BIOLOGICAL RHYTHMS, SLEEP AND COGNITION IN MOOD DISORDERS

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Abstract

This thesis presents research investigating the relationship between, and methods of, measuring circadian rhythms in mood disorders in a population of currently depressed and euthymic individuals with both depression and bipolar disorder. This was first assessed by comparing group differences in subjective sleep and circadian measures with objective sleep and circadian measures. The objective circadian measures involved actigraphy and melatonin profiling. This analysis showed group differences in subjective sleep and circadian parameters compared to controls, however no robust differences between mood groups. Objective melatonin profiling showed a mild agreement with subjective circadian parameters. Next, we studied the external validity of a subjective rating scale measuring biological rhythm disturbance, the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN), against objective measures of sleep and circadian activity rhythmicity. The BRIAN demonstrated some promising external validity, namely correlations with wake after sleep onset (WASO) and sleep efficiency, as well as melatonin levels in each group. These studies provide evidence of the extent to which a self-report may help in assessing parameters of sleep and circadian rhythms in the clinical setting. In doing so, it is expected that the use of subjective ratings will provide insight into the impact of biological rhythms disturbances and mood disorders. Lastly, we conducted an overview of the preclinical and clinical literature investigating the impact of circadian disturbance on cognitive performance. The results from this literature review yielded patterns of rhythmicity in specific parameters in each of the attention, memory, and executive function domains in humans, whereas attention and memory are more of a primary focus in animal studies. However, we also found that there are significant gaps in the understanding of how disturbances in circadian rhythms may influence cognitive function. This review also highlights the importance of cross-species translational validity from a methodological perspective, in order to generate positive clinical results beginning at the preclinical stage in neuropsychiatric disorders.

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List of Abbreviations

6-SM: 6-sulphatoxymelatonin BD: Bipolar disorder BMAL1: Aryl hydrocarbon receptor nuclear translocator-like protein 1, transcriptional activator BRIAN: Biological Rhythms Interview for Assessment in Neuropsychiatry CBT: Core body temperature CCK: Cholecystokinin CLOCK: Circadian locomotor output cycles kaput CRY: Cryptochrome, transcriptional repressor CO: Circadian quotient DLMO: Dim light melatonin onset DMH: Dorsomedial hypothalamus ESS: Epworth Sleepiness Scale GHT: Geniculohypothalamic tract IGL: Intergeniculate leaflet ipRGCs: Intrinsically photoreceptive retinal ganglion cells IS: Inter-daily stability IV: Intra-daily variability L/D: Light/dark MADRS: Montgomery-Asberg Depression Rating Scale MDD: Major depressive disorder MESOR: Midline estimating statistic of rhythm MnPN: Median preoptic nucleus of the hypothalamus PAD: Phase angle difference PER: Period, transcriptional repressor PFC: Prefrontal cortex PSQI: Pittsburgh Sleep Quality Index RHT: Retinohypothalamic tract SCN: Suprachiasmatic nucleus SOL: Sleep onset latency SPZ: Subparaventricular zone TST: Total sleep time VLPO: Ventrolateral preoptic nucleus VTA: Ventral tegmental area WASO: Wake after sleep onset YMRS: Young Mania Rating Scale

Declaration of Academic Achievement

This thesis consists of 5 chapters: Chapter 1 provides a background on major depressive disorder, bipolar disorder, circadian rhythms and cognition. Chapter 2 investigates the relationship between objective and subjective measures of sleep and circadian rhythmicity. Chapter 3 is a study of an objective validation of the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) questionnaire. Chapter 4 is a review of preclinical and clinical literature on the impact of 24h circadian variation, circadian misalignment and sleep deprivation on cognitive function. Chapter 5 presents an overview, final thoughts and conclusion of the results in this thesis. Chapters 2, 3 and 4 are intended for submission in peer-reviewed journals in the coming months.

Data collection for chapters 2 and 3 occurred between June 2015 – June 2016 at the Mood Disorders Program at St. Joseph's Healthcare Hamilton. This study was conceived and designed by Dr. Benicio Frey, William Simpson, Elizabeth Krawczak and myself. I oversaw all aspects of this study including REB approval, subject recruitment, study coordination, study visits, and data collection, analyses and management. I completed processing of biological samples. Melatonin assays were performed by lab technician Marg Coote. I performed all statistical analysis with the assistance of William Simpson and Dr. Luciano Minuzzi. I am very grateful to all contributors.

CHAPTER 1

General Introduction

Bipolar disorder and major depressive disorder remain serious and debilitating mental illnesses. Understanding the pathophysiology behind these disorders is crucial to the development of proper therapeutic interventions in order to allow patients the highest quality of life. An area of research regarding causality of mood disorders that has garnered high interest in the last few decades revolves around circadian rhythms disturbances as a biomarker. Circadian disruption in vulnerable individuals triggers abnormalities in mood, stress regulation and cognitive performance leading to globally reduced psychosocial functioning that persists into remission. Developing, assessing and validating fast, easy-to-use, accurate screening tools for circadian disturbances could potentially provide necessary and efficient insights into episode onset, allowing clinicians developing strategies for episode prevention.

The goal of this work was to investigate the relationship between biological rhythm disturbances and mood disorders, and to evaluate methods of measurement of these disturbances. Chapter 1 provides an introduction into mood disorders, circadian rhythm disruption and cognition. In chapter 2, we investigated objective and subjective parameters of sleep and biological rhythm disruption in bipolar disorder, major depressive disorder and controls. To follow-up, chapter 3 provides an objective validation of the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) as a subjective rating tool of biological rhythm disturbance. Chapter 4 provides a review of preclinical and clinical literature on the impact of circadian disturbances on cognitive performance. Finally, conclusions and future directions are discussed in chapter 5.

Major Depressive Disorder and Bipolar Disorder

Major depressive disorder (MDD) and bipolar disorder (BD) affect approximately 5-8% and 2-4% of adults, respectively in Canada (Pearson et al., 2013; Ratnasingham et al., 2012).

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Depression alone is one of the leading causes of years lived with disability worldwide and one of the leading causes of premature death (WHO, 2000). Bipolar disorder is projected to also be among the top ten causes of disability worldwide by 2020 (Ratnasingham et al., 2012). Mood disorders cause marked impairment in personal, social and occupational functioning, generating substantial societal costs, not only with regard to healthcare expenditures, but also in terms of lost productivity. Furthermore, depression alone costs the economy in Ontario \$12.5 billion per year (Gnam et al., 2006). This is largely in part due to the fact that a comorbidity is present in both bipolar and unipolar depression, often an accompanying psychiatric or physical illness.

