.23	2.56	0.013
PDPI-R Total Score	0.027	(-0.019, 0.073)	0.12	1.16	n.s.
Neuroticism	0.54	(0.28, 0.79)	0.44	4.19	<0.001
Iron	0.33	(-0.03, 0.69)	0.31	1.83	0.07
BRIAN	0.0058	(-0.020, 0.031)	0.05	0.46	n.s.
Awakenings	-0.048	(-0.082, -0.013)	-0.40	-2.75	0.008
MLiT100	0.51	(0.22, 0.80)	0.49	3.52	<0.001
MLiT500	-0.25	(-0.49, -0.0086)	-0.29	-2.07	0.043
pRA night	10.3	(-1.02, 21.56)	0.25	1.82	0.074
Nighttime Activity SD	-6.16e-05	(-0.00011, -1.45e-05)	-0.24	-2.61	0.011
R^2	0.56		**Adj. R^2**	0.50	
F(10,68)	8.70		**P**	<0.001	
Abbreviations: BRIAN - Biological Rhythms Interview of Assessment in Neuropsychiatry; Edinburgh Postnatal Depression Scale; MLiT - Mean timing above light threshold (100 or 500 lux); PDPI-R - Postpartum Depression Predictors Inventory – Revised; pRA - Probability of transitioning from rest to active state.					


a)
XGBoost
RF
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PLS
PCR
0.0
0.4
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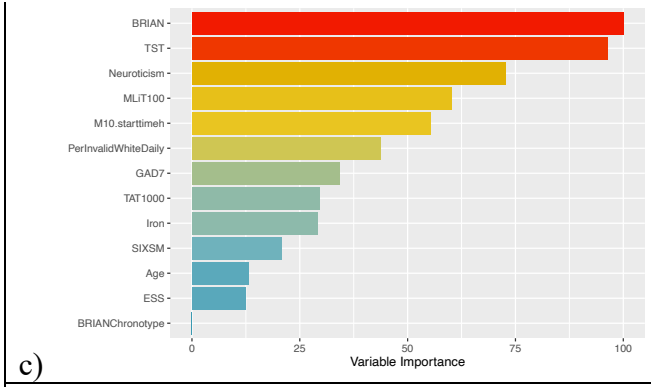
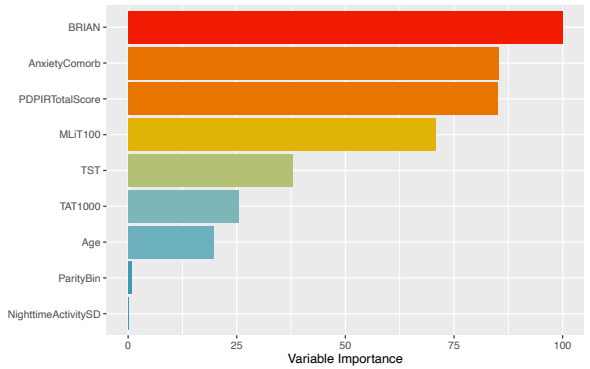
Technique
PCR
PLS
ElasticNet
RF
XGBoost
b)
Predicted (log EPDS)
Observed (log EPDS)
d)
e)



c)



f)

Figure 1: Using Pregnancy Variables to Predict 6-12 Week Postpartum log EPDS Scores

a) Training Normalized Mean Squared Error for all models: 75% – 25% training vs test split;
b) Test predicted vs observed log EPDS for Bagged CART: 75% – 25% training vs test split;
c) Variable importance plot for bagged CART: 75% – 25% training vs test split;
d) Training Normalized Mean Squared Error for all models: tested on external data set;
e) Test predicted vs observed log EPDS for RF: tested on external data set;
f) Variable importance plot for RF: tested on external data set.

Abbreviations: BRIAN – Biological Rhythms Interview of Assessment in Neuropsychiatry; CART – Classification and Regression Trees; EPDS – Edinburgh Postnatal Depression Scale; ESS – Epworth Sleepiness Scale; GAD7 – Generalized Anxiety Disorder -7; MLiT100 – Mean timing of light exposure greater than 100 lux; M10 - ten consecutive hours with highest activity; NRMSE – Normalized Mean Square Root Error; PDPI-R – Postpartum Depression Predictors Inventory – Revised; RF – Random Forest; SD – Standard Deviation; SIXSM – 6-sulfatoxy melatonin; TAT1000 – Time Above Threshold (1000 lux); TST – Total Sleep Time.

Table 3: Test Results of Six Machine Learning Models used to Model Postpartum log EPDS from Pregnancy Variables

a) Using Pregnancy Variables to Predict 6-12 Week Postpartum log EPDS Scores: 75% – 25% training vs test split

Algorithm	Test RMSE	Test MAE	Test R^2	Test Spearman's Rho	Test NRMSE	Final Parameters	
PCR	1.26	0.97	0.00	0.11	0.87	Ncomp	11
PLS	0.93	0.73	0.30	0.63	0.64	Ncomp	1
RF	0.96	0.75	0.35	0.43	0.67	Mtry	1
Bagged CART	0.88	0.67	0.48	0.53	0.61		
Elastic Net	1.17	0.91	0.01	0.25	0.81	Fraction	0.9017241
						Lambda	0.1
Extreme Gradient Boosting	1.12	0.93	0.10	0.08	0.78	Nrounds	150
						Max depth	1
						Eta	0.4
						Gamma	0
						Colsample_by tree	0.8
						Min_child_weight	1
						Subsample	1

b) Using Pregnancy Variables to Predict 6-12 Week Postpartum log EPDS Scores: tested on external data set

Algorithm	Test RMSE	Test MAE	Test R^2	Test Spearman's Rho	Test NRMSE	Final Parameters	
PCR	1.02	0.85	0.05	0.24	0.98	Ncomp	5
PLS	0.95	0.82	0.16	0.31	0.91	Ncomp	1
RF	0.87	0.74	0.38	0.57	0.84	Mtry	1
Bagged CART	0.93	0.80	0.23	0.45	0.89		
Elastic Net	1.00	0.82	0.07	0.26	0.96	Fraction	0.9017241
						Lambda	0.1
Extreme Gradient Boosting	1.12	0.90	0.24	0.45	1.08	Nrounds	50
						Max depth	1
						Eta	0.3
						Gamma	0
						Colsample_by tree	0.6
						Min_child_weight	1
						Subsample	1

Abbreviations: CART – Classification and Regression Trees; EPDS – Edinburgh Postnatal Depression Scale; MAE – Mean Absolute Error; NRMSE - Normalized Root Mean Squared Error; PCR – principal components regression; PLS – partial least squares regression; RF – Random Forest; RMSE – Root Mean Squared Error

3.6 Supplementary Material

3.6.1 Actigraphy:

Actigraphy data were extracted from the Actiwatch 2 monitors using the Philips Actiware Software (v. 6.0). Data were obtained in one-minute epochs continuously for 15 days. Default activity thresholds were used to distinguish between active and sleep periods. Variables concerning sleep and illuminance were extracted from Actiware, and were averaged to produce a single value for each variable: total sleep time (TST, hours); sleep onset latency (minutes) – number of minutes spent transitioning from an active period to a sleep period; sleep efficiency (SE, %) – TST divided by time in bed; wake after sleep onset (WASO, minutes) – time spent in active state from sleep onset to get up time; number of awakenings. Mean mid sleep time was calculated as the midpoint between sleep onset time and sleep offset time. Rest, active, sleep and daily illuminance variables were extracted: light exposure, average light, maximum light, time above light threshold (TAT; 1000 lux), percent invalid light.

During pre-processing, periods during which actigraphs were reported to be removed according to the sleep log were removed. Visual inspection was used to remove intervals of more than 20 consecutive minutes where no movement was captured. Twenty-four hour periods where 4 hours or more of recording were excluded were removed from the analysis.

3.6.2 Cosinor Analysis

Cosinor analysis consists of a regressive model which fits time-series data to a single cosine wave. For each individual, daily activity rhythm period was assessed by extracting a peak between T=23 hours and T=25 hours from the periodogram, to provide a more accurate fit for each individual's endogenous period. The following daily activity rhythm parameters were obtained from cosinor analysis using the cosinor R package (Sachs, 2015): (1) MESOR – midline of the rhythm; (2) amplitude of the rhythm; (3) acrophase – the time of the peak activity; (4) circadian quotient – ratio of amplitude to mesor, a normalized measure of activity rhythm strength.

3.6.3 Non-Parametric Circadian Activity Rhythm Analysis

Non-parametric circadian activity rhythm analysis was conducted using the nparACT (v 0.8) package, obtaining the following measures: (1) intradaily variability – amount of circadian rhythm fragmentation, calculated as the ratio of the mean square difference between successive measurements to the overall data variance, ranging from 0-2. Higher intradaily variability scores represent a greater extent of rhythm fragmentation. (2) Interdaily stability – represents strength of coupling between endogenous daily activity rhythms and external zeitgebers, calculated as a normalized ratio of variance of the mean rhythm over the variance in study duration, ranging from 0-1. Higher interdaily stability indicates higher synchronicity of daily activity rhythms to external cues. (3) L5 consists of 5 consecutive lowest-activity hours, (4) start of L5, (5) ten consecutive hours with highest activity (M10), and (6) start of M10. (7) Relative amplitude of the rhythm is

then calculated as the difference between M10 and L5 divided by the total activity during M10 combined with L5.

Nighttime activity mean and standard deviation (SD) were calculated from nighttime activity measured during sleep periods.

Raw, minute-by-minute illuminance data were used to evaluate TAT across the whole day, and mean timing above light threshold (MLiT) – the mean time during which TAT occurs. These parameters were calculated using 4 different light thresholds: 10, 100, 500, 1000 lux.

3.6.4 Transition Probabilities

Transition probabilities were calculated using methods described by Ortiz(Ortiz, Bradler, Radu, Alda, & Rusak, 2016) and colleagues, and in previous publications from our group(Allega et al., 2018; Slyepchenko et al., 2019). In brief, a transition series was created between rest and activity states, for nighttime (8 hours with lowest mean activity) and daytime periods. The transition series was generated using the probability of remaining in either the rest or the active state for each minute-by-minute record. Probability of transitioning from the rest state to the active state or vice versa was estimated using this transition series (Ortiz et al., 2016).The Hidden Markov Model was used to create this model, based on the concept that the observed time series of data is an outcome of a hidden state variable, and the hidden state series is dependent on the current state. The Python hmmlearn package (v 0.2.0) was used to calculate model parameters, with use of the Baum-Welch algorithm. During daytime and nighttime, mean activity

counts in each state, and probability of transitioning from rest to active (pRA) and active to rest (pAR) states.

3.6.5 References

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Supplementary Table S1: Objective Measures of Sleep and Biological Rhythms (3rd Trimester)										
	Newly Collected Data Set					**External Data Set**				
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
6-sulfatoxymelatonin	34.92	21.61	31.17	19.92	44.48					
SLEEP VARIABLES										
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
TST	7.26	0.94	7.36	7.80	6.88	7.21	1.03	7.24	6.64	7.94
SE	0.82	0.06	0.83	0.80	0.86	0.84	0.05	0.86	0.81	0.87
Sleep Onset Latency	13.77	7.79	12.33	8.80	16.83	11.49	6.44	10.38	6.14	14.38
WASO	63.55	20.91	61.91	47.23	77.36	54.55	20.82	53.37	39.24	70.86
Awakenings	28.5	9.17	26.22	22.06	33.59	23.37	7.85	22.95	17.67	29.35
Mean Mid Sleep Time	3.44	1.11	3.37	2.61	3.98	3.34	1.08	3.16	2.75	3.68
COSINOR										
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
Mesor	196.51	48.09	194.98	163.71	228.01	181.21	91.66	183.23	139.81	242.43
Amplitude	156.78	45.06	150.34	125.73	193.51	177.47	74.64	260.57	127.90	237.79

CQ[$]	0.80	0.13	0.80	0.73	1.09	-0.85	10.42	0.85	0.74	0.94
Acrophase	0.74	0.36	0.76	0.56	0.91	0.068	0.84	0.34	-0.66	0.61
Period	23.51	2.55	23.92	23.68	24	28.16	9.29	24.34	23.82	28.24
NON-PARAMETRIC CIRCADIAN ACTIVITY RHYTHM ANALYSIS										
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
Interdaily Stability	0.57	0.09	0.59	0.52	0.63	0.53	0.12	0.52	0.44	0.63
Intradaily Variability	0.76	0.14	0.75	0.67	0.82	0.78	0.19	0.75	0.63	0.89
Relative Amplitude	0.87	0.07	0.89	0.85	0.91	0.84	0.15	0.89	0.83	0.92
L5	21.08	12.58	17.95	13.17	25.38	24.91	19.15	19.66	12.62	29.94
L5 Start Time	5.45	8.82	1.28	0.77	2.18	6.23	9.08	1.48	0.62	4.33
M10	308.59	77.71	308.18	252.38	356.09	320.47	117.30	305.36	247.36	372.00
M10 Start Time	9.43	2.07	9.5	8.39	10.82	8.53	2.69	8.12	7.58	10.05
Nighttime Activity Mean	7784.25	3610.16	8358.38	5881.14	11187.06	8058.26	3754.65	8201.10	5063.32	9642.84
Nighttime Activity SD	4895.01	4208.77	3370.44	2402.7	5483.34	5236.78	5190.80	3715.60	2612.06	6540.94
LIGHT										
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
MLiT10	13.98	0.82	14.03	13.52	14.53	14.04	0.62	13.83	13.71	14.30
MLiT100	13.57	1.04	13.52	12.83	14.35	13.55	0.86	13.77	12.83	14.02

MLiT500	13.57	1.28	13.70	12.61	14.52	13.61	0.96	13.75	13.21	14.25
MLiT1000	13.40	1.47	13.55	12.57	14.39	13.62	1.01	13.92	12.94	14.28
TAT10	515.86	243.49	499.81	360.90	591.88	475.35	340.49	434.65	295.20	534.05
TAT100$^{\$}$	213.13	268.84	162.45	68.89	237.67	155.92	151.72	131.00	66.10	184.85
TAT500$^{\$}$	120.43	252.01	66.15	15.22	117.34	70.52	97.10	32.35	11.12	98.05
TAT1000	102.89	240.64	46.11	7.27	86.70	50.46	76.66	23.50	3.95	64.30
Average Light Exposure - Active$^{\$}$	1261.19	4937.1	254.78	48.36	651.97	268.19	308.97	172.65	47.75	371.39
Max Light Exposure – Active$^{\$}$	14368.06	12647.37	9115.53	3289.22	22573.66	12311.51	14278.51	9640.84	2317.83	19719.50
Percent Invalid Light - Active$^{\$}$	3.36	3	3.30	0.66	4.92	1.37	1.78	0.26	0.02	2.61
TAT White Light – Active$^{\$}$	59.93	121.96	22.42	4.75	61.55	302.4	33.59	16.17	3.41	48.89
Exposure Light -Active$^{\$}$	791956.63	2886983.5	178929.6	35864.52	475513.37	2e05	242354.1	107067.70	29644.30	267749.90
Average Light Exposure - Daily	1140.12	4782.22	189.61	36.44	479.57	219.46	238.76	133.35	37.93	312.98
Max Light Exposure – Daily	19006.45	14976.51	15707.42	4846.91	31376.52	15234.63	14767.61	13631.16	3119.16	26229.22
Percent Invalid Light - Daily	5.18	4.32	4.01	1.74	7.12	3.75	4.23	1.71	0.15	6.65
TAT White Light – Daily	93.05	222.99	39.40	6.71	79.91	38.96	41.69	21.36	3.57	59.95
Exposure Light -Daily$^{\$}$	1431580.87	6e+06	262653.5	49997.31	643972.77	247115.54	274839.59	167170	43480.88	326135.1-

Average Light Exposure - Rest[$]	944.15	5057.5	2.02	0.53	6.98	11.99	52.04	1.39	0.35	2.85
Max Light Exposure – Rest[$]	1044.68	5286.69	18.44	7.69	40.41	25.93	54.08	11.13	5.73	28.71
Percent Invalid Light - Rest[$]	2.19	3.87	0	0	3.97	2.30	3.05	0	0	4.07
TAT White Light – Rest[$]	16.15	72.71	0	0	0	0.0012	0.007	0	0	0
Exposure Light -Rest[$]	334472.58	1766258.83	288.25	79.83	1081.64	324.03	441.45	158.24	51.31	418.62
Average Light Exposure - Sleep[$]	942.60	5055.51	1.57	0.49	6.23	11.69	52.09	0.84	0.26	2.42
Max Light Exposure – Sleep[$]	1036.77	5261.65	15.72	6.24	34.4	23.25	53.36	8.54	4.53	26.45
Percent Invalid Light - Sleep	2.12	4.05	0	0	3.29	2.25	3.14	0	0	4.12
TAT White Light – Sleep[$]	15.49	70	0	0	0	0.0012	0.007	0	0	0
Exposure Light -Sleep[$]	324653.53	1721915.42	197.78	197.78	936.64	288.15	443.66	120.11	32.73	411.85
TRANSITION PROBABILITIES										
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**	**Mean**	**SD**	**Median**	**P25**	**P75**
pRA day	0.065	0.01	0.066	0.058	0.071	0.067	0.012	0.065	0.058	0.076

pRA night	0.11	0.027	0.10	0.086	0.12	0.094	0.027	0.095	0.079	0.110
pAR day	0.045	0.012	0.046	0.039	0.053	0.044	0.014	0.045	0.034	0.052
pAR night	0.10	0.02	0.099	0.089	0.11	0.099	0.022	0.110	0.086	0.120
Rest day mean	65.82	37.44	65.32	40.34	86.72	77.33	57.37	76.10	34.80	100.95
Rest night mean	0.077	0.38	0.0	0	0.04	0.48	2.67	0.00	0.00	0.00
Activity day mean	425.48	91.93	417.10	368.06	493.42	453.62	170.64	418.93	338.72	589.26
Activity night mean	53.09	24.18	45.43	37.84	62.73	72.95	72.01	51.89	43.76	70.97
CQ - Circadian Quotient; L5 -5 consecutive lowest-activity hours; M10 - 10 consecutive hours with highest activity; MLiT - Mean timing of light exposure; pAR - probability of transitioning from active to rest state; pRA - probability of transitioning from rest to active state; SD - Standard Deviation; SE - Sleep Efficiency; TAT - Time Above Threshold; TST - Total Sleep Time; WASO - Wake After Sleep Onset [$]not included in final model selection										

Chapter 4: Objective and Subjective Measures of Biological Rhythms and Sleep During Pregnancy as Predictors of Postpartum Anxiety: A Longitudinal Study

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Abstract

Study Objectives:

There has been an increasing interest in predictors of postpartum anxiety. While disturbances in sleep and biological rhythms are common during the perinatal period, their relationship with postpartum anxiety are unknown. We used comprehensive assessments during pregnancy, including objective and subjective measures of sleep and biological rhythms, to predict severity of postpartum anxiety.