Diagnosis of major depressive disorder is contingent upon recurrent, sustained presentation of depressive symptoms for at least two weeks or longer (American Psychiatric Association, 2013). Episodes are considered independent of each other, and the patient is considered in sustained remission if the clinical presentation of symptoms subsides for a period of two months or longer. Depressive symptoms include low mood/negative affect, loss of pleasure/interest in things one usually enjoys, sleep/circadian disruption, low energy and fatigue, and feelings of worthlessness and guilt among other symptoms. Major depression has been consistently associated with functional impairment both at home and in the workplace, mediated by cognitive deficits that often persist into remission (Bakish, 2001; Hirschfeld et al., 2001; Miller, 1998; Woo et al., 2016). Two major predictors of recurrence that have been identified are the number of prior episodes and the presence of subclinical residual symptoms during remission (Hardeveld et al., 2010).

Diagnosis of bipolar disorders often first occurs in adolescence/early adulthood after several years presenting symptoms of mania interspersed with episodes of depression, and is often misdiagnosed several times prior to arriving at this stage (Price, 2012). It is a chronic and debilitating illness characterized by manic symptoms that include overactivity, elevated happiness, lack of sleep but still feeling rested, impulsivity and disinhibited behaviours, among other symptoms, that persist for several days or longer (Miller, 2016). Similar to MDD, functional

MSc. Thesis: O. Allega, McMaster University, Neuroscience impairments that persist into clinical remission are considered inter-episodic residual symptoms of the disorder, leading to trait-like differences in individuals who suffer from the condition. Evidence has demonstrated the presence of sleep and circadian rhythm disturbances (Sylvia et al., 2003; Geoffroy et al., 2014), emotional dysregulation (Henry et al., 2008) and cognitive impairments in euthymic BD (Martinez-Aran et al., 2004). It is thought that these residual symptoms exist in an interactive manner with each other, exacerbating the effects of other residual symptoms, producing a lower level of functioning in euthymia for those afflicted. Residual symptoms in euthymic BD are also associated with an increased risk of relapse (Judd et al., 2008).

Most patients with who meet criteria for MDD or BDD are accompanied with lifetime psychiatric comorbid conditions, where anxiety and substance abuse are considered among the top comorbidities (Hirschfeld et al., 2001; Merikangas et al., 2007). 52% of bipolar subjects (Schaffer et al., 2006) and 25% of MDD subjects (Patten et al., 2015) met criteria for a comorbid anxiety disorder in community health surveys. Furthermore, mood disorders are linked to a multitude of other medical conditions involving metabolic disturbance (Fagiolini & Goracci, 2009), overweight/obesity (Depp et al., 2014), cardiovascular disease (Magalhaes et al., 2012). Empirical evidence also shows that, compared to the general population, BD subjects display a decreased life expectancy attributable not only to suicide, but mainly because of chronic comorbid medical conditions such as diabetes, obesity and cardiovascular disease (Manning, 2015; Roshanaei-Moghaddam & Katon, 2009).

Although still unclear, the focus of much biological research has been involved in clearly delineating the phenomena responsible for the development and persistence of mood episodes. Understanding how biological mechanisms manifest into clinical implications depends on establishing causal relationships between major contributors to manic and depressive illness. There are several pathways currently thought to be implicated in the neurobiology of these diseases, however one of the main areas of research in this area in the last two decades has

Circadian Rhythms: Overview, Molecular Function and Neurobiology

Circadian rhythms are daily, entrainable biological processes that display roughly a 24-h endogenous rhythm in behaviour, physiology and metabolism. The term circadian is derived from the Latin term *circa*, meaning "around", and *diem*, meaning "day". Rhythms of activity include, but are not limited to, our sleep/wake, appetite, hormonal and social rhythms. Coordination of these cycles is driven by oscillations of the endogenous circadian clock, known as the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus. The SCN is a bilateral structure composed of approximately 20 000 cells to form an organized network responsible for the transcription and translation feedback loops of "clock" genes that oversee all cyclic activity (Silver & Kriegsfeld, 2014; Welsh et al., 2010). The core feedback loop involves CLOCK and BMAL1, which are the primary transcriptional activators, and two transcriptional repressors, PERIOD (PER) and CRYPTO-CHROME (CRY) (Silver & Kriegsfeld, 2014). CLOCK and BMAL1 activate *Per* and *Cry* genes via promoter binding (E-box) during the daytime, and the proteins translated are delivered to their respective locations throughout the day (Huang et al., 2012), signaling several other peripheral clock pathways throughout the body. Upon accumulation throughout the day, PER and CRY proteins then dimerize and translocate back to the cell nucleus late in the day (Silver & Kriegsfeld, 2014), which occurs to suppress CLOCK:BMAL1 transcription. The PER:CRY complex, which acts to suppress transcription, is then degraded by E3 ubiquitin ligase, again beginning the transcription of CLOCK:BMAL1 transcription, and signaling for the start of a new circadian cycle (Huang et al., 2012).

The L/D cycle is the main exogenous cue that triggers the induction of an endogenous circadian cycle. These cues are known as synchronization signals, or *zeitgeibers*, whose information is controlled by the SCN. Photic information is processed and distributed to the SCN

via the retinohypothalamic tract (RHT). The cells of the RHT are mainly intrinsically photoreceptive retinal ganglion cells (ipRGCs) that contain melanopsin (Gooley et al., 2001; Morin et al., 2013). The ipRGCs channel direct projections with light information to the SCN via the optic chiasm and optic nerve (Morin et al., 2013). The retina also projects to the SCN via a secondary, indirect pathway through the intergeniculate leaflet (IGL) and geniculohypothalamic tract (GHT) (Harrington & Rusak, 1988; Morin & Allen, 2006). The SCN, in turn, processes these cues to produce phase coherence among all peripheral oscillators in body tissues via direct and indirect pathways to sleep promoting and overall arousal promoting systems. The subparaventricular zone (SPZ) of the hypothalamus is one of the main efferent targets from the SCN, and each subdivision of the SPZ relays signals from the SCN to oversee systemic functions. For example, the dorsal subdivision of the SPZ relays signals from the SCN to control body temperature, while the ventral subdivision controls sleep and locomotor activity rhythms (Vujovic et al., 2015). Major structures involved in sleep/wake regulation include the lateral hypothalamic area, median preoptic nucleus (MnPN), ventrolateral preoptic area of the hypothalamus (VLPO) and the dorsomedial hypothalamus (DMH) (Wright et al., 2012). The SCN demonstrates modulatory input to numerous arousal pathways, either through direct projections from the SCN or indirect projections via the DMH (Wright et al., 2012). Sleep promoting systems, including the MnPN and VLPO, are indirectly modulated via the DMH, while wakefulness promoting systems involve direct and indirect projections from the SCN to the brainstem, basal forebrain, cortex and midbrain (Wright et al., 2012). Arousal projections target the autonomic nervous system (Burgess et al., 1997), endocrine regulation (Van Cauter, 1990), cycles of eating activity (Patton & Mistleberger, 2013) and fluctuations in body temperature (Silver & Kriegsfeld, 2014; Refinetti, 2010).