Methods:

During their 3rd trimester of pregnancy, 100 women were enrolled into the study and 79 completed the 6-12 weeks postpartum follow-up assessments. In the baseline assessment, subjective and objective measures of sleep and biological rhythms were assessed using validated questionnaires, ambulatory monitoring through actigraphy, and urinary 6-sulphaxoxymelatonin levels. Objective and subjective measures were used to predict severity of anxiety symptoms at 6-12 weeks postpartum, by using linear regressions and machine learning models.

Results:

Mean mid sleep time, timing of light exposure, circadian activity rhythm fragmentation, and clinical variables explained 49% of variance in postpartum anxiety severity $F(_{13,65}=6.67$, Adj. $R^2=0.49$, $p<0.001$). Findings from machine learning models

indicated that subjective biological rhythm disruption, total sleep time, light exposure and clinical variables, including having a history of panic disorder/ limited symptom attacks and taking iron supplements were significant predictors of postpartum anxiety severity.

Conclusions:

Markers of objective and subjective sleep and rhythms, in conjunction with light exposure and clinical variables during pregnancy can be used to predict severity of anxiety postpartum. These may serve as useful future targets for prevention and management of women at risk of postpartum anxiety.

Keywords: postpartum anxiety, sleep, biological rhythms, perinatal anxiety, actigraphy

Statement of Significance:

Postpartum anxiety is a highly prevalent disorder, which affects mothers and their families. We followed women from pregnancy to the postpartum periods and assessed which sleep and biological rhythms measures were associated with postpartum anxiety worsening. Results from our study show that sleep, timing of light exposure, and biological rhythm markers during pregnancy combined with demographic and clinical variables enhance the prediction of postpartum anxiety worsening. This suggests that strategies aimed to address sleep and biological rhythm disruptions during pregnancy may prevent postpartum anxiety.

4.1 Introduction

Anxiety disorders are highly prevalent during the perinatal period, occurring in as many as 5-13% of women during the postpartum period, and in as many as 15% of women during pregnancy[1,2]. Postpartum anxiety (PPA) has been linked to poor outcomes for mothers and their children, including worsened motor development and excessive crying in infants. Mothers with PPA may also have impairment in bonding with their infants, worsened self-confidence, and stress response, though few studies have investigated longitudinal outcomes linked to parent-child interactions linked to maternal anxiety. Nevertheless, these impairments may pose risk for the child's development[1]. In addition, a population-based investigation in the United States showed that over one third of women with PPA reported symptoms of postpartum depression[3]. Comorbid depression and anxiety are often associated with poor outcomes such as higher risk of suicide[4], higher functional impairment[5], and is linked to more challenging treatment of both disorders[6,7].

In non-perinatal populations, anxiety is often associated with subjective and objective sleep disturbances (reviewed in[8]). Interestingly, a recent meta-analysis identified insomnia as a predictor of the onset of anxiety[9], indicating sleep disruption to be a potential prodrome for anxiety. Disruptions in biological rhythms have also been associated with anxiety: for instance, evening chronotype[10] has been linked to anxiety disorders, and findings from ambulatory monitoring using actigraphy indicate disruptions in sleep and biological rhythms in young adults with anxiety disorders[11]. Sleep and biological rhythms may thus serve as targets for novel therapeutic approaches, including

preventive strategies for PPA, though prior investigations of perinatal sleep and anxiety have largely focused on subjective measures, and have not assess the role of biological rhythms in anxiety[12-14].

Despite the high prevalence of PPA, risk factors for onset and/or worsening of anxiety during the perinatal period have been little-investigated. According to a meta-analysis from our group, previously identified risk factors for development of anxiety symptoms during the perinatal period involve psychosocial risk factors, such as living with extended family, and lower levels of education; factors related to pregnancy such as current hyperemesis gravidarum and multiple pregnancies; and psychiatric risk factors, including having a history of mental health problems and sleep disorders. Risk factors for anxiety worsening during the perinatal period include having comorbid psychiatric disorders and, potentially, age. Finally, oxytocin exposure during pregnancy is linked to both anxiety worsening and onset during the perinatal period[15]. Nevertheless, there have been few studies which investigated predictors of PPA during pregnancy, and few biological markers have been investigated for this disorder. Determining predictors of PPA can improve screening and interventions for women at-risk for this disorder.

In this study, we followed women from pregnancy to postpartum with comprehensive assessments of subjective and objective sleep and biological rhythms, using validated questionnaires, ambulatory monitoring through actigraphy and melatonin metabolite, in addition to clinical variables. Next, we used the measures of sleep, biological rhythms and clinical variables collected during pregnancy, and used these to predict severity of anxiety symptoms during the postpartum period, using linear

regression analysis in addition to several machine learning (ML) techniques. ML approaches to investigating complex data obtained from technologies such as actigraphy may allow detection of complex, non-linear, multivariate relationships that complement traditional statistical approaches.

4.2 Methods

4.2.1 Participants

During their 3rd trimester of pregnancy, women with and without a history of mood disorders were recruited from the community and an outpatient women's mental health clinic (Women's Health Concerns Clinic at St Joseph's Healthcare). A total of 100 participants were enrolled from November 2015 to May 2018. All participants provided written informed consent to participate in the study. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Hamilton Integrated Research Ethics Board (Project #0602). Study inclusion and exclusion criteria were as follows: (1) age ≥16; (2) no history of head trauma with loss of consciousness > 5 minutes; (3) no current major depressive or [hypo]manic episode; (4) ≥ 27 weeks of pregnancy at enrollment. All participants were interviewed using the Mini Neuropsychiatric Interview (MINI) Version 6.00[16], to establish current mood state and psychiatric diagnosis.

4.2.2 Clinical Assessments

Anxiety symptom severity was evaluated using the Generalized Anxiety Disorder-7 (GAD-7) scale[17]. This 7-item scale has been used to screen for generalized anxiety disorder and its symptom severity with a cut-off score of 13 or greater during the perinatal period[18,19]. Depressive symptom severity was assessed using the Edinburgh Postnatal Depression Scale (EPDS, 10 items)[20,21], and the Montgomery-Åsberg Depression Rating Scale (MADRS, 10 items)[22]. Manic symptom severity was evaluated using the Young Mania Rating Scale (YMRS, 11 items)[23]. Diagnosis and mood state were established using the MINI, according to Diagnostic and Statistical Manual-IV-TR criteria. The following current anxiety diagnoses were assessed using the MINI: generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder, agoraphobia, and social anxiety disorder[16]. Additionally, the MINI was used to assess whether participants had a lifetime history of panic disorder or limited symptom attacks, which were coded as a separate variable. Psychosocial risk factors were assessed using the Postpartum Depression Predictors Inventory – Revised (PDPI-R)[24,25].

Subjective biological rhythm disturbance was measured using the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN, 21 items), a questionnaire developed to assess sleep, social, general activity, eating pattern and chronotype domains[26]. The total domain score of the Pittsburgh Sleep Quality Index (PSQI, 19 items)[27] was used to assess sleep quality; and daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS, 8 items)[28]. Seasonality was evaluated using a

continuous Global Seasonality Score, as well as categorical winter seasonality variable obtained from the Seasonal Pattern Assessment Questionnaire (SPAQ). Winter pattern seasonality was obtained from an item that asks which month respondents feel the worst during. If only winter months are selected, winter pattern seasonality is established[29].

Neuroticism, Conscientiousness, Agreeableness,, Openness to Experience and Extraversion were evaluated using the Big Five Inventory (BFI, 44 items), while the Difficulties in Emotion Regulation Scale (DERS, 36 items) was administered to assess emotional regulation difficulties[30].

4.2.3 Study Design

Participants attended visits to St Joseph's Healthcare Hamilton during the 3rd trimester of pregnancy (≥ 27 weeks gestation), and at 6-12 weeks postpartum. Upon enrollment, participants were interviewed with use of the MINI, MADRS and YMRS, following which they completed the GAD-7, EPDS, PDPI-R, BRIAN, PSQI, ESS, SPAQ, BFI and DERS questionnaires. At the end of the visit, participants were instructed to wear a configured actigraph (Actiwatch 2; Philips Respironics Inc., Biolynx, Montreal, QC, Canada) for 2 weeks, and to record actigraph removal periods, wake-up times, naps, and bed times in a sleep log. Participants were instructed to complete first-morning urine sampling on the final day of actigraph wear, upon which urine samples were returned to the lab and processed by investigators. Participants returned at 6-12 weeks postpartum, and completed the GAD-7.

4.2.4 Objective Assessments

To measure levels of 6-sulfatoxymelatonin (6-SM), first morning urine sampling was completed by participants on the last day of actigraphy data collection. After collection, participants were instructed to refrigerate the sample prior to returning it to the lab. Enzyme-linked immunosorbent assay for 6-SM was used to analyze 6-SM levels (Buhlmann Diagnostics Corporation, Amherst, NH, USA). Assay sensitivity was 0.14ng/mL, intra-assay coefficient of variation was 7.1% and inter-assay coefficient of variation was 11.9%. Final 6-SM concentration was reported as a ratio of 6-SM (ng) to creatinine (mg) to account for volume of urine[31-33]. The Jaffe method (kinetic alkaline picrate; Abbott Diagnostics, Santa Clara, CA, USA) was used to measure urine creatinine levels by the Hamilton Regional Laboratory Medicine Program at St Joseph's Healthcare Hamilton (license no. 4037).

4.2.5 Actigraphy

Actigraphy data were collected continuously in 1-minute epochs throughout 15 days. Data were extracted from actigraph monitors using Philips Actiware (v 6.0), including summary sleep and illuminance variables. We conducted pre-processing of the actigraph data, where sleep log-reported actigraph removal periods were removed from the analysis. Next, visual inspection was conducted to remove intervals where actigraphs consecutively captured no activity for at least 20 minutes. Days where 4 or more hours of recording were excluded were ultimately removed from the analysis. Further details regarding these analyses can be obtained from [34].

The following sleep variables were extracted from Actiware: total sleep time (TST, hours); sleep onset latency (minutes) – number of minutes constituting transition from wakefulness to sleep; sleep efficiency (SE, %) – percentage of time in bed spent in sleep; wake after sleep onset (WASO, minutes) – number of wakeful minutes after sleep onset. Next, we calculated the mean midpoint between sleep onset and offset – mean mid sleep time. Finally, illuminance variables were extracted from Actiware, including overall light exposure, average light exposure, maximum light exposure, percent invalid light exposure, and time above light threshold (TAT, 1000 lux).

4.2.5.1 Cosinor, Non-Parametric Circadian Activity Rhythm Analysis, Illuminance

Using cosinor analysis, time-series data were fitted to a cosine wave using a regressive model, where each participant's circadian activity rhythm was processed to extract a single peak from a periodogram. This single peak was used to approximate the individual's endogenous period. Cosinor analysis using the cosinor R package was used to calculate the following values: MESOR – mean activity adjusted to the rhythm; amplitude of the rhythm; acrophase – peak activity timing; circadian quotient – amplitude divided by MESOR, indicating rhythm strength.

The nparACT (v 0.8) package was used to conduct non-parametric circadian activity rhythm analysis. This analysis yielded the following parameters: intradaily variability (IV) – a measure of circadian rhythm fragmentation; interdaily stability (IS) – a measure of the coupling strength of internal rhythms to external environmental stimuli; L5 – the lowest 5 consecutive hours of activity; L5 start time; M10 – highest 10

consecutive hours of activity; M10 start time; and relative amplitude (RA) – L5 subtracted from M10, and divided by total M10 and L5 activity.

Activity detected during sleep periods at night was used to calculate nighttime activity mean and standard deviation (SD).

Illuminance data were used to calculate TAT and mean timing of TAT (MLiT) across 24-hour periods, using the following light thresholds: 10, 100, 500 and 1000 lux.

4.2.5.2 Transition Probability Estimation

The Python hmmlearn package (v. 0.2.0) was used to estimate transition probabilities, as detailed by Ortiz et al. [35], used in prior publications from our group[34,36]. Probabilities of transitioning from rest to active states, and active to rest states were calculated, in addition to mean activity counts in each state for daytime and nighttime.

4.2.6 Data Analysis Approach

Data analyses were performed using R (v. 3.6.1) and Python (v. 2.7.6).

4.2.6.1 Linear Regression

Postpartum GAD-7 scores were modeled using variables collected during the pregnancy visit in multiple linear regression analysis. Variable selection was performed using the sequential replacement method in the leaps package in R (v. 3.0). Model assumptions for linear regression analysis were tested, including linearity, normality,

multicollinearity, homosceidasticity, and independence of variance. Variables were transformed to meet regression model assumptions, when applicable.

4.2.6.2 Machine Learning

Machine learning (ML) models to predict postpartum GAD-7 scores were built with variables collected during pregnancy. In brief, 6 ML approaches were used in the caret R package: (1) principal component regression (PCR), which consists of a linear regression model, where predictors are principal components of variables in the model; (2) partial least squares regression (PLS), which uses components that account for maximum correlation between predictors and the outcome variable in a regression model. (3) Elastic net regularization creates a regression model by using both L1 and L2 regularization penalties. Next, we used several tree-based methods: (4) Random Forest (RF) is an ensemble method, which induces a number of regression trees, and produces a mean regression of the trees as the output. Each tree is created by use of a bootstrap sample of instances, where only a subset of the available variables is used to create each tree. (5) Bagged Classification and Regression Trees (Bagged CART) is also an ensemble method, where a number of regression trees are created. Each regression tree is created with a bootstrap sample of the training set, and bootstrap aggregation is used to prevent overfitting. Finally, (6) extreme gradient boosting (XGBoost)[37] is an ensemble method, which is highly optimized, and uses a gradient descent algorithm to reduce model error, in addition to regularization, the weighted Quantile Sketch algorithm and other methods to optimize model building[37].

To build these models, first, the data were split into a 75% training and 25% test set. Next, data were centered and scaled, and 5-nearest-neighbor imputation was performed on the missing data in completed pregnancy visits[38]. The minimum Redundancy Maximum Relevance (mRMR) method, which selects potential predictor variables with maximum relevance to the outcome variable, and simultaneously minimizes redundancy within the selected set of predictors, was used to select model features[39]. To select optimal models, and choose hyperparameters, 10-fold cross-validation was performed. Model performance was evaluated using R^2, Spearman's Rho, Root Mean Squared Error (RMSE), normalized RMSE (NRMSE) and Mean Absolute Error (MAE).

4.3 Results:

4.3.1 Demographics and Clinical Characteristics

In total, 100 women completed the pregnancy visit, 79 of whom returned for a follow-up at 6-12 weeks postpartum (Table 1 shows demographic and clinical characteristics of the sample). Of women who completed both visits, 39.2% met criteria for a current anxiety disorder during the pregnancy visit. Additionally, 54.4% had a history of major depressive or bipolar disorder, and 29.1% had a lifetime history of panic disorder or limited symptom attacks. On average, women in this sample were 31.19 years of age, had a pre-pregnancy Body Mass Index of 25.01, and had 17.11 years of education, and 60.8% had earned a University degree. Upon enrolment, participants were on average at 31.85 weeks gestation. A majority of women in the sample were partnered or married

(94.9%), and had a household income of >$50,000 (81.0%). Most of the women in the sample were taking prenatal vitamins (88.6%), but not iron supplements (60.8%) or psychotropic medication (84.8%). Table 2 shows objective measures of sleep and biological rhythms obtained during pregnancy.

4.3.2 Linear Regression: Modeling Postpartum GAD-7 from Pregnancy Data

In a multiple linear regression analysis which used clinical, data from the pregnancy visit (See Table 3), postpartum anxiety symptoms according to the GAD-7 were independently predicted by neuroticism (Std. β=0.44, t=3.71, p<0.001), openness (Std. β=0.22, t=2.13, p=0.037), winter seasonality (Std. β=-0.66, t=-3.38, p=0.001), Mean Mid Sleep Time (Std. β=-0.54, t=-4.62, p<0.001), MLiT10 (Std. β=0.43, t=3.91, p<0.001) and IV (Std. β=-0.20, t=-2.08, p=0.042). However, total score on the PDPI-R (Std. β=0.18, t=1.48), lifetime history of mood disorders (Std. β=0.41, t=1.90), household income <$50,000 (Std. β=-0.45, t=1.80), BRIAN scores (Std. β=0.14, t=1.18), chronotype according to the BRIAN (Std. β=0.16, t=1.53), TAT 10 (Std. β=0.19, t=1.87) and amplitude (Std. β=-0.21, t=-1.99) did not predict postpartum GAD-7 scores. Notably, 49% of variance in GAD-7 scores were explained by this model ($F_{13,65}$=6.67, Adj. R^2=0.49, p<0.001).

4.3.3 Machine Learning Analyses: Modeling Postpartum GAD-7 from Pregnancy Data

The available dataset was used to extract 72 possible predictor variables. Of these variables, mRMR was used to identify 8 most predictive features, according to performance of the training model (See: Figure 1). Results from the ML models (See: Table 4) showed that the model with the lowest test error (NRMSE) were PCR (0.50) and PLS (0.50), followed by Elastic Net (0.51), RF (0.55) and Bagged CART (0.55), and XGBoost (0.59). For the best-performing algorithm (PCR) (See: Figure 2), variables were ranked by their feature importance (Figure 3): PDPI-R Total Score, BRIAN scores, Neuroticism, History of Panic Disorder or Limited Attacks, TST, MLiT 10, daily percentage of invalid light, and taking iron supplements.

4.4 Discussion

In this study, objective and subjective measures of sleep and biological rhythms collected during the 3rd trimester of pregnancy, combined with demographic and clinical variables, predicted 49% of variance in anxiety symptoms at 6-12 weeks postpartum. In order to identify predictors of PPA symptoms, we used an approach with use of ML techniques and multiple linear regression, finding a set of measures collected during pregnancy which may be used together to predict PPA symptoms. Using ML modeling techniques may allow predictive models to be more sensitive to non-linear relationships between variables, which are more than simply building linear models, even if linear variable interactions are accounted for. Building both traditional statistical models and ML models may deliver different types of information when modeling multifaceted

phenomena such as sleep and mood. Traditional statistical modeling can be used to understand inferential relationships between variables, whereas ML modeling can be used for its predictive properties.