Mood Disorders and Circadian Rhythms

It is widely known that sleep disturbances, and by extension, biological rhythm disturbances are one of the main symptoms manifested in the course of MDD and BD. It remains

MSc. Thesis: O. Allega, McMaster University, Neuroscience unclear, however, whether circadian disruption causes mood symptoms, whether mood disorders cause biological rhythm disruption, or whether there is a bi-directional relationship exacerbating the opposing entity (McClung, 2013). Betchel (2015) also considers a fourth possibility: Both biological rhythm disturbance and mood disorders are either a common or pleiotropic effect of a third, unidentified party. The work of Hinton (1963) was the first to link circadian cycles and mood disorders, demonstrating greater sleep disturbance in depression and higher levels of nighttime activity in current depression. Later work aimed at discriminating between sleep and circadian cycles with forced desynchrony protocols in bipolar and unipolar depression (Boivin et al., 1997; Kripke et al., 1978; Souêtre et al., 1989). Furthermore, researchers proposed the *phaseshift hypothesis*, implying that mood disorders may result from circadian disturbances (Lewy et al., 1982; Rosenthal et al., 1984). The phase-shift hypothesis was suggested when subjects with a diagnosis of seasonal affective disorder (SAD) displayed reduced depressive symptom severity upon administration of low-dose melatonin to correct circadian phase.

The exact mechanism by which biological rhythm disturbances and mood disorders interact remains unclear. One of the main indicators of a biological rhythm linkage to mood disorders is that the SCN has the densest serotonergic innervation of all brain structures, and this innervation overlaps with several areas targeted via the RHT mentioned above. This suggests that a large contributor to the modulation of the circadian clock in local environments may be mood (Betchel, 2015). Sollars et al. (2010) further corroborated this theory when by eliminating serotonergic innervation by lesioning the raphe nuclei, the major distributors of serotonin to the brain, they observed an alteration in entrainment as a result. Other than serotonin, several monoamines such as norepinephrine and dopamine also demonstrate a circadian rhythm in their signaling, all of which express indirect connections from the SCN via the DMH to areas implicated in mood (i.e. raphe nuclei, (VTA) tegmental area and locus coereleus) (Betchel, 2015; Wright et al., 2012). In turn, monoamine regulation is modulated by the SCN in these tissues.

MSc. Thesis: O. Allega, McMaster University, Neuroscience mice displayed altered monoamine levels accompanied by manic-like symptoms. Furthermore, chronic treatment with lithium reduced manic-like behaviour and recovered normal levels of dopaminergic activity (Coque et al., 2011). Other preclinical studies have also demonstrated a link between circadian rhythmicity and monoamines involved in mood regulation (Chung et al., 2014; Tye et al., 2013).

Other candidate pathways have also been suggested as contributors to the relationship between circadian rhythmicity and mood. Metabolic disorders are a common comorbidity with affective disorders. There are circadian rhythms of metabolic peptides in the liver, stomach, adipose tissue and gut such as ghrelin, orexin, leptin and cholecystokinin (CCK) (Cagampang & Bruce, 2012; McClung, 2013; Turek et al., 2005). Each of these peptides cycle throughout the 24h day promoting feeding behaviours, wakefulness and sleepiness. CCK is also expressed in GABAergic neurons of the prefrontal cortex (PFC), VTA, and in the SCN (Dockray, 2012). Both the peptide itself and CCK receptor agonists have been implicated in mood and anxiety behaviours (Becker et al., 2008; Zwanzger et al., 2012). Moreover, CLOCK Δ 19 mice show arrhythmia in orexin and ghrelin, where levels of these peptides are dramatically and consistently reduced, indicating their regulation is modulated by the SCN (Turek et al., 2005). These mice also exhibited features of obesity and metabolic syndrome, and anxiousness due to glucocorticoid feedback dysregulation (McClung, 2013). Stress is also highly associated with mood disorders, resulting in increased synthesis of glucocorticoids. There are two CLOCK proteins known to be implicated in the regulation of glucocorticoid levels. CRY proteins suppress glucocorticoid receptors on the PVN and adrenal glands, while the receptors are also acetylated by CLOCK, modifying sensitivity throughout the day (Charmandari et al., 2011; McClung, 2013). Circadian rhythm disruption may also affect the immune system, resulting in greater levels of proinflammatory cytokines (McClung, 2013), which are also implicated in depression and bipolar disorder (Suarez et al., 2003; Zhu et al., 2006).

Circadian Rhythms and Cognition

Evidence exists of temporal fluctuations on cognitive performance throughout the day. There are two main interacting processes that drive these variations in performance: homeostatic sleep drive, which increases with increased wakefulness, and the endogenous circadian clock, which operates in a 24h oscillation (Schmidt et al., 2007). These opposing components act to create times throughout the day that would be considered optimal for cognitive performance. It is well established that circadian variation exists for cognitive performance (Dijk et al., 1992; Van Dongen et al., 2000; Wright et al., 2002), however the impact of disturbance to rhythmicity and its effects on performance in clinical populations remains largely unexamined. Animal models have shown, for example, that spatial memory and contextual fear conditioning are modulated as a function of time (Chaudhury et al., 2002; Gritton et al., 2012), and deficits in recall are more pronounced at different times of day (Devan et al., 2001). Selective CLOCK gene knockouts have shown deficits in acquisition and recall in working memory (Snider et al., 2016; Wardlaw et al., 2016). Moreover, SCN ablation shows deficits in recall in a hippocampal-dependent contextual fear-conditioning task (Phan et al., 2011). These studies provide evidence of clock-gated circuitry involved in cognitive performance, thus, opening up opportunities for translational models of circadian disturbance in populations involved in shift work, mental illness and other conditions.

In humans and animals alike, it appears that cognitive parameters involved in memory, attention and executive do not follow the same rhythmicity throughout the day that aligns with core body temperature (CBT). In fact, different cognitive processes have shown varying sensitivity to daily fluctuations in performance, and some may not be affected at all (Horowitz et al., 2003; Valdez et al., 2005; Wyatt et al., 1999). Furthermore, there is very little agreement between studies that have observed circadian variation in particular cognitive parameters. For instance, studies evaluating working memory have found performance to be parallel with CBT (Cajochen et al., 1999), 1-3h phase delays with respect to CBT (Ramirez et al., 2006), or no time-of-day effects (Hidalgo et al., 2004).

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The properties of the circadian pacemaker in humans are usually revealed via temporal isolation studies (forced desynchrony or constant routine paradigms), to parse through the contributory effects of *both* the pacemaker and homeostatic sleep drive. These studies will mask any influences that indicate the time of day (i.e. rotating researchers every three hours, small snacks provided every two hours, lighting in room stays the same at a constant lux), and also remove any physiological confounds (i.e. influences of body posture, stress, digestion) (Schmidt et al., 2007). Isolation studies usually assess the extent of "free-running" rhythmicity an individual possesses under continually increased pressure to sleep, and thus, desynchronization.

A review update of preclinical and clinical literature on the impact of circadian rhythm dysregulation on cognition will provide an idea of where this field of research is with regard to proper translational models that allow for targeted intervention in psychiatric conditions, as circadian disturbance is a crucial symptom of episode onset in mood disorders. Circadian disturbance is a facet of several disorders that persists into remission (Benson et al., 1993; Gulevich et al., 1967; St-Amand et al., 2013; Ulbricht et al., 2015), unfortunately offering a lower level of psychosocial function during euthymia for its carriers.

Aims and Hypotheses

The overall objective of the work outlined in this thesis is to address several gaps in the literature regarding assessment of sleep and biological rhythm disturbance in their relationship to MDD and BD. Our first aim was addressed by comparing objective and subjective measures of sleep and circadian rhythmicity in BD, MDD and matched controls. Sleep-wake disturbances are considered a trait marker of both depression and bipolar disorder known to cause onset of and worsening of current affective episodes (Kennedy et al., 1996; Thase, 1998). Often, disruptions in sleep are a symptom of the disorders that persist into remission (Rumble et al., 2015). 72% of remitted patients on citalopram reported issues with sleep in a study conducted by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, citing it as the most common residual symptom (Nierenberg et al., 2010). Additionally, bipolar patients in remission show rest-

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activity disturbance in actigraphy accompanied by self-reports of sleep disturbance resulting in less, and more variable activity throughout the day (St-Amand et al., 2013). It is hypothesized that subjective and objective measurements will display consistency in group differences in controls, bipolar and unipolar patients.. Plans for analysis with a larger sample and completion of a manuscript are expected to take place between August and October of 2016. The manuscript is intended to be submitted to *Journal of Clinical Psychiatry*, entitled "An objective and subjective study of sleep and biological rhythms in bipolar and major depressive disorder."

Next, we examined whether the BRIAN showed significant correlation with objective parameters of sleep and circadian rhythmicity. The BRIAN is a self-report questionnaire that has been used in several studies as a subjective measurement of biological rhythm disruption in mood disorders. The BRIAN has detected significantly worse biological rhythm disturbance in mood groups and even across mood states (Faria et al., 2015; Giglio et al., 2010; Krawczak et al., 2016; Mondin et al., 2015), however it has yet to be validated against objective parameters. Higher scores indicate greater biological rhythm disturbance. The decision to use subjective or objective measurements in clinical practice depends on several elements to consider, such as costeffectiveness, limited time, invasiveness, accessibility to the patient and external validity of the assessment. For instance, polysomnography examinations with EEG require the patient to stay overnight in a sleep laboratory, while proper collection of melatonin profiles requires fasting, maintenance in dimly lit rooms all evening, and abstinence from any televisions, laptops or smartphones. The aim of this study is to validate a subjective rating scale, the BRIAN, against objective parameters of sleep and biological rhythmicity in controls, bipolar and unipolar patients to empirically test which parameters of sleep and biological rhythms correlate with this questionnaire. It is hypothesized that BRIAN scores will positively correlate with objective sleep and biological rhythm measurements. Objective parameters will be evaluated via actigraphic sleep and circadian measurements, and biological measurements with salivary and urinary melatonin profiles. This study will be described in Chapter 3. The recruitment for this study was

MSc. Thesis: O. Allega, McMaster University, Neuroscience successfully completed with a final sample of 103 subjects, 3 subjects above our original targeted sample of 100 individuals. Plans for statistical analysis and completion of a manuscript are expected to take place between August and October of 2016. The manuscript is intended to be submitted to *Chronobiology International*, entitled "An objective validation of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)".

Finally, a review paper was completed investigating the impact of circadian rhythm disturbance on cognition in preclinical and clinical populations. There is a large body of literature in both human and animal studies reporting periodicity in cognitive parameters such as attention, memory and executive function. However, there are very few reports of the literature to date that clearly delineate standardized temporal fluctuations in cognitive parameters that align between species. There is a crucial interplay between homeostatic sleep drive and circadian regulation of arousal that modulates performance throughout the waking day. Notwithstanding, circadian variation exhibits variance in modulation on different cognitive parameters. This notion warrants inquiries of whether or not certain cognitive functions are more sensitive to time of day variables than others, to what magnitude of difference is observed for particular cognitive parameters, and task sensitivity and/or selectivity. The aim of this review is to (1) provide an update on the existing literature regarding preclinical and clinical studies on the impact of 24-h circadian variation, circadian misalignment and sleep deprivation on cognitive performance, and (2) critically compare and contrast reports between human and animal studies from a translational approach. This review will be presented in the form of a manuscript in Chapter 4, titled "The impact of circadian rhythms on cognitive function: A review of clinical and preclinical research". Upon further revision, the manuscript is intended to be submitted to Neuroscience & Biobehavioural Reviews within the next month.

CHAPTER 2

An objective and subjective study of sleep and biological rhythms in bipolar and major depressive disorder

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Abstract

Background: The clinical presentation of sleep disturbances is a field of research that only recently has received greater attention for its contribution to affective disorders both in current episodes and remission, and these findings overlay the importance of having diagnostic tools in the clinical setting that are able to provide sensitivity to the underlying markers of mood variability. The aim of this study is to offer a comparison of group differences in circadian rhythmicity as assessed by the BRIAN, PSQI, actigraphic parameters and melatonin profiles. **Methods:** A total of 103 subjects (40 controls, 23 euthymic MDD, 9 currently depressed MDD, 21 euthymic BD, 10 currently depressed BD) wore an actiwatch for fifteen days. Subjects also completed one evening of saliva sampling, and completed one first morning urine sample, both to be assessed for melatonin profile. BRIAN and PSQI were completed at the end of the 15 days. Group differences were determined with ANOVA or non-parametric equivalent.

Results: Currently depressed MDD displayed worse self-reported sleep quality compared to controls, (H(4)= 17.3, p < 0.01). All four mood groups reported worse subjective biological rhythm disturbance compared to controls (F(4,103) = 9.95, p < 0.00). Actigraphy data revealed that currently depressed MDD and BD, and euthymic BD had longer WASO times compared to controls (F(4,77) = 4.81, p < 0.01). Currently depressed BD displayed lower levels of 6-SM than controls and euthymic MDD (H(4) = 10.9, p = 0.02). No differences between the groups were observed in DLMO, PAD, or objective measures of daily activity rhythms.

Conclusion: Our results suggests that number of night awakenings and low nocturnal secretion of melatonin may be driving the subjectively reported sleep and biological rhythm disturbances in BD and MDD subjects. Consistent with previous studies, objective and subjective sleep parameters show moderate agreement with each other, while objective and subjective measures of biological rhythm disturbance show no agreement.

Introduction

Biological rhythms are daily cycles of activity that include our sleep/wake, appetite, hormonal and social rhythms. Research strongly suggests that biological rhythm disruptions are common features involved in the pathogenesis of bipolar and major depressive disorders. Biological rhythm disturbance can lead to development of mood disorders, if not the commencement of mood episodes in both major depressive disorder and bipolar disorder (Salvatore, 2008; Bunney & Bunney, 2000; Giglio et al., 2010). In bipolar disorder, these disruptions can also often signal a switch from a depressive to a manic state (Konno, 2013) and can cause further functional impairment persisting into remission (Boland & Alloy, 2013).