4.4.1 Sleep and Biological Rhythms: Subjective and Objective Measures

Subjective biological rhythm disruption in pregnancy according to the BRIAN had second to highest variable importance in predicting PPA symptom severity. However, BRIAN scores were not an independent predictor of PPA symptoms according to the linear regression model. This may indicate that pregnancy BRIAN scores are predictive of PPA scores in combination with other variables in the model. To our knowledge, subjective rhythm disruption has not been previously investigated in relation to symptoms of PPA, however previous studies from our group have reported subjective rhythm disruptions to be linked to depressive symptoms in the perinatal period[40,41].

A number of previous studies have investigated the role of subjective sleep and insomnia in PPA symptoms, with mixed findings. For instance, Tham and colleagues did not find subjective sleep quality during the 3rd trimester of pregnancy to be linked to PPA symptoms at 3 months postpartum[14]. Bei and colleagues found that subjective sleep dysfunction, but not overall subjective sleep quality in pregnancy was linked to PPA symptoms at 1 week postpartum[12]. However, in a large Norwegian cohort of women during the perinatal period (n=1,563), Osnes and colleagues found that insomnia during the 3rd trimester of pregnancy was a risk factor for developing an anxiety disorder at 8 weeks postpartum[13]. In an American sample (n=578), Menke and colleagues found that

subjective sleep quality during the perinatal period was linked to severity of anxiety symptoms[42].

According to our investigation, having winter seasonality was a predictor of lower PPA symptoms, according to the linear regression model. A previous study found no association between season and trait anxiety symptoms, according to the State-Trait Anxiety Inventory during pregnancy[43]. As well, chronotype during pregnancy according to the BRIAN was not a predictor of PPA scores in a multiple linear regression model. To our knowledge, chronotype has not been previously investigated as a risk factor for PPA.

Objectively assessed TST during pregnancy was one of the predictors of postpartum anxiety in the ML model. In contrast, a previous smaller study by Bei and colleagues (n=44) found that objective sleep during pregnancy, including TST, SE, and sleep fragmentation, did not predict postpartum anxiety scores. However, the number of naps taken per day was linked to anxiety[12]. Another study found that neither total sleep time, nor number of awakenings during the night >5 minutes, nor SE were correlated with anxiety scores during pregnancy[44].

Several biological rhythm variables assessed through actigraphy in pregnancy were independent predictors of PPA severity according to multiple linear regression. In particular, later mean mid sleep time and higher rhythm fragmentation (IV) in pregnancy were associated with lower PPA symptom severity. Rhythm amplitude during pregnancy, however, was not a significant independent predictor of PPA severity. To our knowledge, circadian activity rhythm variables and melatonin have not been previously studied in relation to postpartum anxiety. Nonetheless, one prior study found that during the 3rd

trimester of pregnancy, increased trait anxiety was linked to a flatter decline in the afternoon of cortisol rhythms[45].

4.4.2 Light Exposure

Using variables extracted from actigraphy during pregnancy, later timing of light exposure during pregnancy (MLiT10), but not total time of light exposure (TAT 10), was a significant independent predictor of increased postpartum anxiety symptom severity in a multiple linear regression. MLiT10 during pregnancy was also one of the predictors of PPA in the ML models. The ML model also showed that daily percentage of invalid white light was a predictor of PPA. To our knowledge, this is the first study to link light exposure during pregnancy to severity of postpartum anxiety symptoms, finding light exposure to be a novel predictor for PPA severity. This study provides the rationale for investigating light-based therapies for PPA, both as potential preventive measures and possible treatment interventions, such as bright light therapy. Light-based therapies have not been investigated as treatment for PPA. However small studies have found evidence for improvements in postpartum depressive symptoms for bright light therapy[46] and blue light-blocking glasses[47].

4.4.3 Clinical Variables: Psychiatric History, Personality, Demographics

Risk factors associated with postpartum depression, according to the PDPI-R, had the highest variable importance in our ML approach as a predictor of postpartum anxiety. However, risk factors for depression according to the PDPI-R were not an independent

predictor of anxiety severity according to multiple linear regression analysis. This may indicate that the PDPI-R is an important predictor of PPA, when combined with other variables assessed in the study. Though the PDPI-R is a tool which was developed to estimate risk for developing postpartum depression. some of the risk factors for postpartum depression and anxiety may overlap, particularly considering the high degree of comorbidity of these disorders[48]. The PDPI-R questionnaire assesses a number of factors which have been previously linked to risk of developing PPA: whether individuals experienced anxiety or depression during pregnancy, presence of social support, maternal education, marital dissatisfaction, and self-esteem[15,49]. However, other risk factors assessed by the PDPI-R such as household income[15], marital status, history of depression, and intention of motherhood have not been shown to be risk factors for PPA[49].

In terms of psychiatric history, having a lifetime history of panic disorder or limited symptom attacks was one of the ML predictors of anxiety symptoms. Having a history of mood disorders, however, was not an independent predictor of GAD-7 scores according to multiple linear regression analysis. This is consistent with a prior study which assessed risk factors for PPA, finding anxiety and depressive disorders during pregnancy, and anxiety disorders but not depressive disorders prior to pregnancy to be risk factors for PPA[49].

Taking iron supplements during pregnancy was one of the predictors of anxiety symptoms according to the ML model. Though to our knowledge, taking iron supplements or iron-deficient anemia have not been systematically investigated in PPA, a

prior study found that mean corpuscular volume and hemoglobin levels were positively correlated with severity of anxiety in women at nine months postpartum[50].

Two personality factors were linked to severity of postpartum anxiety symptoms in this investigation. Neuroticism was a predictor of GAD-7 in the ML models, and higher neuroticism was a predictor of higher anxiety symptoms according to the linear regression model. Higher openness was also a significant predictor of higher PPA symptoms according to the linear regression model. These results replicate in part a previous study showing that high neuroticism was linked to high levels of PPA, and antenatal anxiety, though there was no link of openness to PPA[51].

4.4.4 Strengths and Limitations

One of the strengths of this investigation is that this investigation prospectively followed women from the 3rd trimester of pregnancy to 6-12 weeks postpartum. Assessments of sleep and biological rhythms were conducted through both subjective and objective measures, whereas clinical variables, including diagnosis, were assessed through validated interviews, and questionnaires. In addition, we used both linear regression and ML models which provide complementary insights into the link between sleep and biological rhythms and PPA.

Some limitations of this study include its modest sample size. However, this is one of the first (and largest) studies looking at biological rhythms in perinatal anxiety, and objective measures of sleep. Additionally, this study was designed to look primarily at postpartum depression and, as a result, we did not use a structured interview to assess

whether participants developed anxiety disorders during the postpartum timepoint. Another limitation comes from the heterogeneity of anxiety diagnoses within this study. We were not able to look at impact of individual diagnoses. Several factors may have impacted the anxiety, sleep and rhythm measurements obtained from our study. Participants who had a history of psychiatric disorders were being followed by clinicians throughout their pregnancy and postpartum period, and may have had uncommonly good sleep hygiene, due to access to information about the link between poor sleep and mood. We did not assess whether participants were adhering to sleep hygiene recommendations, or whether they were undergoing psychotherapy during the study.

In summary, this prospective study showed that subjective and objective sleep and biological rhythm markers, as well as light exposure collected during the 3rd trimester of pregnancy with clinical variables can be used predict anxiety symptom severity during 6-12 weeks postpartum. This study used complimentary methods of linear regression and ML techniques, in order to investigate inferential relationships and improve the prediction ability of our models. These findings emphasize the importance of screening for sleep and biological rhythm disturbances during the perinatal period, as they are associated with severity of anxiety throughout this period. Given our findings regarding the predictive value of light exposure during pregnancy to postpartum anxiety symptoms, future studies should also investigate light-based therapies as a potential intervention for postpartum anxiety.

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Table 1: Demographics and Clinical Characteristics					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
Age	31.19	3.71	31	28	33.5
Pre-Pregnancy Body Mass Index	25.01	5.76	23.56	21.37	26.26
Years of Education	17.11	2.61	17	16	18
Weeks Gestation	31.85	3.24	32	29	35
PDPI-R Total Score	4.76	4.75	3	2	6
DERS	90.86	23.48	78	60	97
GSS	8.42	4.45	9	5	11.5
Neuroticism	2.81	0.86	2.75	2.25	3.44
Openness	3.221	0.5	3.2	2.9	3.6
Conscientiousness	4	0.61	4.11	3.56	4.44
Agreeableness	4.01	0.52	4	3.67	4.44
Extraversion	3.38	0.82	3.38	2.62	3.88
MADRS*	7.99	6.64	7	3	11
YMRS*	2	1	3	2.18	2.22
GAD-7 – Pregnancy (n=78) *	4.38	4.86	3	1	6
GAD-7 - Postpartum	4.67	4.16	3.5	1	7
ESS	8.24	3.88	8	6	11
PSQI	9.82	3.9	9	8	11
BRIAN	39.15	9.98	39	31.5	46.5
BRIAN Chronotype	6.11	1.83	6	5	7
EPDS – Pregnancy*	6.2	4.89	5	2	9.5

Variable	**N (%)**	**Variable**	**N (%)**
Marital Status		Shift Worker	
Single	4 (5.1%)	*Yes*	7 (8.9%)
Partnered	75 (94.9%)	*No*	72 (91.1%)
Household Income		Prenatal Vitamins	
> 50,000	64 (81.0%)	*No*	9 (11.4%)
< 50,000	15 (19.0%)	*Yes*	70 (88.6%)
Highest Level of Education		Iron	
Less than High School	1 (1.3%)	*Yes*	31 (39.2%)
High School Diploma or Trade Certificate	2 (2.5%)	*No*	48 (60.8%)

College certificate/ diploma	28 (35.4%)	Current Smoker*	
University – bachelor's degree and higher	48 (60.8%)	*Yes*	2 (2.5%)
		No	77 (97.5%)
Lifetime History of Panic Disorder or Limited Symptom Attacks		Sleep Apnea*	
Yes	23 (29.1%)	*Yes*	1 (1.3%)
No	56 (70.9%)	*No*	78 (98.7%)
Mood Disorder History		Parity	
No History of Mood Disorders	36 (45.6%)	*Nulliparous*	32 (40.5%)
History of Major Depressive or Bipolar Disorder	43 (54.4%)	*Multiparous*	47 (59.5%)
Current or Past Anxiety Disorder		Psychotropic Medication	
Yes	38 (48.1%)	*No*	67 (84.8%)
No	41 (51.9%)	*Yes*	12 (15.2%)
Current Anxiety Disorder (Agoraphobia; Past month Panic Disorder, Social Anxiety Disorder, Obsessive Compulsive Disorder; Past 6 months Generalized Anxiety Disorder)		Family Mood History	
Yes	31 (39.2%)	*Yes*	38 (48.1%)
No	48 (60.8%)	*No*	41 (51.9%)

Abbreviations: BRIAN - Biological Rhythms Interview of Assessment in Neuropsychiatry; DERS – Difficulties in Emotion Regulation; ESS – Epworth Sleepiness Scale; GAD-7 - Generalized Anxiety Disorder -7; GSS – Global Seasonality Scale; MADRS – Montgomery Åsberg Depression Rating Scale; PDPI-R - Postpartum Depression Predictors Inventory – Revised; PSQI – Pittsburgh Sleep Quality Index; YMRS – Young Mania Rating Scale
* not included in model selection due to multicollinearity or lack of cases

Table 2: Objective Measures of Sleep and Biological Rhythms (3rd Trimester of Pregnancy)					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
6-sulfatoxymelatonin (ng/mg)	34.92	21.61	31.17	19.92	44.48
SLEEP VARIABLES					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
TST	7.26	0.94	7.36	7.80	6.88
SE	0.82	0.06	0.83	0.80	0.86
Sleep Onset Latency	13.77	7.79	12.33	8.80	16.83
WASO	63.55	20.91	61.91	47.23	77.36
Awakenings	28.5	9.17	26.22	22.06	33.59
Mean Mid Sleep Time	3.44	1.11	3.37	2.61	3.98
COSINOR					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
Mesor	196.51	48.09	194.98	163.71	228.01
Amplitude	156.78	45.06	150.34	125.73	193.51
CQ*	0.80	0.13	0.80	0.73	1.09
Acrophase	0.74	0.36	0.76	0.56	0.91
Period	23.51	2.55	23.92	23.68	24
NON-PARAMETRIC CIRCADIAN ACTIVITY RHYTHM ANALYSIS					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
Interdaily Stability	0.57	0.09	0.59	0.52	0.63
Intradaily Variability	0.76	0.14	0.75	0.67	0.82
Relative Amplitude	0.87	0.07	0.89	0.85	0.91
L5	21.08	12.58	17.95	13.17	25.38
L5 Start Time	5.45	8.82	1.28	0.77	2.18
M10	308.59	77.71	308.18	252.38	356.09
M10 Start Time	9.43	2.07	9.5	8.39	10.82
Nighttime Activity Mean	7784.25	3610.16	8358.38	5881.14	11187.06

Nighttime Activity SD	4895.01	4208.77	3370.44	2402.7	5483.34
LIGHT					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
MLiT10	13.98	0.82	14.03	13.52	14.53
MLiT100	13.57	1.04	13.52	12.83	14.35
MLiT500	13.57	1.28	13.70	12.61	14.52
MLiT1000	13.40	1.47	13.55	12.57	14.39
TAT10	515.86	243.49	499.81	360.90	591.88
TAT100*	213.13	268.84	162.45	68.89	237.67
TAT500*	120.43	252.01	66.15	15.22	117.34
TAT1000	102.89	240.64	46.11	7.27	86.70
Average Light Exposure – Active*	1261.19	4937.1	254.78	48.36	651.97
Max Light Exposure – Active*	14368.06	12647.37	9115.53	3289.22	22573.66
Percent Invalid Light – Active*	3.36	3	3.30	0.66	4.92
TAT White Light – Active*	59.93	121.96	22.42	4.75	61.55
Exposure Light - Active*	791956.63	2886983.5	178929.6	35864.52	475513.37
Average Light Exposure – Daily	1140.12	4782.22	189.61	36.44	479.57
Max Light Exposure – Daily	19006.45	14976.51	15707.42	4846.91	31376.52
Percent Invalid Light - Daily	5.18	4.32	4.01	1.74	7.12
TAT White Light – Daily	93.05	222.99	39.40	6.71	79.91
Exposure Light - Daily*	1431580.87	6e+06	262653.5	49997.31	643972.77
Average Light Exposure – Rest*	944.15	5057.5	2.02	0.53	6.98
Max Light Exposure – Rest*	1044.68	5286.69	18.44	7.69	40.41
Percent Invalid Light – Rest*	2.19	3.87	0	0	3.97

TAT White Light – Rest*	16.15	72.71	0	0	0
Exposure Light - Rest*	334472.58	1766258.83	288.25	79.83	1081.64
Average Light Exposure – Sleep*	942.60	5055.51	1.57	0.49	6.23
Max Light Exposure – Sleep*	1036.77	5261.65	15.72	6.24	34.4
Percent Invalid Light – Sleep	2.12	4.05	0	0	3.29
TAT White Light – Sleep*	15.49	70	0	0	0
Exposure Light - Sleep*	324653.53	1721915.42	197.78	197.78	936.64
TRANSITION PROBABILITIES					
Variable	**Mean**	**SD**	**Median**	**P25**	**P75**
pRA day	0.065	0.01	0.066	0.058	0.071
pRA night	0.11	0.027	0.10	0.086	0.12
pAR day	0.045	0.012	0.046	0.039	0.053
pAR night	0.10	0.02	0.099	0.089	0.11
Rest day mean	65.82	37.44	65.32	40.34	86.72
Rest night mean	0.077	0.38	0.0	0	0.04
Activity day mean	425.48	91.93	417.10	368.06	493.42
Activity night mean	53.09	24.18	45.43	37.84	62.73

CQ - Circadian Quotient; L5 -5 consecutive lowest-activity hours; M10 - 10 consecutive hours with highest activity; MLiT - Mean timing of light exposure; pAR - probability of transitioning from active to rest state; pRA - probability of transitioning from rest to active state; SD - Standard Deviation; SE - Sleep Efficiency; TAT - Time Above Threshold; TST - Total Sleep Time; WASO - Wake After Sleep Onset
*not included in model selection due to multicollinearity

Table 3: Regression Model of Postpartum log Generalized Anxiety Disorder-7 Using Data Collected During Pregnancy

	Beta	95%CI	Std. Beta	T	p
Intercept	-7.06	-11.36, -2.76	0.26	-3.28	0.002
Mood Disorder History - Yes	0.41	-0.002, -0.84	0.41	1.90	0.062
PDPI-R Total Score	0.04	-0.001, 0.009	0.18	1.48	0.14
Household Income < $50,000	-0.46	-0.96, 0.05	-0.45	1.80	0.077
Neuroticism	0.51	0.24, 0.79	0.44	3.71	<0.001
Openness	0.43	0.03, 0.84	0.22	2.13	0.037
Winter Seasonality - Yes	-0.66	-1.05, -0.27	-0.66	-3.38	0.001
BRIAN	0.01	-0.001, 0.004	0.14	1.18	0.244
BRIAN Chronotype	0.09	-0.003, 0.21	0.16	1.53	0.130
Mean Mid Sleep Time	-0.50	-0.72, -0.29	-0.54	-4.62	<0.001
MLiT10	0.54	0.27, 0.82	0.43	3.91	<0.001
TAT 10	0.00	-5.55e-5, 1.73e-3	0.19	1.87	0.066
Amplitude	0.00	-9.63e-3, 1.89e-5	-0.21	-1.99	0.051
IV	-1.53	-3.01, -0.06	-0.20	-2.08	0.042
R^2	0.57		**Adj. R^2**	0.49	
F(13,65)	6.67		**P**	<0.001	