There are several ways of monitoring sleep and biological rhythm disruptions objectively. From a biological perspective, the gold standard of obtaining a measure of circadian phase is melatonin profiling. Melatonin can be obtained from serum, however salivary and urinary samples provide an easy and non-invasive method of obtaining measurements either in the morning or evening. Salivary profiles are usually employed to obtain a measure of the dim light melatonin onset (DLMO), which is the evening production in melatonin, and is considered the most reliable measure of the timing of the biological clock. Melatonin usually begins to rise in the 2-3 hours before nocturnal sleep onset, peaks in the early hours of the morning at approximately 3:00 am, thereafter tapering off to low daytime levels (Molina & Burgess, 2011). Manic subjects exhibit differences in circadian profiles in that elevated melatonin levels are present during the daytime compared to their depressed counterparts, suggesting that the functional state of the circadian system in BD is at the fundamental level of the SCN (Novakova et al., 2015). Evidence exists of abnormal melatonin levels in as determined by urinary melatonin metabolite 6sulphatoxymelatonin (6-SM) in both MDD (Crasson et al., 2004) and BD (Kennedy et al., 1996), suggesting not only may circadian phase be altered in affective disorders, but that a melatonin secretion abnormality compounds the magnitude of disturbance contributing to symptom severity. The most common, gold standard method to monitor sleep patterns from a technical perspective

is currently EEG and polysomnography, which requires participants to stay overnight in a sleep clinic. Similar profiles of sleep have been detected when comparing bipolar patients and patients with major depression, with differences emerging only in hypomania having higher levels of slow wave sleep, and currently depressed patients experiencing decreases in sleep efficiency and REM latency (Asaad et al., 2016). However, the use of polysomnography is limited by cost and burden to patients. Another objective measure of obtaining sleep and circadian profiles include actigraphy, which is a wristwatch like device that uses an accelerometer to quantify movement from motor activity. The data obtained from the actiwatch is quantified into levels of daily activity, and the patterns obtained from analyzing this activity gives us parameters of the daily activity rhythm (DAR). Actigraphy has been well-validated against gold-standard polysomnography measures in both healthy volunteers and mood disorder subjects (Baandrup & Jennum, 2015; Kaplan et al., 2012). It has detected differences in disruptions between mood groups in several sleep and circadian parameters in bipolar disorder (Geoffroy et al., 2015). Furthermore, actigraphy use has distinguished between unstable rest-activity patterns in bipolar disorder in relationship to greater variability of mood during euthymia (Krane-Gartiser et al., 2016), providing valid insight into the higher levels of disruption in euthymia as a risk factor associated with episode onset.

Subjective measurements of sleep and biological rhythm disruption usually involve paper and pencil reports on scales indicating severity of self-reported worsening of symptoms, providing an easy-to-use method of screening for symptoms in the clinical setting. The Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) is a self-report questionnaire that monitors biological rhythm disruption over the last 15 days, that includes measures of disturbance in sleep, activity, eating patterns, and social domains (Giglio et al., 2009). Recent studies have supported the BRIAN as a measure of biological rhythm disturbance between groups (Giglio et al., 2010) and across mood states, showing the greatest frequency of disturbance in bipolars in a current depressive episode (Faria et al., 2015). Bipolar euthymic individuals also

showed the same magnitude of disruption as MDD subjects in a current episode, further corroborating the notion that subsyndromal symptoms of bipolar disorder persist into remission (Kapczinski et al., 2009). The Pittsburgh Sleep Quality Index was actually first developed to evaluate sleep quality in subjects with affective disorders (Buysse et al., 1989), and has also shown greater abnormality in sleep profiles in bipolar patients in remission compared to controls (Rocha et al., 2013). Other circadian subjective measurements include the Morningness Eveningness Questionnaire (Horne & Ostberg, 1976), Munich-Chronotype Questionnaire (Roenneberg et al., 2003) and Circadian Type Inventory (Folkard et al., 1979), all of which are considered markers of circadian phase.

Depression symptom severity correlates with greater biological rhythm dysregulation (Hasler et al., 2010; Robillard et al., 2013). The clinical presentation of sleep disturbances is a field of research that has received great attention for its contribution to affective disorders both in current episodes and remission, and these findings overlay the importance of having diagnostic tools in the clinical setting that are able to provide sensitivity to the underlying markers of mood variability. Exploring suitable interventions targeted at the circadian system are at the crux of these investigations. In order to better characterize the interplay between mood and circadian disturbance, the aim of this study is to offer a comparison of group differences in circadian rhythmicity as assessed by the BRIAN, PSQI, actigraphic parameters and melatonin profiles. There are several studies published that assess subjective sleep against objective circadian profiles, or actigraphy in either BD or MDD (Boudebesse et al., 2014; Geoffroy et al., 2014; Ng et al., 2016; Millar et al., 2004; Robillard et al., 2013), but not all objective and subjective measures in both populations across mood states. To our knowledge, this will be the first study to assess objective and subjective measures of both sleep and biological rhythms between bipolar and unipolar groups in comparison to controls in an adult population. We hypothesize that MDD and BD subjects will display worse self-reported and objectively-measured sleep and circadian rhythmicity.

Methods

Participants

A total of 103 subjects have already completed this study: 40 controls, 23 euthymic MDDs, 9 currently depressed MDDs, 21 euthymic BDs, and 10 currently depressed BDs were recruited from the Mood Disorders Program and Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton, Ontario, or from the community. All subjects gave written informed consent to participate in the study, as approved by the Hamilton Integrated Research Ethics Board (HIREB). The diagnosis and mood state of MDD or BD was confirmed with the Mini International Neuropsychiatric Interview (MINI) English Version 6.0.0. (Sheehan et al., 1998). Subjects were enrolled in the healthy control group if they did not meet criteria for current or past history of any Axis I disorder. All subjects were excluded if they (1) had a current or lifetime history of a sleep disorder, (2) had a current or longstanding use of melatonin, (3) were employed in shiftwork, (4) were currently using medication specifically prescribed for sleep, (5) were currently using prescribed medication for pain relief with sedative effects, (6) were currently using recreational drugs such as marijuana as a sleep aid at any time throughout the day, (7) met criteria for current alcohol/substance abuse or dependence, and (8) if they were currently experiencing jetlag from a recent trip outside the Eastern Time Zone. There were no bipolar subjects who met criteria for a current hypomanic, manic or mixed episode in this study.

Study Design

Study participation included two visits over the span of 15 days to St. Joseph's Healthcare Hamilton. At visit 1, informed consent was first obtained. Subjects were interviewed using the MINI. Participants were then fitted with a configured actiwatch, and sent home with a set of saliva sample tubes, a urine sample container, and a sleep log. Subjects wore the actiwatch for the full 15-day duration of the study. A sleep log was given to participants to record periods of actiwatch removal, if necessary, morning wake up times, naps, and bed times to ensure actiwatch concurrence. Subjects were then instructed to choose one night throughout study participation,

any night of their choosing that inclined to be most convenient, to take one saliva sample each hour from 6:00 pm until their habitual bedtime. Subjects were instructed to begin a fast from 5:00 pm onward until saliva collection was complete, and to rinse mouth out with water 10 minutes before collection of each sample. Upon completion of each sample, subjects immediately placed each tube in the freezer until returning to the laboratory. Subjects were also instructed to (1) avoid brushing teeth, flossing and drinking any liquids (from the start of 1 hour before collection began), (2) maintain a dimly lit environment the evening of saliva collection, and to avoid any laptop, television or smartphone use, (3) maintain a modified diet the day of saliva collection, avoiding any foods high in sugar including fruit, and any foods with high levels of acidity, (4) avoid naps on the day of saliva collection and (5) refrain from smoking or any alcohol use on the day of collection. On day 15, or the day of the second and final visit, subjects were asked to complete a first morning urine sample. Subjects then returned to the laboratory, returned the watch, saliva tubes, urine container, and sleep log, and completed several questionnaires including the BRIAN, PSQI, MADRS, and YMRS.

Assessments

Clinical Assessments

Depression symptom severity was assessed at the second visit with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). Manic symptom severity was assessed at the second visit with the Young Mania Rating Scale (YMRS) (Young et al., 1978).

Subjective biological rhythm disturbance was measured with the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009). The BRIAN is a 21item self-report questionnaire that inquires about how often one feels they have experienced rhythm disruption over the last 15 days. The BRIAN can be broken down into 4 domains over 18 questions: sleep, general activity, social, and eating pattern. There is a 5th domain that is not

Subjective sleep disturbance was measured with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a 19-item self-assessment questionnaire that inquires about subjective sleep quality over the last month. The 19 items are categorized into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. All components are scored on a scale of 0-3, where higher global scores indicating greater overall sleep disturbance.

Actigraphy

Actigraphy is the use of a wrist-worn piezoelectric device with microprocessors that are able to measure motility and light levels, thereby distinguishing sleep from waking, allowing from the analysis of specific phases of sleep and activity. Objective measures of sleep and circadian rhythmicity were obtained with the Actiwatch 2 monitor, purchased from Philips Respironics Inc., (Biolynx, Montreal, Quebec, CA). Data was collected in one-minute epochs continuously for 15 days. Actiwatch data was retrieved and processed using Philips Actiware Version 6.0. Sleep measures obtained from Actiware included total sleep time, sleep onset latency (SOL), sleep efficiency, and wake after sleep onset (WASO). Cosinor analysis was employed to further explore underlying circadian rhythmicity. This procedure fits time-series data to a single cosine wave. The measurements obtained from the cosinor analysis give a mean value over 15 days, fitted to the wave over a 24h period. The cosinor analysis generated the following parameters: (1) MESOR (midline-estimating statistic of the rhythm), (2) amplitude (a value indication ½ the variation in the data, or the activity range from mean level to the peak/trough of the cosine wave), (3) acrophase (a measure of when peak activity occurs, converted to 24h time). MESOR and amplitude are then computed to the (4) circadian quotient (CO), which is the

MSc. Thesis: O. Allega, McMaster University, Neuroscience amplitude/MESOR ratio, providing a normalized measure of the strength of an individual rhythm.

Non-parametric measures of circadian function were also obtained from the cosinor analysis. (1) Intradaily variability (IV): This is a measure of rhythm fragmentation, and is calculated as the ratio of the mean square difference between successive measurements over the overall variance in the data. IV scores range from 0 - 2, with higher scores indicating greater rhythm fragmentation. (2) Interdaily stability (IS): This is a measure of the strength of coupling between endogenous daily activity rhythms and external zeitgebers, or how well internal activity is synchronized to external cues. IS is calculated as the normalized ratio of the variance of the mean 24h rhythm over the overall variance in the study duration. Scores range from 0 - 1, with higher scores indicated greater synchronization of daily activity rhythms to external cues.

Melatonin

The saliva samples were used to measure dim light melatonin onset (DLMO) as an objective biological measure of phase assessment. 2 mL of salivary melatonin was collected each hour from 6:00 pm until habitual bedtime using 15 mL presterilized conical centrifuge tubes (VWR, Radnor, Pennsylvania). Each sample was immediately frozen upon collection and returned to the laboratory. Saliva samples were later assayed using an ELISA salivary melatonin enzyme immunoassay kit (Salimetrics, State College, Pennsylvania, USA). Each subject's samples were analyzed in the same batch. The sensitivity of the assay was 1.42 pg/mL. The interassay coefficient of variation for low endogenous melatonin was 23.6%. The intra-assay coefficients of variation for the mean of low levels of endogenous melatonin were between 5.9% and 6.5%.

The morning urine sample was used to measure urinary melatonin metabolite, 6sulphatoxymelatonin (6-SM). Morning urine was refrigerated until arrival to the laboratory for return. Urine samples were analyzed using ELISA for 6-SM (Buhlmann Diagnostics Corporation, Amherst, New Hampshire, USA). The sensitivity of the assay was 0.14 ng/mL. The inter-assay

MSc. Thesis: O. Allega, McMaster University, Neuroscience coefficient of variation was 11.9%. The intra-assay coefficient of variation was 7.1%. Urinary melatonin aliquots were also analyzed for creatinine levels by the Hamilton Regional Laboratory Medicine Program at St. Joseph's Healthcare Hamilton (license #4037).

Statistical Analysis

For each evening melatonin profile, one DLMO time was derived. Due to the high interindividual variability in our sample, and relatively high levels of melatonin secretion, we chose a DLMO threshold of 10 pg/mL to fit our data (Benloucif et al., 2008; Lewy, 2009). The DLMO was therefore interpreted as the interpolated time that melatonin concentrations reached and exceeded 10 pg/mL for at least two hours thereafter. From this data, phase angle differences (PAD) were also calculated. PAD was calculated as the [midpoint of sleep – DLMO] (Lewy et al., 2006). Urinary melatonin measurement was normalized by calculating a melatonin-creatinine ratio [absolute melatonin/creatinine], which has proven to be a reliable standardized measure comparable to plasma melatonin levels (Chang et al., 2016; Nowak et al., 1987; Sturgeon et al., 2014).

All analyses were performed with R (Version 3.0.2, R Development Core Team, 2012). Non-parametric circadian parameters, as measured by the actiwatch, were obtained using actogram double-plot (Figure 1) and cosinor analysis. One-way analysis of variance (ANOVA) was used to compare differences between five groups. If variables did not meet assumptions of normality after transformation, or homogeneity of variance, then non-parametric Kruskal-Wallis test equivalent was employed. Post-hoc comparisons between groups were computed using Tukey's Test, or the non-parametric pair-wise comparison Kruskal test.