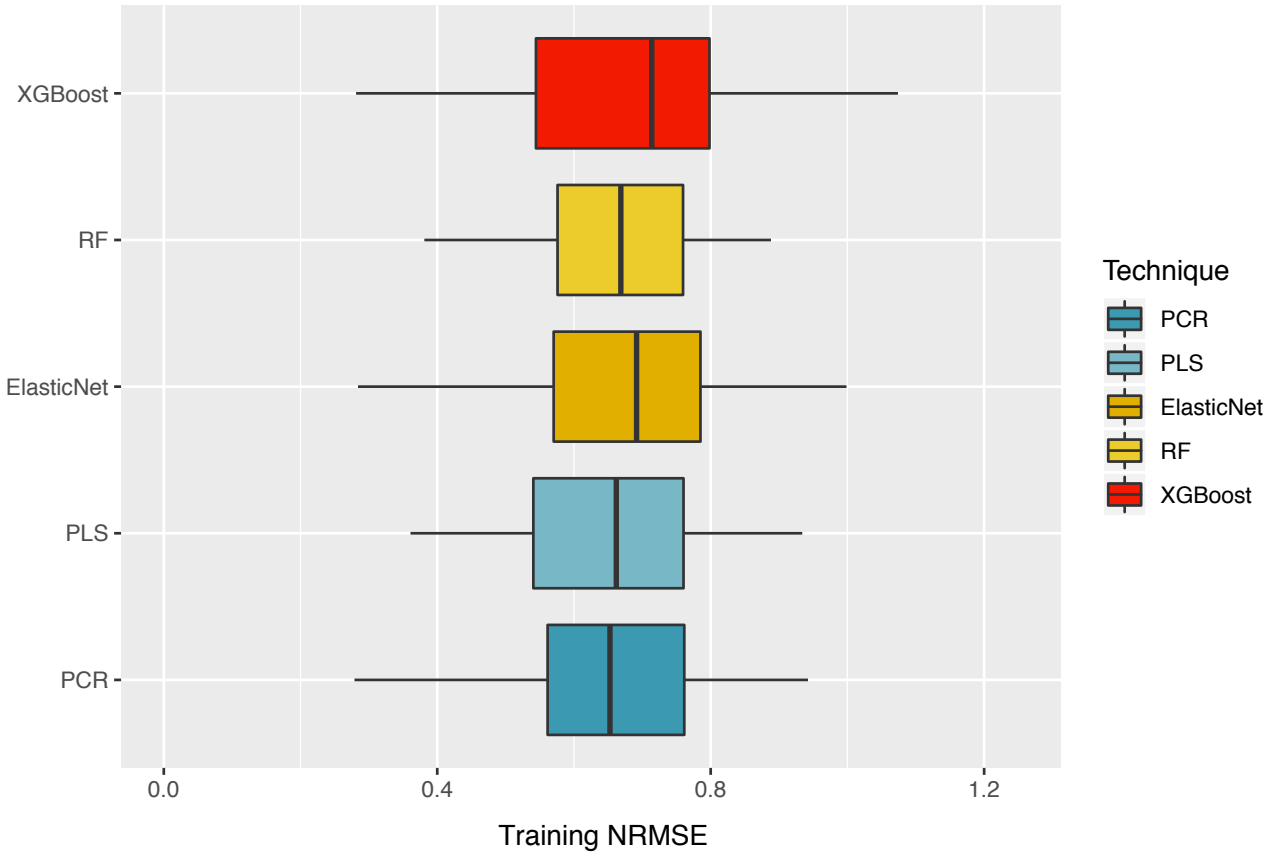
Abbreviations: BRIAN - Biological Rhythms Interview of Assessment in Neuropsychiatry; Edinburgh Postnatal Depression Scale; MLiT - Mean timing above light threshold (100 or 500 lux); PDPI-R - Postpartum Depression Predictors Inventory – Revised; pRA - Probability of transitioning from rest to active state.

Table 4: Test Results of Six Machine Learning Models used to Model Postpartum log Generalized Anxiety Disorder-7 from Pregnancy Variables

Algorithm	Test RMSE	Test MAE	Test R^2	Test Spearman's Rho	Test NRMSE	Final Parameters	
PCR	0.65	0.55	0.41	0.70	0.50	Ncomp	5
PLS	0.66	0.56	0.39	0.62	0.50	Ncomp	1
RF	0.72	0.61	0.28	0.56	0.55	Mtry	
Bagged CART	0.73	0.58	0.29	0.56	0.55		
Elastic Net	0.66	0.55	0.39	0.67	0.51	Fraction	0.9344828
						Lambda	0.1
Extreme Gradient Boosting	0.77	0.63	0.24	0.61	0.59	Nrounds	50
						Max depth	1
						Eta	0.3
						Gamma	0
						Colsample_bytree	0.6
						Min_child_weight	1
						Subsample	0.75

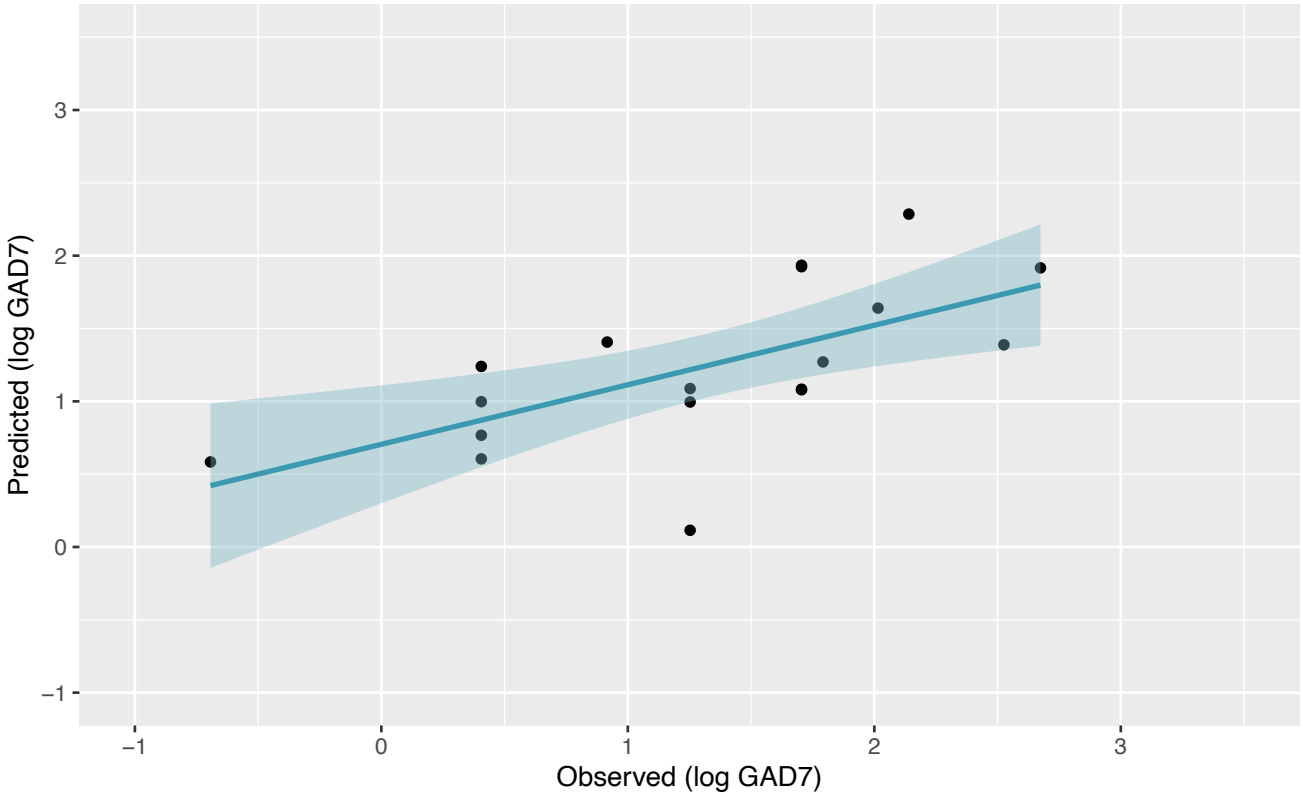
Abbreviations: CART – Classification and Regression Trees; GAD-7 – Generalized Anxiety Disorder – 7; MAE – Mean Absolute Error; NRMSE - Normalized Root Mean Squared Error; PCR – principal components regression; PLS – partial least squares regression; RF – Random Forest; RMSE – Root Mean Squared Error

Figure 1: Training Normalized Mean Squared Error for All Models - Pregnancy Variables used to Predict 6-12 Week Postpartum log Generalized Anxiety Disorder-7 Scores



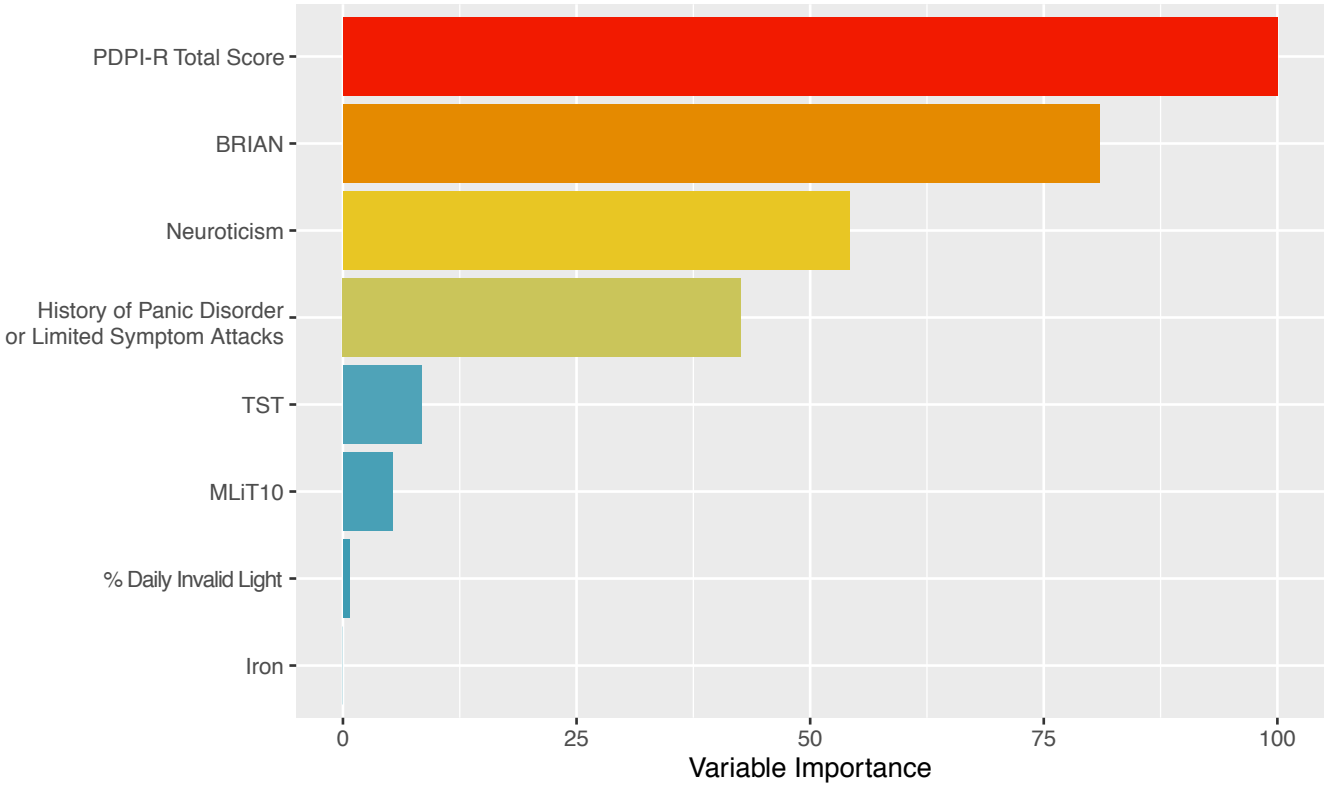
Abbreviations: NRMSE – Normalized Mean Square Root Error; PCR – Principal Component Regression; PLS – Partial Least Squares; RF – Random Forest; XGBoost – Extreme Gradient Boosting.

Figure 2: Test Predicted vs Observed Plot of log Generalized Anxiety Disorder-7 Scores at 6-12 Weeks Postpartum for Principal Component Regression Model



Abbreviations: GAD-7 – Generalized Anxiety Disorder -7.

Figure 3: Variable Importance Plot for Principal Component Regression Model Predicting log Generalized Anxiety Disorder -7 Scores at 6-12 Weeks Postpartum



Abbreviations: BRIAN – Biological Rhythms Interview of Assessment in Neuropsychiatry; GAD-7 – Generalized Anxiety Disorder -7; MLiT10 – Mean timing of light exposure greater than 100 lux; PDPI-R – Postpartum Depression Predictors Inventory – Revised; TST – Total Sleep Time.

Chapter 5: Longitudinal Changes in Sleep, Biological Rhythms and Light Exposure from Pregnancy to Postpartum

This chapter describes work that is currently in progress, which will be included in future manuscripts.

5.1 Introduction

Subjective sleep quality decreases among a large proportion of women throughout pregnancy (Sedov, Cameron, Madigan, & Tomfohr-Madsen, 2018), and throughout postpartum, where new mothers often report sleep disturbances, particularly in the 3rd trimester of pregnancy and the first month postpartum (Lee, Zaffke, & McEnany, 2000; Matsumoto, Shinkoda, Kang, & Seo, 2003; Signal et al., 2007). As detailed in the general introduction, subjective sleep disturbances in pregnancy and postpartum have been extensively linked to depressive and anxiety symptoms during the perinatal period (e.g.(Gallaher, Slyepchenko, Frey, Urstad, & Dorheim, 2018; Okun, Hanusa, Hall, & Wisner, 2009; Okun, Mancuso, Hobel, Schetter, & Coussons-Read, 2018)).

In spite of this link, there have been few studies that have investigated changes ins biological rhythms from pregnancy to postpartum. Matsumoto and colleagues followed 10 women continuously from the 3rd trimester of pregnancy to 16 weeks postpartum, continuously measuring sleep and activity using actigraphy. They found that mean amplitude, TST and SE decreased from pregnancy to early postpartum. WASO increased from pregnancy to early postpartum. These changes improved from early to late postpartum, and amplitude increased during this period (Matsumoto et al., 2003). Another study of 10 primiparous women from the 3rd trimester of pregnancy to 12 weeks postpartum found that peaks of rhythm autocorrelograms decreased from pregnancy to early postpartum, and improved by the 12th week postpartum (Nishihara, Horiuchi, Eto, Kikuchi, & Hoshi, 2012).

Two prior studies have investigated the longitudinal relationship between biological rhythms and mood. Sharkey and colleagues showed that a large proportion of euthymic women (n=12) with a history of MDD had phase shifts in dim light melatonin onset from 33 weeks of pregnancy to 6 weeks postpartum. On average, their phases were delayed 42 minutes. This study found that average light exposure over the 24-hour period decreased from pregnancy to postpartum. In this study, dim light melatonin onset phase and phase angle were linked to depressive symptom severity from pregnancy to postpartum (Sharkey, Pearlstein, & Carskadon, 2013).

A prior investigation from our lab (n=83) found that changes in subjective biological rhythms from pregnancy to postpartum, but not subjective sleep quality, were associated with changes in depressive symptoms from the 3rd trimester of pregnancy to 6-12 weeks postpartum (Krawczak, Minuzzi, Hidalgo, & Frey, 2016). In a subsample of these women (n=33), who had worn actigraphs , changes in subjective biological rhythms and objective sleep efficiency were associated with changes in EPDS scores (Krawczak, Minuzzi, Simpson, Hidalgo, & Frey, 2016).

As few longitudinal studies have investigated the relationships between biological rhythms and sleep from pregnancy to postpartum, it is unknown how these change together from pregnancy to early postpartum (1-3 weeks postpartum, the onset period for postpartum blues) (Henshaw, 2003), to 6-12 weeks postpartum (the onset period for postpartum depressive episodes) (Gavin et al., 2005).

5.2 Aim

In this investigation, we aimed to characterize the longitudinal trajectory of subjective and objective sleep quality and biological rhythms, levels of melatonin, and light exposure in women from the 3rd trimester of pregnancy, to 1-3 weeks and 6-12 weeks postpartum.

5.3 Methods

5.3.1 Participants

During the 3rd trimester of pregnancy, 100 women were recruited from the community, and an outpatient clinic (Women's Health Concerns Clinic at St Joseph's Healthcare Hamilton). Participants were recruited from November 2015 – May 2018, and provided written informed consent to participate in this study. Study procedures were approved by the Hamilton Integrated Research Ethics Board (Project #0602). To enroll in the study, the following inclusion and exclusion criteria were applied: age ≥16; no history of head trauma with loss of consciousness > 5 minutes; current euthymia: no current major depressive or [hypo]manic episode; ≥ 27 weeks of pregnancy at enrollment. Current mood state and diagnosis were established using the Mini Neuropsychiatric Interview (MINI) Version 6.00 (Sheehan et al., 1998).

5.3.2 Study Procedure

Clinical assessments used in this study are detailed in Chapters 3 and 4. During the 3rd trimester of pregnancy, at 1-3 weeks postpartum and at 6-12 weeks postpartum, participants attended study visits at St Joseph's Healthcare Hamilton.

During the pregnancy visit, participants were interviewed using the MINI, Montgomery Åsberg Depression Rating Scale (MADRS, depressive symptoms) (Montgomery & Asberg, 1979), and Young Mania Rating Scale (YMRS, manic symptoms) (Young, Biggs, Ziegler, & Meyer, 1978). Participants completed the following questionnaires: Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN, subjective biological rhythm disturbance) (Giglio et al., 2009); Pittsburgh Sleep Quality Index (PSQI, sleep quality) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989); Epworth Sleepiness Scale (ESS, daytime sleepiness) (Johns, 1991); Seasonal Pattern Assessment Questionnaire (SPAQ, seasonality) (Raheja, King, & Thompson, 1996). The Big Five Inventory (BFI) was used to assess Neuroticism, Conscientiousness, Agreeableness, Openness to Experience and Extraversion (John & Srivastava, 1999). The Difficulties in Emotion Regulation Scale (DERS) was used to assess emotion regulation difficulties (Gratz & Roemer, 2004).

At 1-3 weeks postpartum and 6-12 weeks postpartum, participants were interviewed using the MADRS, and YMRS, and completed the EPDS, GAD-7, BRIAN, PSQI and ESS questionnaires.