Results

Demographic and clinical data are displayed in Table 1. There were no differences between groups in sex, age, years of education and age of onset (p > 0.05). BMI differed

Subjective and Objective Sleep Parameters (Actiwatch)

Subjective sleep quality differed significantly between controls and currently depressed MDD (H(4)= 17.3, p < 0.01), where current MDD reported worse sleep quality as measured by the PSQI. With regard to objective parameters, a significant effect of mood state was seen where currently depressed MDD, currently depressed BD, and euthymic BD each displayed a longer WASO compared to controls (F(4,77) = 4.81, p < 0.01). No significant differences between groups were detected for total sleep time, sleep efficiency or sleep onset latency (p > 0.05). Means and contrasts are reported in Table 2.

Subjective and Objective Biological Rhythm Parameters (Actiwatch)

Significant group differences by mood state on subjective biological rhythm disturbance were revealed for euthymic MDD, euthymic BD, currently depressed MDD and currently depressed BD compared to controls (F(4,103) = 9.95, p < 0.01) as measured by the BRIAN. All four mood groups displayed significantly higher BRIAN scores compared to controls, but no differences between each other. All objective circadian data was split into weekend and weekday variables. No group differences were observed for weekend and weekday IS, acrophase, and CQ (Figure 3). A trending result was observed for the effect of mood state on weekday IV (F(4,77) = 2.21, p = 0.07). Post-hoc tests revealed a marginally significant difference between currently depressed BD and controls, where BD experienced a higher IV (p = 0.056). No group differences were revealed for weekend IV (p > 0.05). Means and contrasts are reported in Table 3.

Melatonin Measures

One-way ANOVA revealed significant group differences in urinary 6-SM between (1) currently depressed BD and controls, and (2) currently depressed BD and euthymic MDD, where currently depressed BD displayed lower levels of 6-SM (H(4) = 10.9, p < 0.03). No significant differences between groups were observed for DLMO (Figure 2) or PAD. Means and contrasts are reported in Table 4.

Exploratory Clinical Analyses

Total PSQI scores were positively correlated with MADRS scores ($\rho = 0.34, p < 0.01$). Total BRIAN scores were positively correlated with MADRS scores ($\rho = 0.67, p < 0.01$). BRIAN and PSQI scores also positively correlated with each other ($\rho = 0.64, p < 0.01$).

Discussion

To our knowledge, this is the first study to examine subjective and objective actigraphy and melatonin profiles as measures of sleep and circadian rhythmicity in a population of euthymic and depressed MDD and BD. There are a few main findings revealed from this study: Subjective parameters of sleep with PSQI detected differences between controls and currently depressed MDD only. Objective sleep parameters from actigraphy detected differences between currently depressed MDD and BD, as well as euthymic BD compared to controls for WASO, but not total sleep time, SOL, or sleep efficiency. Additionally, subjective biological rhythm disturbance as measured by the BRIAN displayed significant differences between all five groups, whereas objective measures of rhythmicity determined from actigraphy revealed no differences. With regard to melatonin profiles, group differences were observed for 6-SM, where currently depressed bipolars showed significantly lower levels of nocturnal melatonin secretion. No differences were observed in DLMO or PAD.

Sleep disturbance is a highly reported symptom revealed in the clinical presentation of the onset of and during mood episodes (Rumble et al., 2015). Currently depressed MDD reported more sleep disturbance compared to controls. Although not significant, higher scores on PSQI

MSc. Thesis: O. Allega, McMaster University, Neuroscience were also observed for the remaining mood groups. This result is consistent with previous reports that MDD patients account worse subjective sleep quality than BD in remitted to mildly depressed patients when compared to controls (Breslau et al., 1996; Fava, 2004; Lai et al., 2014), however accounts of worse subjective sleep quality in BD do exist (Cretu et al., 2016; Geoffroy et al., 2014). The level of severity of currently depressed MDD subjects may have been greater compared to BD subjects throughout the study. PSQI scores also agree with MADRS scores in that currently depressed MDD scored much higher than BD, thereby reporting overall worse sleep quality. Additionally, the currently depressed MDD group had the lowest number of subjects who were stable on psychotropic medications, who also reported greater ESS scores compared to the remaining groups.

Objective parameters of sleep as measured by actigraphy showed differences in WASO in all groups compared to controls, except for euthymic MDD who did not significantly differ from controls. This result is in line with several actigraphy studies assessing sleep fragmentation in current and remitted mood episodes (Arfken et al., 2014; Geoffrov et al., 2015; Hori et al., 2016). It is known that longer durations of WASO in currently depressed subjects exist, contributing to both shortened sleep durations, as well as daytime hypersomnia, or longer sleep durations that reflect a lower quality of sleep. This is also true for bipolar subjects in remission. Although there is some heterogeneity in the literature, two meta-analyses reported greater WASO durations in remitted bipolar subjects compared to healthy controls (Geoffroy et al., 2015; Ng et al., 2016), as well as greater variability of WASO between BD subjects (Geoffroy et al., 2015). Furthermore, Ng et al., (2015) found no difference in WASO between primary insomnia patients and inter-episode bipolars. In our study, euthymic BD displayed greater WASO compared to controls, whereas euthymic MDD showed no difference. This result suggests abnormality of sleep patterns that persist into bipolar remission; implying euthymic bipolars display overall reduced quality and stability of sleep during remission. A lower quality of sleep throughout remission is associated with psychosocial and functional impairments, putting BD individuals at higher risk of

MSc. Thesis: O. Allega, McMaster University, Neuroscience affective relapse (Samalin et al., 2016). An interaction exists between residual symptoms such as reduced sleep quality, further circadian rhythm disturbance, emotional dysregulation and cognitive impairments during euthymia in BD patients (Boland et al., 2015; Harvey et al., 2005), which predisposes patients to subsequent negative impacts on mood of continually greater magnitudes. Importantly, Samalin et al., (2016) reported sleep disturbance as a residual symptom in euthymic BD is negatively associated with the duration of euthymia. In our study, no differences between groups were observed for total sleep time, SOL and sleep efficiency. It is possible that these distinctions were not apparent because of the mild level of current depression our subjects were experiencing. Actogram outputs appeared to be quite similar for all MDD subjects in comparison to controls, and BD subjects generally showed the same amount of sleep, however at more variable times. For example, BD subjects may still show a 7 hour duration in bed, but at a delayed time. Whereas controls may go to sleep on a weekday at 11:00 pm and wake up at 6:00 am, euthymic BD subjects would generally go to sleep at later times, around 1:00 or 2:00 am, and wake up slightly later in the mornings. Additionally, the majority of BD subjects were currently euthymic, with only a small sample of current depression. These factors explain why we saw no differences total sleep time, SOL and sleep efficiency, yet saw greater disturbance measured by WASO. Once again, the literature is divided as to whether or not these distinctions do exist. Several individual studies have reported no differences in remitted BD compared to controls in sleep efficiency, sleep duration, SOL and WASO (Bullock & Murray, 2013; Jones et al., 2005; Gershon et al., 2012; Millar et al., 2004; St-Amand et al., 2013), whereas others have reported worse sleep efficiency, total sleep time, and SOL (Harvey et al., 2005; Ritter et al., 2012; Salvatore et al., 2008). Meta-analyses in remitted BD examining total sleep time, SOL and sleep efficiency report similar results as to whether or not these disturbances persist inter-episodically, however individual studies generally show no differences (Geoffroy et al., 2015; Ng et al., 2016). In MDD, lower levels of activity counts have been reported daily,

however sleep statistics have not been made readily available for assessment (Burton et al.,
2013). Current bipolar depression in actigraphy has also rarely been assessed.