At all 3 visits, participants were fitted with a configured actigraph (Actiwatch 2, Philips Respironics Inc., Biolynx, Montreal, QC, Canada) to be worn for 2 weeks.

Participants used a sleep log to record actigraph removal, wake-up time, time in bed, and nap periods. Participants completed a first morning urine sample on the final day of actigraph wear, which was then analyzed for levels of 6-sulfatoxymelatonin, adjusted for creatinine. Details regarding actigraphy and urine collection, processing and analysis are provided in detail in Chapters 3 and 4.

5.3.3 Statistical Analysis

Statistical analyses were performed using R (v. 3.6.1) and Python (v. 2.7.6). Normality of variable distributions was tested using the Shapiro-Wilk test. Changes in clinical variables, sleep and biological rhythm variables in normally distributed variables were examined using repeated-measures analyses of variance (ANOVAs), and the Friedman test in non-normally distributed variables. The Greenhouse-Geisser sphericity correction was automatically applied to factors violating sphericity assumption in the repeated-measures ANOVAs. The Bonferroni correction was applied to control for multiple comparisons. Post-hoc tests were applied to variables which were significantly different according to the repeated-measures analyses.

5.4 Preliminary Results

In total, 73 women returned for all 3 visits, completing the clinical questionnaires. Of these women, 57 completed actigraphy and 6-SM sampling across all 3 visits.

5.4.1 Demographics

In our sample, women were on average 31.27 years old, had a pre-pregnancy BMI of 23.56. Most were married or partnered (95.9%), and had a household income of at least $50,000 (80.8%). Demographics and clinical variables are presented in Table 1.

5.4.2 Longitudinal Changes in Clinical Variables

Longitudinal changes in clinical variables are presented in Table 2 and Figures 1-6. There were significant changes in depressive symptoms (MADRS) over time (χ^2=4.10, p=0.0001), between the 3rd trimester of pregnancy and 1-3 weeks postpartum (p=0.0001). Trends were seen in longitudinal changes in manic symptoms (YMRS), subjective sleep quality (PSQI), self-perceived biological rhythms (BRIAN), and daytime sleepiness (ESS), but these did not survive Bonferroni correction.

5.4.3 Melatonin

No significant longitudinal changes were seen in melatonin levels (Table 3).

5.4.4 Longitudinal Changes in Sleep Variables

In sleep variables, significant changes were seen over time in sleep efficiency (SE, χ^2=5.43, p=1.31e-7), and WASO (F=28.73, p=8.51e-11). There was a significant decrease in SE and increase in WASO from the 3rd trimester of pregnancy to 1-3 weeks postpartum and SE increased and WASO decreased from 1-3 weeks to 6-12 weeks postpartum,

where. Number of awakenings (F=23.46, p=3.10e-9) was lower in the two postpartum timepoints, as compared to pregnancy.

5.4.5 Longitudinal Changes in Biological Rhythms

Variables obtained from cosinor analysis showed that mesor (F=15.13, p=8.47e-6) was higher at 6-12 weeks postpartum compared to 1-3 weeks postpartum and pregnancy. Amplitude was higher at 6-12 weeks postpartum compared to pregnancy (χ^2=4.59, p=1.32e-5). Circadian quotient (CQ), which is the ratio of amplitude to mesor, was higher at 6-12 weeks postpartum compared to pregnancy (χ^2=4.30, p=5.99e-5).

Non-parametric circadian activity rhythm analysis showed that intradaily variability (IV) was significantly higher at 1-3 weeks postpartum than during pregnancy and at 6-12 weeks postpartum (F=19.00, p=7.84e-8). Relative amplitude (RA) was lower at 1-3 weeks postpartum compared to pregnancy and 6-12 weeks postpartum (χ^2=7.23, p=5.61e-12).

Nighttime activity mean (F=55.41, p=1.87e-17) and standard deviation (F=40.33, p=6.45e-14), as well as activity during the 5 lowest activity hours (L5) (F=34.48, p=5.32e-11) were higher at 1-3 weeks postpartum than during pregnancy and 6-12 weeks postpartum. Activity during the 10 most active hours (M10) was higher at 6-12 weeks postpartum than 1-3 weeks postpartum and in pregnancy (F=17.94, p=1.75e-7).

Activity during rest during the day was higher during the 3rd trimester of pregnancy than 1-3 weeks postpartum (χ^2=5.58, p=6.53e-8). Probability of transitioning from rest to activity during the day was lower during pregnancy than 1-3 weeks and 6-12

weeks postpartum (χ^2=7.12, p=1.49e-12). At night, probability of transitioning from rest to activity was higher during pregnancy than 1-3 weeks and 6-12 weeks postpartum (χ^2=4.87, p=2.96e-6). Probability of transitioning from activity to rest at night was lower at 1-3 weeks postpartum than during pregnancy and at 6-12 weeks postpartum (F=18.62, p=4.65e-7).

Mean activity during active phases at night was higher at 1-3 weeks postpartum than during pregnancy and 6-12 weeks postpartum (F=37.76, p=6.35e-11).

5.4.6 Longitudinal Changes in Light Exposure

No significant differences were seen in light exposure variables throughout the perinatal period. However, trends were seen in mean timing of light exposure above 100, 500, and 1000 lux; in addition to total light exposure during the whole day; and total light exposure above 100 lux; average or maximum levels of light exposure during active periods. These differences did not survive Bonferroni correction.

5.5 Discussion

In this study, we investigated the longitudinal trajectory of sleep, biological rhythms and light exposure over several timepoints in the perinatal period, using actigraphy and melatonin profiling. While previous studies have described changes in objective and subjective sleep parameters over the perinatal period, few longitudinal studies have described biological rhythms at different points in the perinatal period

We found that in our sample of women, objective sleep worsened significantly at 1-3 weeks postpartum (marked by lower SE and longer WASO) compared to the 3rd trimester of pregnancy, and improved by 6-12 weeks postpartum. However, women had a lower number of awakenings during the postpartum period. Findings of decreased SE and higher WASO in the early postpartum are consistent with a previous study of 10 women by Matsumoto and colleagues, who found that compared to the 3rd trimester of pregnancy, SE decreases and WASO increases, in the early postpartum. These early sleep disruptions improved over time in the postpartum period (Matsumoto et al., 2003). Unlike Matsumoto and colleagues, who found decreased TST in the early postpartum, which increased until 15 weeks postpartum (Matsumoto et al., 2003), we did not find changes in TST in the perinatal period. Consistent with our findings, in a sample of 50 women, Montgomery-Downs and colleagues also did not find changes in TST from 2-16 weeks postpartum, and found increases in SE from week 2 to 16 postpartum (Montgomery-Downs, Insana, Clegg-Kraynok, & Mancini, 2010).

Interestingly, we found a number of changes in daily activity rhythm variables and transition probabilities from pregnancy to 1-3 weeks and 6-12 weeks postpartum. To our knowledge, changes in transition probabilities have not been previously described in the perinatal population.

Some of the changes in sleep and biological rhythms observed in this study occurred only during the early postpartum period, and returned to their late pregnancy values by 6-12 weeks postpartum. These included decreased SE, relative amplitude and probability of transitioning from activity to rest at night; as well as increased WASO, IV,

L5 activity, mean and standard deviation of nighttime activity. Additionally, there were several differences in sleep and daily activity rhythms at 6-12 weeks postpartum compared to pregnancy. These included lower number of awakenings, increased mesor, higher M10, and higher probability of transitioning from rest to activity during the day and night.

Longitudinal changes in daily activity rhythms have been little-investigated over the perinatal period. Previously, Nishihara and colleagues found autocorrelogram peaks to be lower in the early postpartum compared to the 3rd trimester of pregnancy, which improved by 12 weeks postpartum (Nishihara et al., 2012). Additionally, Matsumoto and colleagues found that daily activity rhythm period was longest during the 3rd trimester of pregnancy, and during the first 3 postpartum days. Amplitude from power spectra decreased in the first 3 weeks postpartum, and increased later into the postpartum period, up to 15 weeks (Matsumoto et al., 2003). Finally, Thomas and colleagues followed 43 mothers and their infants during 4, 8, and 12 weeks postpartum, finding that maternal mesor, acrophase, M10 midpoint and L5 midpoint stayed constant throughout this period. However, throughout this period, there was an increase in amplitude, increase in IS and decrease in IV during these timepoints (Thomas, Burr, Spieker, Lee, & Chen, 2014). This was mostly consistent with our results, as we also found decreased IV and increased relative amplitude, and stable acrophase and L5 and M10 start periods from early (1-3 weeks) to late (6-12 weeks) postpartum. However, in our study, mesor increased from 1-3 weeks to 6-12 weeks postpartum.

Though we found some differences in light exposure across the perinatal period, these did not survive Bonferroni correction. Previously, Sharkey and colleagues found that a smaller sample (n=12) of women had lower light exposure during 6-12 weeks postpartum compared to the 3rd trimester (Sharkey et al., 2013).

Another interesting finding of this investigation is that though there were a number of changes in daily activity rhythms, there were no significant indicators of change in circadian phase over the perinatal period, including chronotype, mean mid sleep time, acrophase, L5 or M10 start time. This finding emphasizes the importance of investigating biological rhythm disturbances beyond sleep and chronotype, as they may not be reflective of a broad range of disruptions in activity patterns.

Additionally, there were no changes in 6-SM over the perinatal period in our sample. Thomas and Burr previously found in a cross-sectional study that women during the postpartum period had lower mean and maximum 6-SM levels across a 24 hour period, in addition to a lower percent rise compared to non-pregnant, nulliparous women (Thomas & Burr, 2006). Sharkey and colleagues have previously reported that in a similar population of women (n=12), phase shifts occurred in dim light melatonin onset from the 3rd trimester of pregnancy to 6 weeks postpartum (Sharkey et al., 2013). We were not able to confirm these findings, as a single 6-SM measurement cannot provide information about melatonin phase.

5.6 Future Directions

Recently, studies have emerged which have modeled trajectories of depressive and anxiety symptoms as a function of subjective sleep disturbances through pregnancy to

postpartum (e.g. (Tomfohr, Buliga, Letourneau, Campbell, & Giesbrecht, 2015; Wang et al., 2018)). These studies have reported that clusters of women who had worsened sleep quality from pregnancy to postpartum have worsened symptoms of depression and anxiety during this period (Tomfohr et al., 2015; Wang et al., 2018).

To our knowledge, prior studies have not investigated trajectories of depressive symptoms or anxiety symptoms from pregnancy to postpartum using measures of objective sleep or biological rhythms.

In future analyses, we aim to model changes in clinical variables (e.g. depressive, anxiety symptoms; subjective sleep and biological rhythms) using objective measures of sleep, biological rhythms and light exposure. One approach to investigating this could involve using objective measures of sleep, biological rhythms and light exposure in a generalized linear mixed model with clinical variables as possible outcome variables. Understanding sleep patterns from pregnancy to postpartum may help health care professionals understand expected sleep and biological rhythm patterns from pregnancy to postpartum, and ensure that appropriate interventions are applied when necessary.

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Table 1: Demographics and Clinical Variables			
Variable	**Mean±SD Median [IQR]**	**Variable**	**Mean±SD Median [IQR]**
Age	31.27±3.82	Extraversion	3.29±0.80
Years of Education	17 [2]	Agreeableness	4.02±0.53
Pre-Pregnancy BMI	23.56 [6.61]	Conscientiousness	4.11 [0.77]
GSS	9.00 [7.00]	Neuroticism	2.80±0.88
DERS	78.00 [37.00]	Openness	3.24±0.48
	Yes	**No**	
Shift Worker	7 (9.6%)	66 (90.4%)	
Prenatal Vitamins	65 (89.0%)	8 (11.0%)	
Iron	30 (41.1%)	43 (58.9%)	
Psychotropic Medication	10 (13.7%)	63 (86.3%)	
Current Smoker	0 (0%)	73 (100%)	
Family Mood History	33 (45.2%)	40 (54.8%)	
Sleep Apnea	1 (1.4%)	72 (98.6%)	
Summer Seasonality	0 (0%)	73 (100%)	
Winter Seasonality	43 (58.9%)	30 (41.1%)	
	Single/ Divorced	**Married/ Partnered**	
Marital Status	3 (4.1%)	70 (95.9%)	
	<$50,000	**>$50,000**	
Household Income	14 (19.2%)	59 (80.8%)	
	High School Diploma or Trade Certificate	**College Certificate or Diploma**	**University – Bachelor's Degree and Higher**
Highest Level of Education	2 (2.7%)	25 (34.2%)	46 (63.0%)
	Yes – History of Major Depressive or Bipolar Disorder	**No History of Mood Disorders**	

History of Mood Disorders	38 (52.1%)	35 (47.9%)	
	Yes	**No**	
Current or Past Anxiety Disorder	35 (47.9%)	38 (52.1%)	
	Yes	**No**	**Mixed**
Breastfeeding 1-3 weeks	47 (64.4%)	7 (9.6%)	15 (20.5%)
Breastfeeding 6-12 weeks	42 (57.5%)	12 (16.4%)	10 (13.7%)
	Vaginal	**C-Section**	
Delivery Method	53 (76.8%)	16 (23.2%)	
	No	**Vacuum/Forceps**	
Vacuum Forceps	61 (91.0%)	6 (9.0%)	
	Multiparas	**Nulliparas**	
Parity	43 (58.9%)	30 (41.1%)	
Abbreviations: BMI – Body Mass Index; DERS – Difficulties in Emotion Regulation; GSS – Global Seasonality Scale.			

Table 2: Longitudinal Changes in Clinical Variables (n=73)								
Variable	**3rd Trimester Mean±SD Median [IQR]**	**1-3 Weeks Postpartum Mean±SD Median [IQR]**	**6-12 Weeks Postpartum Mean±SD Median [IQR]**	**Test**	**P value**	**P value: Multiple Comparisons:**		
						3rd Trimester vs 1-3 Weeks Postpartum	**3rd Trimester vs 6-12 Weeks Postpartum**	**1-3 Weeks Postpartum vs 6-12 weeks Postpartum**
EPDS	5 [6]	7 [8]	5 [7]	χ^2=2.21	0.070			
EPDS3A	3 [3]	3 [3]	3 [3]	χ^2=2.32	0.053			
EPDS7D	2 [3]	3 [5]	2 [3]	χ^2=1.98	n.s.			
GAD7	3 [5]	4 [6]	3.75 [6]	χ^2=2.02	n.s.			
MADRS	**6 [7]**	**10 [8.5]**	**6 [9.5]**	**χ^2=4.10**	**0.0001**	**0.0001**	n.s.	0.0003
YMRS	2 [2.5]	3 [2.0]	2 [2.5]	χ^2=3.32	0.0027	0.003	0.08	n.s.
ESS	8 [4.25]	9.5 [5.25]	8 [6.25]	χ^2=3.64	0.00076	0.0008	0.003	n.s.
PSQI	9 [3]	8 [2.5]	8 [3]	χ^2=2.60	0.025	n.s.	0.025	n.s.
BRIAN (n=60)	38.00 [15.25]	39.50 [16.4375]	36.50 [15.00]	χ^2=2.44	0.039	n.s.	n.s.	0.038
BRIAN Chronotype (n=60)	6 [2]	5 [3]	5 [2]	χ^2=1.32	n.s.			

Bolded text: survived Bonferroni Correction
Abbreviations:
BRIAN - Biological Rhythms Interview of Assessment in Neuropsychiatry; ESS – Epworth Sleepiness Scale; GAD-7 – Generalized Anxiety Disorder -7; MADRS – Montgomery Åsberg Depression Rating Scale; PDPI-R - Postpartum Depression Predictors Inventory – Revised; PSQI – Pittsburgh Sleep Quality Index; YMRS – Young Mania Rating Scale

Table 3: Longitudinal Changes in Sleep and Biological Rhythm Variables (n=57)								
Variable	**3rd Trimester Mean±SD Median [IQR]**	**1-3 Weeks Postpartum Mean±SD Median [IQR]**	**6-12 Weeks Postpartum Mean±SD Median [IQR]**	**Test**	**P value**	**P value: Multiple Comparisons:**		
						3rd Trimester vs 1-3 Weeks Postpartum	**3rd Trimester vs 6-12 Weeks Postpartum**	**1-3 Weeks vs 6-12 weeks Postpartum**
MELATONIN								
6-SM	35.56±23.68	36.42±25.34	35.88±23.06	F=0.05	n.s.			
ACTIGRAPHY (n=57)								
SLEEP VARIABLES								
TST	7.37 [1.00]	6.90 [1.34]	7.17 [1.02]	χ^2=2.15	0.079			
SE	**84.05 [5.02]**	**80.05 [4.20]**	**83.53 [3.38]**	**χ^2=5.43**	**1.31 e-7**	**3.08e-5**	n.s.	**1.17e-7**
WASO*	**62.75±20.37**	**85.40±22.25**	**64.91±18.99**	**F=28.73**	**8.51 e-11**	**2.49e-8**	n.s.	**1.69e-9**
Mean mid sleep time	3.37[1.39]	3.33[1.54]	3.42[0.89]	χ^2=0.47	n.s.			
Awakenings*	**28.12±8.55**	**23.02±5.34**	**23.44±6.31**	**F=23.46**	**3.1e-9**	**5.30e-7**	**8.73e-7**	n.s.
COSINOR VARIABLES								
Mesor*	**194.63±49.24**	**200.93±50.08**	**223.17±62.87**	**F=15.13**	**8.47e-6**	n.s.	**4.77e-5**	**1.27e-5**

Amplitude	**146.55 [62.18]**	**147.37 [59.56]**	**178.22 [65.95]**	**χ^2=4.59**	**1.32e-5**	n.s.	1.04e-3	**1.89e-5**
Acrophase	0.74 [0.36]	0.71 [0.35]	0.71 [0.34]	χ^2=1.40	n.s.			
CQ	**0.78 [0.16]**	**0.77 [0.12]**	**0.84 [0.13]**	**χ^2=4.30**	**5.99e-5**	1.80e-2	n.s.	**4.29e-5**
Period	23.94 [0.28]	23.99 [0.20]	23.94 [0.32]	χ^2=1.73	n.s.			
NON-PARAMETRIC CIRCADIAN ACTIVITY RHYTHM ANALYSIS								
IS	0.58 [0.13]	0.52 [0.13]	0.58 [0.16]	χ^2=3.00	0.008	0.008	n.s.	0.024
IV*	**0.78±0.13**	**0.89±0.15**	**0.76±0.13**	**F=19.00**	**7.84e-8**	**2.20e-6**	n.s.	**1.80e-7**
RA	**0.88 [0.08]**	**0.75 [0.10]**	**0.87 [0.13]**	**χ^2=7.23**	**5.61e-12**	**1.05e-12**	n.s.	**2.46e-10**
L5	**21.45±13.63**	**45.51±18.70**	**31.10±23.25**	**F=34.48**	**5.32e-11**	**5.96e-15**	0.003	**5.27e-5**
L5 Start time	**0.77 [1.21]**	**0.52 [2.16]**	**0.60 [1.61]**	χ^2=0.52	Ns.			
M10*	**303.64±78.08**	**313.76±78.27**	**354.79±102.54**	**F=17.94**	**1.75e-7**	n.s.	**5.64e-6**	**1.77e-5**
M10 Start time	**33.88[2.33]**	**33.73[1.82]**	**33.33[2.00]**	χ^2=1.48	n.s.			
Nighttime Activity Mean*	**8800.68 ± 3835.39**	**17395.83 ± 6646.48**	**12080.49 ± 5158.74**	**F=55.41**	**1.87e-17**	**7.95e-15**	2.00e-3	**7.36e-10**
Nighttime Activity SD*	**5134.26 ± 4634.81**	**11939.40 ± 9199.01**	**6561.43 ± 5255.53**	**F=40.33**	**6.45e-14**	**2.25e-12**	1.20e-2	**1.55e-8**
TRANSITION PROBABILITIES								
pAR day	0.05 [0.01]	0.04 [0.02]	0.04 [0.01]	χ^2=2.53	0.031	n.s.	0.031	n.s.
pAR night	**0.10 ± 0.02**	**0.08±0.02**	**0.09±0.02**	**F=18.62**	**4.65e-7**	**8.05e-8**	0.066	**2.69e-5**

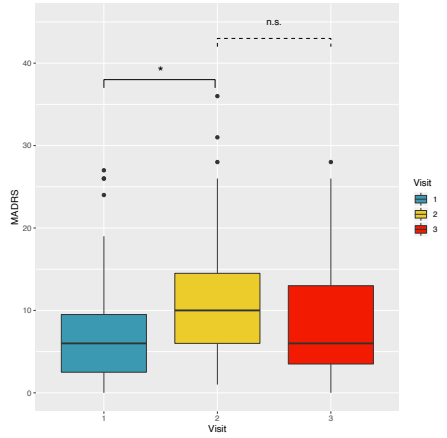
Activity day mean	410.43 [124.75]	394.55 [162.91]	443.78 [164.61]	χ^2=3.28	0.0031	0.098	n.s.	0.003
Activity night mean*	**54.41±25.98**	**89.71±29.79**	**73.26±39.75**	**F=37.76**	**6.35e-11**	**3.28e-16**	8.96e-4	**2.79e-5**
pRA day	**0.06 [0.01]**	**0.08 [0.03]**	**0.08 [0.01]**	**χ^2=7.12**	**1.49e-12**	**2.30e-11**	**3.28e-5**	1.82e-2
pRA night	**0.10 [0.03]**	**0.08 [0.03]**	**0.09 [0.03]**	**χ^2= 4.87**	**2.96e-6**	**2.66e-6**	**9.55e-6**	n.s.
Rest day mean	**69.76 [52.60]**	**34.81 [32.85[**	**45.35 [51.77]**	**χ^2=5.58**	**6.529e-8**	**5.39e-8**	3.89e-2	4.61e-3
Rest night mean	0.00 [0.04]	0.00 [0.00]	0.00 [0.00]	χ^2=2.99	0.008	0.008	0.010	n.s.
LIGHT EXPOSURE								
MLiT10	14.00 [1.07]	14.18 [0.99]	14.09 [1.09]	χ^2=0.84	n.s.			
MLiT100	13.53±1.01	14.03±0.87	13.58±1.14	F=4.87	0.013	0.022	n.s.	0.008
MLiT500	13.58±1.28	14.09±1.14	13.43±1.62	F=4.26	0.023	0.035	n.s.	0.0008
MLiT1000	13.50 [1.79]	14.06 [1.65]	13.30 [1.86]	χ^2=2.65	0.022	n.s.	n.s.	0.022
TAT10	505.00 [223.95]	443.27 [244.79]	424.92 [325.15]	χ^2=1.40	n.s.			
TAT100	164.21 [162.38]	103.57 [104.69]	139.07 [191.51]	χ^2=2.53	0.031	0.031	n.s.	n.s.
TAT500	64.31 [97.89]	42.82 [70.63]	57.85 [115.63]	χ^2=2.15	0.079			
TAT1000	45.57 [77.93[	28.92 [57.14]	44.38 [92.45]	χ^2=2.25	0.063			

White Exposure - Rest	240.41 [1517.66]	375.34 [783.36]	260.62 [2675.55]	χ^2=0.47	n.s.			
Average Light Exposure – Rest	2.19 [6.85]	2.12 [5.82]	2.35 [8.59]	χ^2=1.12	n.s.			
Maximum Light Exposure – Rest	18.35 [33.31]	22.07 [32.38]	19.61 [50.29]	χ^2=1.31	n.s.			
TAT Light – Rest	0 [0]	0 [0]	0 [0]	χ^2=1.19	n.s.			
% Invalid Light – Rest	0 [4.42]	0 [2.72]	0 [3.97]	χ^2=0.40	n.s.			
White Exposure - Active	173352.80 [377212.2]	105955 [188162.1]	242582.2 [414466.3]	χ^2=2.25	0.063			
Average Light Exposure – Active	230.02 [518.78]	170.25 [268.76]	311.30 [563.60]	χ^2=2.43	0.040	n.s.	n.s.	0.039
Maximum Light Exposure – Active	9047.23 [18121.69]	10805.89 [12631.73]	12913.48 [20250.70]	χ^2=2.44	0.040	n.s.	n.s.	0.040
TAT Light – Active	22.00 [44.13]	16.74 [28.05]	24.19 [55.64]	χ^2=2.25	0.063			

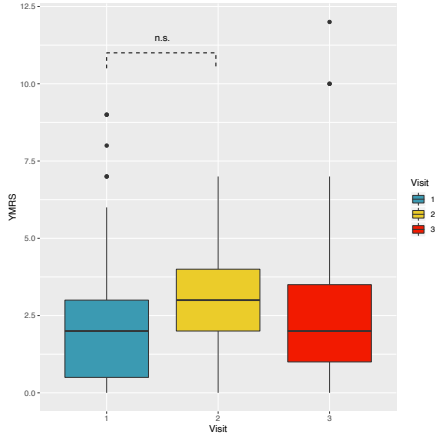
% Invalid Light – Active	3.25 [4.10]	2.35 [3.35]	2.11 [4.07]	χ^2=0.75	n.s.			
White Exposure - Sleep	191.69 [1387.26]	343.19 [735.13]	265.88 [2116.02]	χ^2=1.50	n.s.			
Average Light Exposure – Sleep	1.49 [5.88]	2.13 [5.08]	2.51 [9.89]	χ^2=1.03	n.s.			
Maximum Light Exposure – Sleep	15.19 [31.25]	19.72 [28.22]	17.72 [54.03]	χ^2=1.50	n.s.			
TAT Light – Sleep	0 [0]	0 [0]	0 [0]	χ^2=1.13	n.s.			
% Invalid Light – Sleep	0 [2.04]	0 [2.73]	0 [4.05]	χ^2=0.92	n.s.			
White Exposure - Daily	219746.8 [491295.9]	193809.9 [329590.8]	374895.6 [659211.7]	χ^2=1.92	n.s.			
Average Light Exposure – Daily	163.52 [365.01]	161.91 [262.10]	337.68 [522.37]	χ^2=1.74	n.s.			
Maximum Light Exposure – Daily	13293.15 [24961.76]	18310.66 [23305.52]	23436.92 [29491.73]	χ^2=1.67	n.s.			
TAT Light – Daily	36.67 [67.21]	25.46 [46.95]	43.53 [83.20]	χ^2=2.54	0.030	n.s.	n.s.	0.030

% Invalid Light – Daily	3.51 [5.43]	3.45 [5.98]	5.48 [7.75]	χ^2=1.55	n.s.			
* log transformed; Bolded text: survived Bonferroni Correction Abbreviations: 6-SM – 6-sulfatoxymelatonin; CQ – Circadian Quotient; L5 -5 consecutive lowest-activity hours; M10 – 10 consecutive hours with highest activity; MLiT – Mean timing of light exposure; pAR – probability of transitioning from active to rest state; pRA – probability of transitioning from rest to active state; SD – Standard Deviation; SE – Sleep Efficiency; TAT – Time Above Threshold; TST – Total Sleep Time; WASO – Wake After Sleep Onset.								

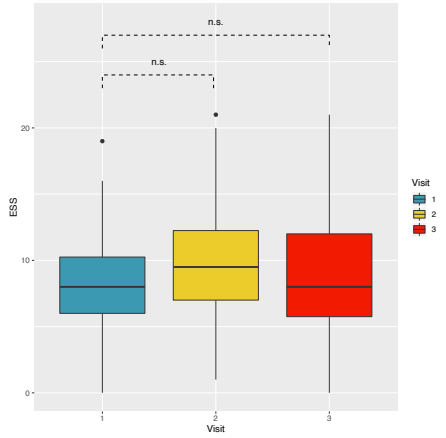
Figure 1: Longitudinal Changes in Clinical Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



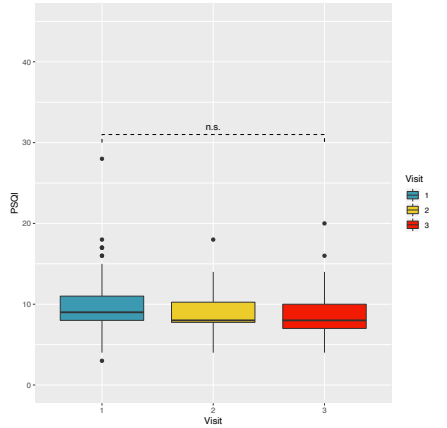
a) Montgomery Åsberg Depression Rating Scale (MADRS)



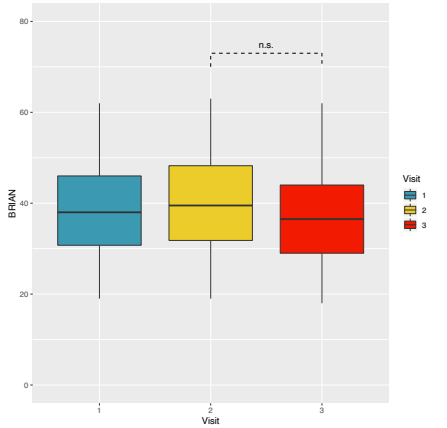
b) Young Mania Rating Scale (YMRS)



c) Epworth Sleepiness Scale (ESS)



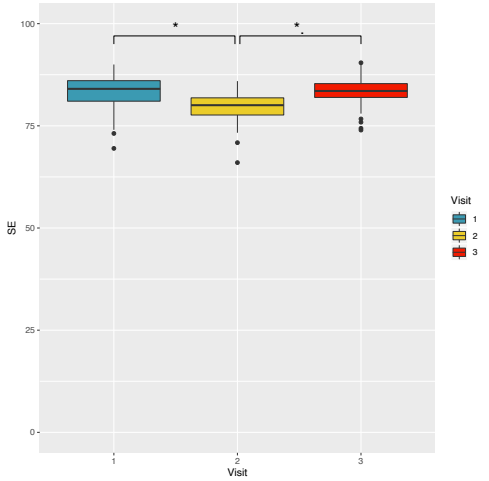
d) Pittsburgh Sleep Quality Index (PSQI)



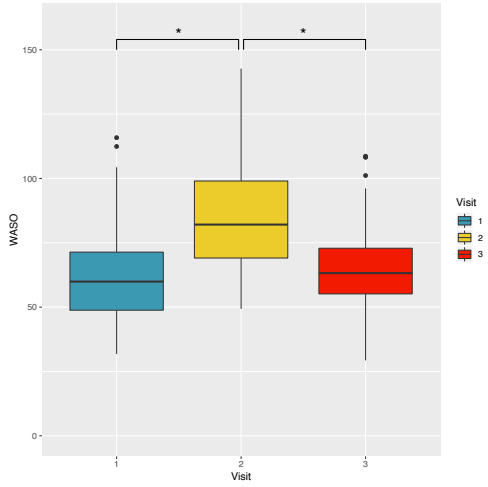
e) Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)

*significant ($p<0.05$).

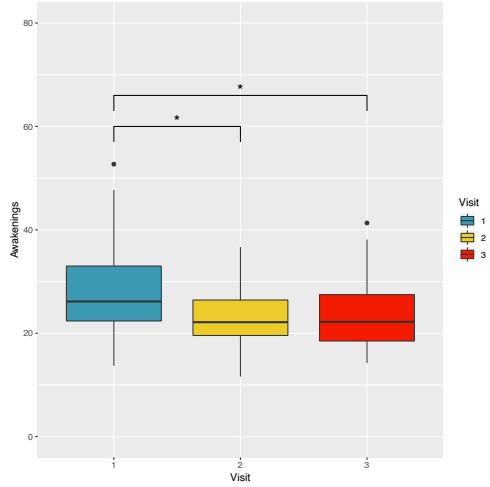
Figure 2: Longitudinal Changes in Sleep Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



a) Sleep Efficiency (SE)



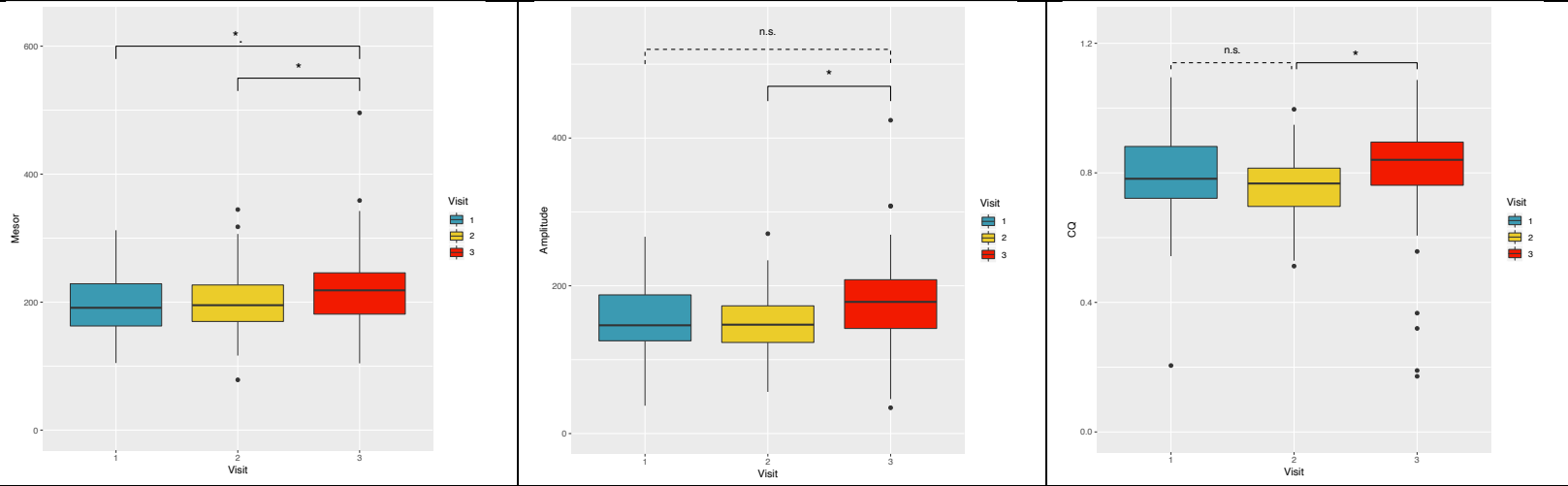
b) Wake After Sleep Onset (WASO)



c) Number of Awakenings

*significant ($p<0.05$)

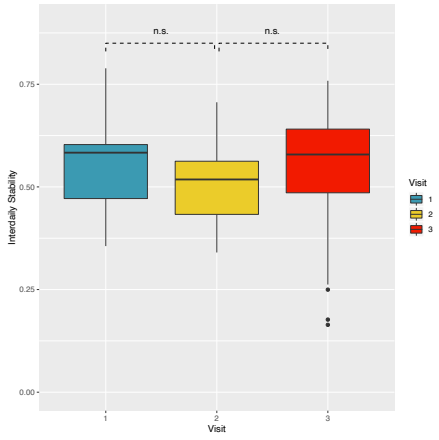
Figure 3: Longitudinal Changes in Cosinor Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



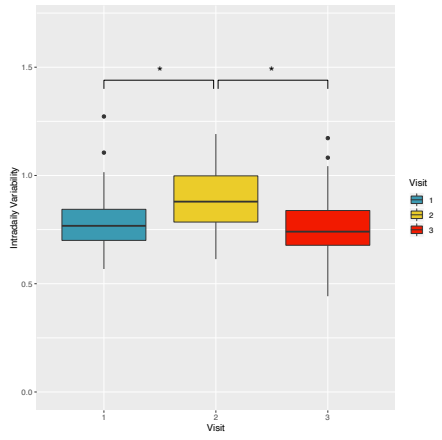
a) Mesor | b) Amplitude | c) Circadian Quotient (CQ)

*significant ($p<0.05$)

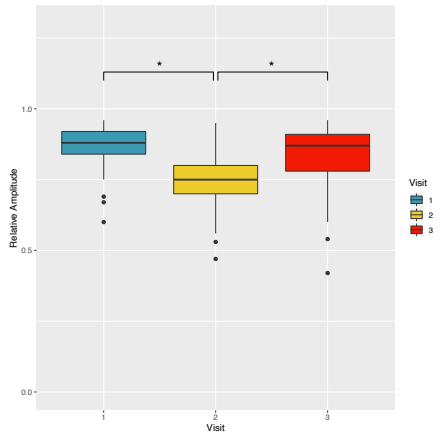
Figure 4: Longitudinal Changes in Non-Parametric Circadian Activity Rhythm Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



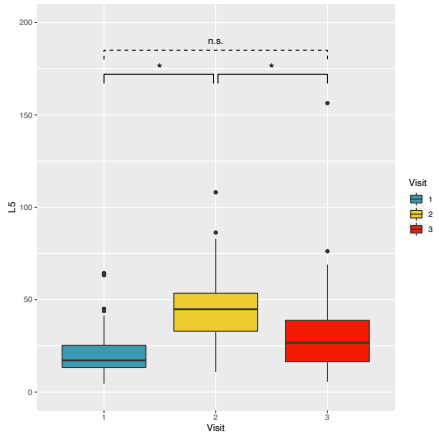
a) Interdaily Stability (IS)



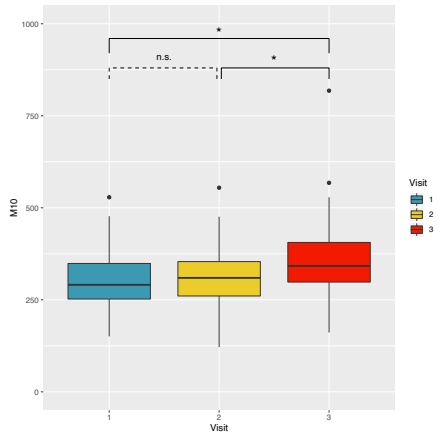
b) Intradaily Variability (IV)



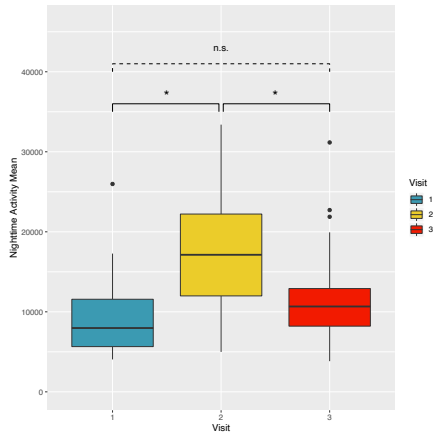
c) Relative Amplitude (RA)



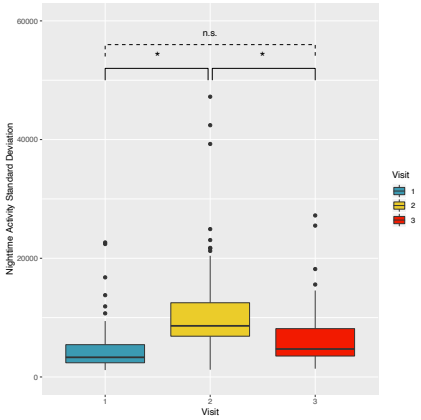
d) Lowest 5 Hours of Activity (L5)



e) Highest 10 Hours of Activity (M10)



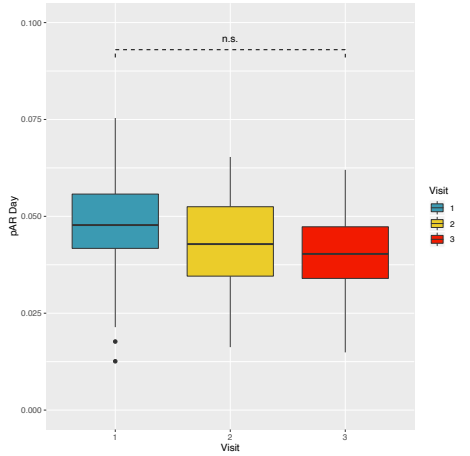
f) Nighttime Activity Mean



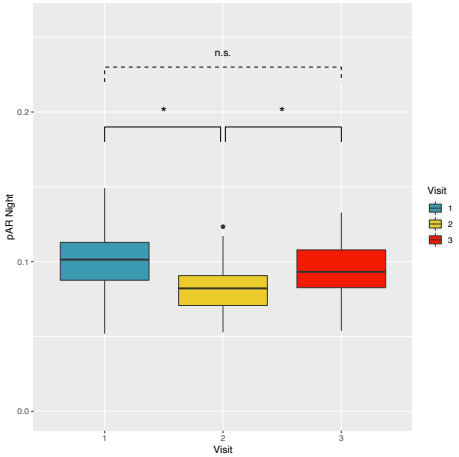
g) Nighttime Activity Standard Deviation

*significant ($p<0.05$)

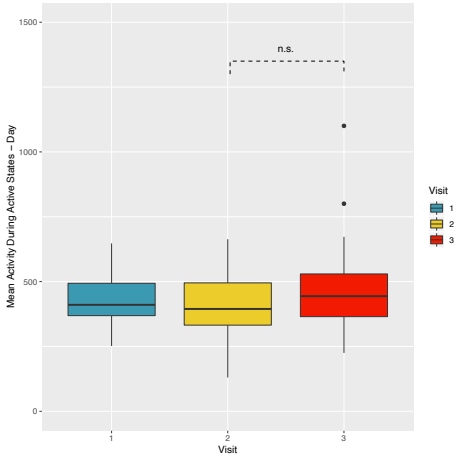
Figure 5: Longitudinal Changes in Transition Probabilities Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



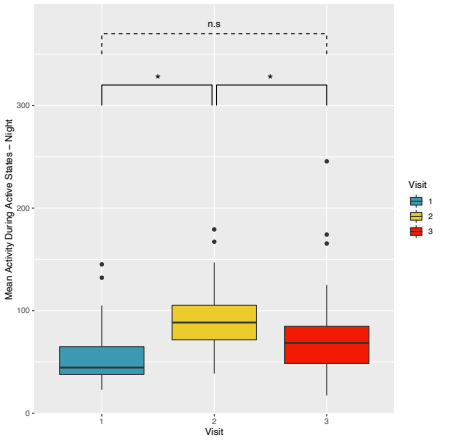
a) Probability of Transitioning from Active to Rest States During the Day

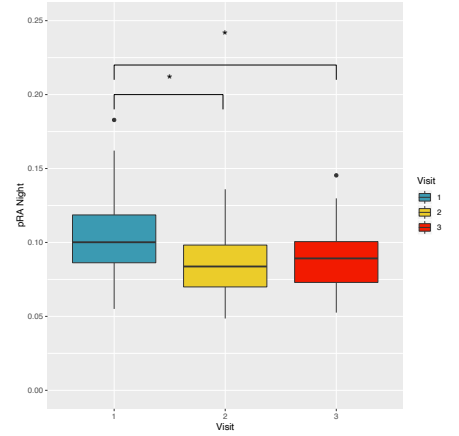


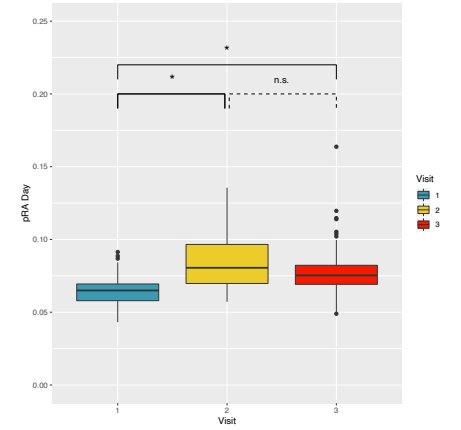
b) Probability of Transitioning from Active to Rest States During the Night



c) Mean Activity during Active States During the Day







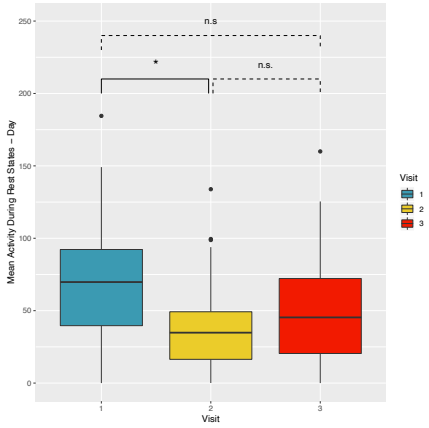
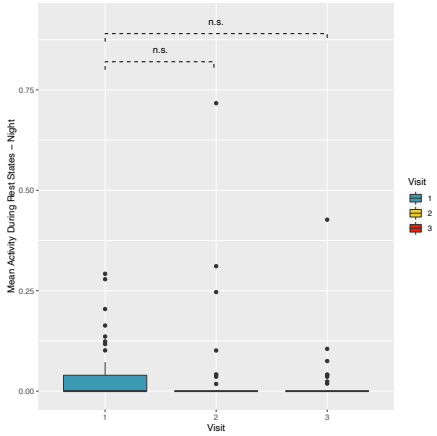
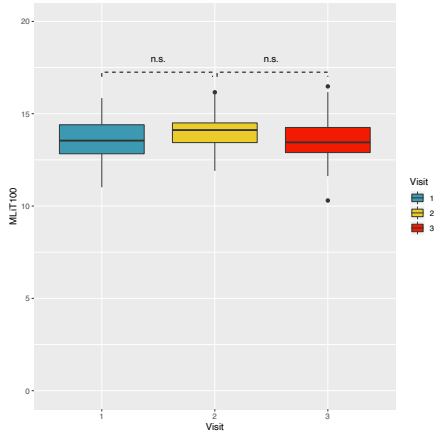
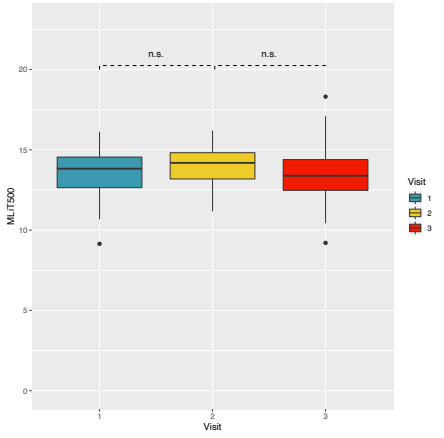
d) Mean Activity during Active States During the Night	e) Probability of Transitioning from Rest to Active States During the Night	f) Probability of Transitioning from Rest to Active States During the Day
		
g) Mean Activity during Rest States During the Day	h) Mean Activity during Rest States During the Night	
*significant ($p<0.05$); pAR - Probability of Transitioning from Active to Rest State; pRA - Probability of Transitioning from Rest to Active State.		

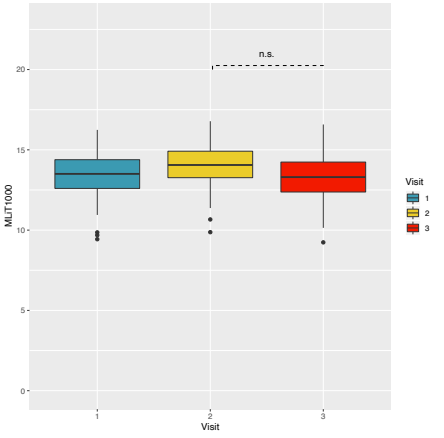
Figure 6: Longitudinal Changes in Light Exposure Variables from the 3rd Trimester of Pregnancy to 1-3 Weeks and 6-12 Weeks Postpartum



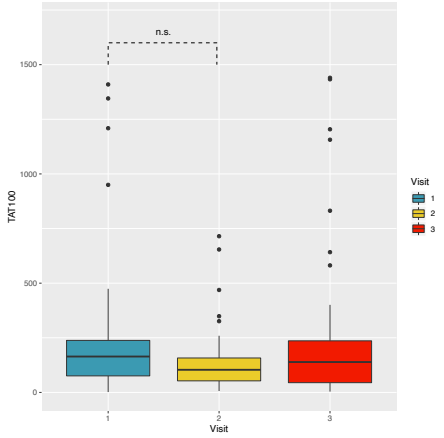
a) Mean Light Timing Above Threshold – 100 lux (MLiT100)

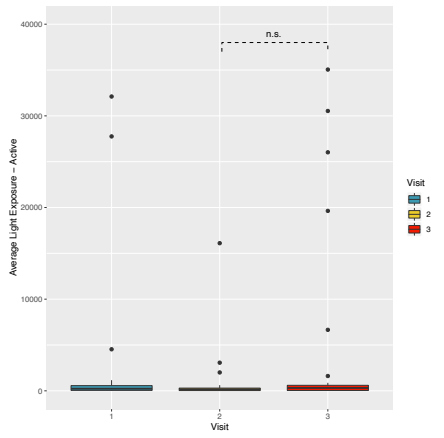


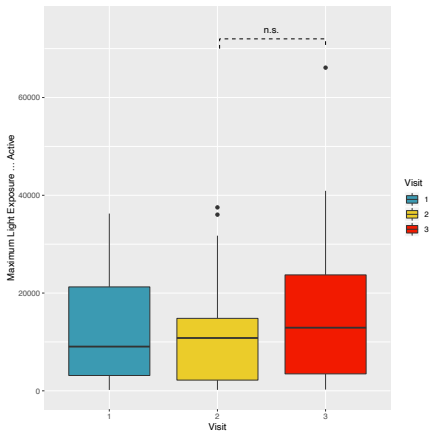
b) Mean Light Timing Above Threshold – 500 lux (MLiT500)

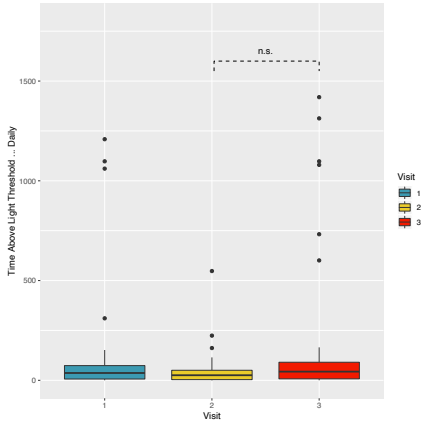


c) Mean Light Timing Above Threshold – 1000 lux (MLiT1000)







d) Time Above Threshold – 100 lux (TAT100)	e) Average Light Exposure- Active	f) Maximum Light Exposure – Active
		
g) Time Above Light Threshold – Daily		
*significant ($p<0.05$)		

Chapter 6: Discussion

6.1 Summary of Findings

Biological rhythms and sleep change prior to the onset of mood episodes and as part of the pathophysiology of mood disorders (American Psychiatric Association, 2013; Jackson, Cavanagh, & Scott, 2003; Van Meter, Burke, Youngstrom, Faedda, & Correll, 2016). Methods of investigating biological rhythms and sleep continue to be refined, with novel methods of analyzing ambulatory actigraphy data emerging in recent years (Fasmer, Fasmer, Berle, Oedegaard, & Hauge, 2018; Ortiz, Bradler, Radu, Alda, & Rusak, 2016; Parro & Valdo, 2018). Prior studies of biological rhythms and sleep in mood disorders have been limited by studies investigating only objective or subjective changes in sleep and biological rhythm variables, a lack of investigations of light exposure, or monitoring activity only for short periods, which reduces the reliability of actigraphy. Moreover, prior studies have not investigated the impact of objective and subjective measures of sleep and biological rhythms on functioning and quality of life.

In the first study, described in Chapter 2, we thoroughly characterized sleep and biological rhythms in individuals with major depressive and bipolar disorders, using well-established (sleep variables, cosinor analysis, melatonin secretion) and novel non-linear (transition probabilities) techniques of assessing mood and biological rhythms (Slyepchenko et al., 2019). We found evidence of wide-spread disturbance in sleep and rhythms in MDD and BD, particular to each disorder, across multiple domains, including

subjective sleep and biological rhythms, including circadian activity rhythms, transition probabilities, activity, light exposure, and overnight melatonin secretion.

One of the novel findings of our study was that we explained a high proportion of the variance in quality of life and functional impairment using subjective and objective measures of sleep and rhythms in a mixed-diagnosis population. To our knowledge, this study was also one of the first to quantify light exposure in mood disorders. The findings of this study emphasize the importance of sleep, biological rhythms and light exposure as a component of the pathophysiology of mood disorders, extending to impairment of psychosocial functioning and quality of life.

In pregnancy and postpartum, investigations of the impact of sleep and biological rhythms on mood and anxiety have been largely limited by small sample size, lack of thorough clinical characterization, cross-sectional design, use of only objective or subjective methods of characterizing biological rhythms and sleep. Additionally, there have been very few investigations of the impact of sleep and biological rhythms on anxiety during the perinatal period, in spite of the high prevalence of perinatal anxiety. Therefore, we investigated the role of biological rhythms and sleep assessed during pregnancy as predictors of mood and anxiety in the postpartum period, by following women who were not experiencing a mood episode during pregnancy to postpartum.

In Chapter 3, we show that objective and subjective measures of biological rhythms and sleep, in combination with clinical variables and demographics collected during pregnancy were able to account for 50% of variance in severity in symptoms of postpartum depression. Interestingly, levels of overnight melatonin, and objective

measures of sleep and light exposure were found to be some of the most important predictors of PPD in our model. This highlights the importance of assessing the melatonin system and light exposure in future studies of biological rhythms in mood, and provides rationale for future investigations of light-based therapies as preventive and/or adjunctive treatments of PPD.

Due to the high prevalence of anxiety disorders in the perinatal period, and the paucity of literature of predictors of perinatal anxiety, in Chapter 4, we investigated the role of sleep and biological rhythms assessed in pregnancy as potential predictors of postpartum anxiety. These variables, in conjunction with clinical variables were able to explain 49% of variance in postpartum anxiety symptoms. Daily activity rhythms, light exposure, and other objective and subjective variables were important in modeling this relationship, indicating that sleep, biological rhythms, and light may serve as important targets in preventing and managing anxiety in women during the perinatal period.

In Chapter 5, we present a number of analyses describing the longitudinal trajectories of sleep, biological rhythms and light exposure over the perinatal period. We found a number of significant changes in objective sleep parameters from the 3rd trimester of pregnancy to 1-3 weeks and 6-12 weeks postpartum, most notably in SE, WASO, and number of awakenings. A number of significant changes were also seen in biological rhythms through the perinatal period, including variables obtained from cosinor analysis, biological rhythm variability, activity parameters, and probabilities of transitioning between rest and activity. These findings emphasize that the perinatal period is associated

with robust changes in biological rhythms that may or may not affect mental health outcomes.

6.2 Significance and General Discussion

The significance of the major findings of the studies described in this thesis is discussed at length within each chapter. Overall, this work characterized sleep and biological rhythm disruption as an important transdiagnostic factor in mood disorders and anxiety within and outside of the perinatal period. While sleep disruptions are a well-established characteristic of many psychiatric disorders (Baglioni et al., 2016), investigations of biological rhythms beyond sleep provide unique information regarding individuals' 24-hour patterns of rest and activity. Understanding biological rhythms disruptions associated with mood and anxiety may therefore provide important targets for therapeutic interventions to prevent mood and anxiety worsening, and associated impairment in functioning and quality of life.

Prior studies have revealed subjective disruptions in sleep and biological rhythms to be linked to symptom severity, QOL, and functioning in MDD and BD (Cudney, Frey, Streiner, Minuzzi, & Sassi, 2016; De la Fuente-Tomas et al., 2018; Giglio, Magalhaes, Kapczinski, Walz, & Kapczinski, 2010; Li, Lam, Chan, Yu, & Wing, 2012; Pinho et al., 2016). In Chapter 2, we present novel findings, where we modeled QOL and functional impairment as a function of sleep and biological rhythm disruption across individuals with BD, MDD and a group of non-psychiatric controls. Considering that individuals with MDD and BD continue to experience impaired functioning and QOL in

remission/euthymia (IsHak et al., 2015; Kessler et al., 2003; Martín-Subero et al., 2014; Pascual-Sanchez, Jenaro, & Montes-Rodriguez, 2019), our findings indicate that sleep and biological rhythms could be targeted for development of interventions to improve functioning and QOL in mood disorders across and beyond mood episodes.

In Chapters 3 and 4, we presented findings of clinical variables, light exposure, subjective and objective measures of sleep and biological rhythms as predictors of PPD and postpartum anxiety symptoms. Some previous studies did not find subjective or objective sleep measures during pregnancy to be predictive of PPD (Bei, Milgrom, Ericksen, & Trinder, 2010; Coo Calcagni, Bei, Milgrom, & Trinder, 2012; McEvoy et al., 2019), while others indicated that 3rd trimester sleep quality was linked to PPD symptom severity at 8 weeks and 3 months postpartum (Osnes, Roaldset, Follestad, & Eberhard-Gran, 2019; Tham et al., 2016). Our studies add to this body of literature, suggesting that it is important to collect subjective and objective information on both sleep and biological rhythms, in addition to light, in order to predict PPD and postpartum anxiety symptoms. These findings indicate that biological rhythm disruptions beyond sleep may pose risk for PPD and postpartum anxiety. For instance, we confirmed previously established clinical and demographic factors being predictive of PPD symptoms, including neuroticism and antenatal anxiety (Lee, Yip, Leung, & Chung, 2000; Martin-Santos et al., 2012; Robertson, Grace, Wallington, & Stewart, 2004). Some of the most robust predictors of PPD and PPA severity in our models were variables describing light exposure, particularly, measures which describes timing of light exposure throughout the day. To our knowledge, this is a novel finding within the perinatal population, suggesting that

light exposure may serve as an important therapeutic target for the prevention and treatment of perinatal mental disorders.

In Chapter 4, we present a number of clinical variables, sleep variables and biological rhythm variables which predicted postpartum anxiety. There are few well-established risk factors for anxiety during the perinatal period (Furtado, Chow, Owais, Frey, & Van Lieshout, 2018). For new onset anxiety, these include psychosocial factors (lower levels of education, family history of mental illness, cohabitating with extended family), hyperemesis gravidarum, and a history of sleep disorders. Meanwhile, anxiety worsening may be linked to maternal age and having a psychiatric comorbidity (Furtado et al., 2018). The study described in Chapter 4 provides new potential biological and psychosocial markers for development of postpartum anxiety, that can be assessed in pregnancy, including personality factors (neuroticism, openness), having winter seasonality, iron use and having a history of panic disorder/ limited symptom attacks, light exposure (mean timing of light exposure over 10 lux, daily percentage of invalid light), intradaily variability, subjective biological rhythm disruption, objective TST, and mean mid sleep time.

Chapter 5 describes preliminary results of longitudinal changes in sleep and biological rhythms across several domains, including subjective changes, sleep variable changes, and changes in several different measures of biological rhythms. To our knowledge, changes in objective biological rhythm measures, including daily activity rhythm parameters from cosinor and non-parametric circadian activity rhythm analysis, and transition probabilities from pregnancy to postpartum have not been previously

described. Our findings are partially consistent with Matsumoto and colleagues, who found that SE decreased from pregnancy to early postpartum, while WASO increased. However, while their findings showed significantly decreased TST and decreased amplitude in early postpartum, we did not see this pattern (Matsumoto, Shinkoda, Kang, & Seo, 2003). Some changes in sleep and daily activity rhythms that occur early in the postpartum period are transient, appearing only during the first 1-3 weeks postpartum (e.g. decreased SE, increased WASO, increased IV and L5 activity, increased mean and standard deviation of night time activity, and decreased relative amplitude and probability of transitioning from activity to rest at night). Other changes from pregnancy remained significant at 6-12 weeks postpartum, such as lower number of awakenings, increased mesor, higher M10, and higher probability of transitioning from rest to activity during the day and night, which suggest progressive normalization of sleep and biological rhythms later in the postpartum period. However, as we did not include a pre-pregnancy timepoint or a non-pregnant comparison group, we are unable to conclude whether these changes indicate return to pre-pregnancy values, or whether they indicate a persistent disruption in biological rhythms. However, given reports indicating that parental subjective sleep duration does not return to pre-pregnancy norms until up to 6 years postpartum (Richter, Kramer, Tang, Montgomery-Downs, & Lemola, 2019), the former option seems less likely.

In the studies described in this thesis, we investigated several domains of sleep, biological rhythms and light exposure in adults outside of the perinatal period, and within the perinatal period using similar methods. In the perinatal and non-perinatal

investigations, light exposure was associated with several outcomes. Interestingly, mean timing of light exposure occurred later in the day for individuals with MDD and BD in Chapter 2. In addition, mean timing of light exposure during pregnancy was a predictor of both PPA severity (Chapter 4) and PPD severity (Chapter 3). In a longitudinal analysis, from pregnancy to 1-3 weeks and 6-12 weeks postpartum, we saw changes in light exposure across this period, including changes in mean timing of light exposure at 1-3 weeks postpartum, compared to the 3rd trimester of pregnancy and 6-12 weeks postpartum. Additionally, we saw a decrease in time spent in lighting conditions below 100 lux from pregnancy to 1-3 weeks postpartum, and lower average light exposure at 6-12 weeks postpartum compared to 1-3 weeks postpartum. However, these changes did not survive a strict Bonferroni correction (Chapter 5). To our knowledge, this is the first investigation to look at the effect of timing and quantity of light exposure during pregnancy on postpartum mood. Previously, Crowley & Youngstedt speculated that women may spend more time in dim light conditions during the perinatal period, to potentially make up for lost nighttime sleep (Crowley & Youngstedt, 2012). Overall, little is known about light exposure in mood and anxiety disorders, in spite of prior investigations of bright light therapy and blue light blocking glasses found to be effective in mood disorders (Henriksen et al., 2016; Perera et al., 2016; Sit et al., 2018), and preliminary investigations showing improved mood in the perinatal population from light-based therapies (Bennett, Alpert, Kubulins, & Hansler, 2009; Corral, Wardrop, Zhang, Grewal, & Patton, 2007; Swanson, Burgess, Zollars, & Todd Arnedt, 2018). In our studies, we did not investigate the mechanism behind changes in light exposure and

timing in BD and MDD, or the effect of light exposure on PPD and PPA. Changes in the timing of light exposure could be reflective of a later phase of activity throughout in BD and MDD, indicating that those with BD and MDD are outdoors or exposed to higher amounts of light indoors later in the day, when they're more active, compared to their counterparts. Considering that light exposure can also suppress melatonin secretion (Claustrat, Brun, & Chazot, 2005), it is possible that later timing of exposure to light leads to a later phase of melatonin secretion, and consequent phase delay. However, in Chapter 2, we did not see other markers of phase delay (e.g. mean mid sleep time, M10 and L5 start time, or either chronotype measure) in MDD or BD. Interestingly, changes in light exposure can also interact with the hypothalamic-pituitary-adrenal axis, as light exposure affects the phase and amplitude of cortisol secretion (Dijk et al., 2012).

Use of actigraphy methods that do not rely on fitting to 24 hours may be more adept at describing biological rhythm disturbances, particularly in populations where there are significant disturbances in sleep (Gonzalez, Tamminga, Tohen, & Suppes, 2014). Populations studied in this thesis – individuals with mood disorders, and women during the perinatal period -- are well known to have disruptions in sleep. Additionally, variability measures in actigraphy are increasingly becoming acknowledged as important beyond solely relying on means. Krane-Gartiser and colleagues recently published a study where they used actigraphy to differentiate between healthy controls and currently euthymic individuals with BD, finding that to optimally discriminate between these groups, it was necessary to combine the means of sleep variables, their variability and non-parametric circadian activity rhythm measures (Krane-Gartiser et al., 2019).

Advances in technology and increased collection of large datasets have now provided the opportunity for researchers to monitor and model complex phenomena, such as sleep, biological rhythms, neural function and other related physiological and behavioural domains. An important methodological consideration of Chapters 3 and 4 was using machine learning methods in combination with traditional statistical methods. This approach aimed to utilize the inferential nature of traditional statistical methods, where the model was created to determine whether there is a relationship between the predictor and outcome variables, and to estimate the confidence of the existence of this relationship through hypothesis testing. Inferential approaches using traditional statistics become less feasible, as predictors become more numerous, and the relationships between predictors and outcomes therefore become more numerous and complex, particularly when it comes to non-linear relationships. Traditional statistical modeling often relies upon creating linear models, with linear interactions added to the model to account for relationships between the variables (Bzdok, 2017; Bzdok, Altman, & Krzywinski, 2018).

Machine learning models, however, may improve the predictive power of a model, without considering potential inferential relationships *a priori*, and are data-driven. ML approaches are able to account for complex, non-linear relationships between variables. Importantly, they are well-matched to high-dimensional data, and are able to approach large datasets with many predictor variables (Jordan & Mitchell, 2015). In neuroscience, these types of datasets are becoming increasingly available, with the advance of technologies including high-throughput methods like actigraphy, neuroimaging, and whole genome sequencing, in addition to large, multisite studies,

investigating numerous predictors of, for instance, treatment response (e.g.(Lam et al., 2016)).

Machine learning models and classical statistical inference models can therefore serve different, complimentary modeling purposes. In our investigation, we used both of these approaches to address inference and prediction, finding similarities and differences in findings. For instance, in Chapter 3, we used an externally collected data set to test our ML models, mimicking the use of these models in settings outside of our lab. We encountered that model accuracy was decreased in this set of analyses, compared to those where we split the newly collected data set into a 75% training – 25% test set, despite the larger sample size. The externally collected dataset differed from ours in several ways: actigraphy assessments in the external dataset were collected over a longer period (3 weeks, compared to this dataset's 2 weeks), and levels of 6-SM were not collected. Moreover, in Chapter 4, we were not able to test our model on an externally collected dataset, as this external data set did not assess perinatal anxiety. This example highlights important real-world clinical and research conditions. By using machine learning models, we were able to account for more complex, non-linear relationships between the variables in the model, which is not possible to do using linear regression. Given the complexity of the human experience, it is likely that mood and anxiety do not strictly follow linear patterns. However, other investigations or clinicians may not have access to clinical instruments or biological sampling methods, or may not assess certain variables in their practice. In this situation, it is not possible for other clinicians or researchers to adjust the

final machine learning models from these investigations to fit their sampling methods. Linear regressions, however, allow for external adjustment.

A prior study used electronic health record data to create machine learning algorithms from pregnancy data to predict PPD, achieving high sensitivity (0.87-0.99), but very low specificity (0.39-0.62) (Wang, Pathak, & Zhang, 2019).Variables in this model included race, obesity, anxiety and depressive symptoms during pregnancy, pain and current medications (Wang et al., 2019)). Due to the methodological differences, in that our investigation used continuous, rather than categorical outcomes, we are unable to compare the performance of our algorithm to the one presented in Wang, Pathak and Zhang's study.

6.3 Limitations

The limitations of each individual study are described in detail within each chapter of this thesis. The overall limitations of the studies are highlighted below.

One important limitation to our investigations is that prior studies suggest that actigraphy is less reliable than polysomnography in detecting quiet wakefulness compared to sleep, particularly in individuals with worse sleep quality. Longer periods of recording activity (7-14 nights) improve the assessment capability of actigraphy to record sleep parameters (Van de Water, Holmes, & Hurley, 2011). To partially address this, our studies included longer periods of actigraphy collection (15 days), allowing for more accurate characterization of sleep and daily activity rhythm patterns.

Additionally, in both studies presented in this thesis (Chapters 2-5), some of the participants enrolled were taking psychotropic medications. Overall, many psychotropic medications can affect sleep and biological rhythms, including melatonin secretion (Harding, Alford, & Powell, 1985; Mayers & Baldwin, 2005; Moreira & Geoffroy, 2016; Waters, Faulkner, Naik, & Rock, 2012). Therefore, we could not ascertain the impact of medication on sleep and biological rhythms within our studies. Similarly, we did not assess whether participants were undergoing psychotherapy, which may also impact sleep and biological rhythms. The psychoeducation component of psychotherapy often teaches clients regarding importance of sleep hygiene. It is important to note that many women in our perinatal sample were being followed by clinicians throughout the perinatal period, if they had a history of psychiatric disorders. Psychoeducation about sleep hygiene and mood may have influenced the sleep hygiene in these women, and we did not investigate participants' adherence to sleep hygiene.

In Chapter 2, we were unable to compare currently depressed and euthymic patients, due to our sample size limitations. We also did not recruit individuals in [hypo]manic and mixed states, and therefore were unable to investigate associated differences in light exposure, transition probabilities, and daily activity rhythm patterns across all mood states. Moreover, Chapter 2 was a cross-sectional study, indicating that we could not evaluate the causal relationships between mood, sleep and biological rhythms within this investigation.

In Chapter 3, we were not able to look at predicting postpartum depression categorically. Our sample of women was euthymic at enrolment, and the rates of PPD

development in our sample are consistent with population-based studies that have found 7-13% of women to develop PPD (Gavin et al., 2005). As this study was primarily designed to investigate postpartum depression, in Chapter 4, we did not assess anxiety disorder diagnoses in the postpartum period with a structured interview. Moreover, we were not able to look at the influence of individual anxiety disorder diagnoses on sleep and biological rhythm variables, due to the heterogeneity of anxiety disorders within our sample. Since the study's primary aim was to investigate mood worsening, we did not include measures such as intolerance of uncertainty, different types of anxiety-related disorder symptoms (e.g. OCD), which are known to also influence anxiety. We did not look at all extant anxiety disorders, such as specific phobias, though prevalence of specific phobias during pregnancy is as low as 0.03% (Goodman, Watson, & Stubbs, 2016). Additionally, prior evidence suggests that different anxiety and related disorders may have different associated sleep disturbances (Cox & Olatunji, 2016). This may add heterogeneity to the sleep disturbances seen in this investigation.

6.4 Future Directions

The work described in this thesis provides a basis for several future lines of investigation. The first of these is to more thoroughly investigate the role of light in mood disorders and in perinatal mood and anxiety. There have only been small, preliminary trials investigating light-based therapies in PPD, showing promising improvements in depressive symptoms following bright light therapy and blue light blocking glasses (Bennett et al., 2009; Corral et al., 2007; Swanson et al., 2018). Larger randomized

controlled trials should be conducted investigating these effects. To our knowledge, no study has previously investigated the effects of bright light therapy on postpartum anxiety. Additionally, with the advent and popularity of consumer "smart" technologies which allow users to control the timing, colour and brightness of the lighting in their homes, future studies could attempt to optimize the timing and brightness of this ambient light exposure to better suit individuals who are more prone to disruptions in biological rhythms (Bedrosian & Nelson, 2017).

As outlined in Chapter 5 of this thesis, prior studies have yet to address trajectories of depressive or anxiety symptoms as a function of objective sleep and biological rhythms. Based on the findings outlined in Chapter 2, future investigations could look at therapies targeting sleep and biological rhythms as adjunct therapies to help improve functioning and quality of life in individuals with mood disorders. Prior investigations have found that treating insomnia with cognitive behavioural therapy for insomnia improves mood and functioning in BD (Harvey et al., 2015) and QOL in MDD (Shimodera et al., 2014), however randomized controlled trials to target functioning and QOL in individuals with remitted mood disorders have not been conducted to our knowledge. Therapeutic interventions targeting biological rhythms, such as interpersonal and social rhythm therapy, bright light therapy, or blue-light blocking glasses could also be investigated as an intervention to improve functioning and quality of life.

Future investigations could also look at the influence of sleep and biological rhythms on different types of anxiety symptoms during the perinatal period. Our Chapter 4 focused only on GAD symptoms, and did not, for instance, investigate symptoms of

PTSD, OCD, or panic disorder. A recent systematic review suggested that there are differences in subjective and objective sleep across different anxiety disorders (Cox & Olatunji, 2016). Studies should therefore investigate whether different markers of sleep and biological rhythms during pregnancy are predictive of different types of postpartum anxiety. Another line of investigation could look at the influence of sleep and biological rhythms on development of new onset anxiety during postpartum as compared to postpartum anxiety worsening. According to a recent meta-analysis, having a history of sleep disorders is a risk factor for developing new onset perinatal anxiety (Furtado et al., 2018).

It would be interesting to assess whether these predictors of postpartum anxiety and depression are valid cross-culturally. As prevalence of perinatal anxiety is higher in low- to middle-income countries (Dennis, Falah-Hassani, & Shiri, 2017), future studies could assess the validity of the novel markers presented in Chapter 4 across different countries and cultures.

While these studies described differences in light exposure timing in MDD and BD, and the predictive effect of light exposure timing on PPD and PPA, the mechanism behind these differences is unknown. Future studies should prospectively monitor light exposure changes in conjunction with measures of biological rhythm, sleep, and mood, in order to disentangle the temporal relationship between light exposure, biological rhythms, sleep and mood.

A final note for future investigators is that the machine algorithms used in Chapters 3 and 4 are relatively standard machine methods. Future studies could use more

advanced ML methods, and could try to predict categorical diagnosis of postpartum depression or postpartum anxiety within larger samples.

6.5 Conclusion

The work described within this thesis shows that sleep and biological rhythm disruptions occur across many domains in mood disorders, including sleep, light exposure, rhythms of activity beyond sleep and, melatonin. We found that these disruptions are associated with quality of life and functioning in an adult sample of individuals with BD, MDD and healthy controls. Additionally, we found that biological rhythms and sleep in combination with clinical variables predict severity of postpartum depressive and anxiety symptoms. This work highlights the importance of sleep and biological rhythms as targets for interventions across different outcomes, and across different mood diagnoses.

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