Our findings in BRIAN scores are consistent with the literature in that biological rhythm disruptions are greater in mood disorders. However, we did not detect differences between mood states, which the BRIAN has demonstrated in past studies compared controls (Faria et al., 2015; Rosa et al., 2013). Euthymic MDD and BD scored almost exactly the same means, and currently depressed MDD and BD scored similarly as well. This result is probably due to the fact that individuals who qualified as currently depressed scored low in the MADRS, suggesting relatively lower levels of depressive symptoms, similar to the euthymic group. Furthermore, BRIAN scores significantly correlated with MADRS scores in the overall sample. Self-reports of disruptions in sleep, social patterns, general activity and eating patterns in both MDD and BD offer evidence of circadian disturbance playing a critical role in the etiological mechanisms of mood disorders. A previous report of biological rhythm disturbance in rapid cycling BD demonstrated that patients perform fewer activities, display irregular diet and work habits, and engage in fewer social activities compared to controls (Ashman et al., 1999). Shen et al. (2008) also noted irregularity in social rhythms to be associated with the onset of mood episodes. Personal relationships and tasks assigned from work can act as "social zeitgebers" (Ehlers et al., 1988), and high variability in routine, or lack thereof, may support increases in biological abnormalities.

Group differences in circadian actigraphy parameters did not reach statistical significance in this study. However, our data still provide a clinically meaningful context for each parameter (Table 3). Data for circadian parameters were segregated into weekend and weekday values, as weekends tend to be quite variable even for controls, so for this purpose, discussion will be based on weekday functions. IS is quite similar across groups, which suggests similar synchronization of the internal clock to the light/dark cycle for mood groups during euthymia. While we do observe lower IS values for currently depressed MDD and BD, no significant differences were observed. This could potentially be due to the small sample size studied compared to the larger

groups of euthymics and controls, or due to the relatively low severity of depression in these groups. Weekday IV displayed a trending result, where marginal differences were observed between controls and currently depressed BD, who displayed greater rhythm fragmentation within days. Although not significant, this finding suggests bipolar depressed subjects experience higher variability in activity within a 24-hour period. Rock et al. (2013) also reported no differences between groups in bipolar phenotypes and controls with regard to IS and IV. In another study, BD patients in remission or who were experiencing subsyndromal depressive symptoms did display differences in both IS and IV measures, where BD patients showed low IS and high IV compared to controls (Jones et al., 2005). Is it possible that our IS and IV results did not reach statistical significance due to approximately 35% of our sample being undergraduate students, who experience high variability in sleep/wake schedules, and therefore disruption to the circadian system. This is further supported by the fact that our controls actually show the highest standard deviations in the whole sample, along with currently depressed BD, an aspect that could be driving control data.

Currently depressed MDD and BD display lower weekday mean activity levels over a 24hour period compared to controls (MDDC (M[SD]: 182.8[43.8]; BDC (M[SD]: 191.8[53.9]; HC (M[SD]: 207.6[50.5]) (Figure 3), which is in line with several studies (Burton et al., 2013; Hori et al., 2015). Although not statistically significant, these mean levels provide evidence attributable to the psychomotor retardation associated with current depression (Buyukdura et al., 2011; Hori et al., 2015). Lastly, although acrophase times were similar across groups, mood groups tended to be one or two hours later in the day compared to controls, with the exception of currently depressed MDD. Even though the time of peak levels of activity were similar, mean levels of activity tended to be lower in mood.

Interesting differences were seen between currently depressed BD, and controls and euthymic MDD when measuring 6-SM. Bipolar subjects displayed significantly lower levels of 6-SM compared to controls, while MDDs did not differ from controls. This result is in line with the

MSc. Thesis: O. Allega, McMaster University, Neuroscience literature indicating that melatonin secretion abnormalities can be considered a vulnerability marker to affective illness, specifically BD. The melatonin curve and, therefore the amplitude of secretion seems to be lower in individuals with BD (Lewy et al., 1985; Srinivasan et al., 2006). Although not significant, differences in PAD can be observed from the DLMO calculations, which show an approximate three-hour PAD in currently depressed BD compared to controls. A typical PAD lies around six hours, whereas a PAD greater than six indicates a phase-advance (Lewy, 2010). This is typically true of both bipolar and unipolar depressed individuals, which is in line with our results. However, one study reported no differences in evening melatonin profiles for currently depressed BD compared to controls- only the manic profile exhibited circadian misalignment (Novakova et al., 2015). Furthermore, it has been suggested that the waveform produced in mania could be a result of the desynchronization of the right and left SCN. Nurnberger et al. (2000) reported delayed melatonin peaks and lower overall concentrations of melatonin in BD compared to unipolar patients and controls. Our findings suggest BD subjects display significantly lower levels of melatonin as a baseline (Table 4) making them more vulnerable to sleep disturbance. Notably, this pattern of melatonin secretion has been shown to contribute to the induction of mood episodes, and in particular the switch from a depressive to a

manic state (Konno, 2013).

The limitations of this study must be discussed. First, compliance levels in saliva sampling to obtain DLMO were quite poor in both mood and control groups. Subjects were instructed to fast from 5:00 pm onward until collection was complete, as oral resting is required starting one hour before collection to obtain the best sample. The day sampling was to be completed several dietary restrictions were implemented, such as avoidance of acidic and sugary foods, alcohol, smoking, along with avoidance of bright screens at nighttime including laptops, tablets, prolonged use of cell phones, etc. Therefore, only a small number of samples were usable. For these reasons, the results reported here are based on a total of ten or eleven samples available for analysis per group (this yields approximately 30% of our total n). Another limitation of this

study is the heterogeneity in psychotropic medication use and adherence of the MDD and BD groups. We included subjects who were both using and not using medication, not considering the effects different medications may have on melatonin secretion, the amplitude of secretion, and circadian pathways. It is possible that medication use contributed to the high inter-individual variability in melatonin levels, in addition to sleep, exercise and nutrition. A number of bipolar subjects were using mood stabilizers, particularly lithium. This needs to be considered since lithium impacts the endogenous oscillator via multiple molecular pathways. Lithium is an inhibitor of glycogen synthase 3 beta (GSK- 3β), which phosphorylates and inhibits several clock proteins (PER2 & NR1D1), acting to attenuate the period of a rhythm and induce phase advances (Klein et al., 1996; Novakova et al., 2015; Ryves & Harwood, 2001; Yin et al., 2006). Lithium also activates early growth response 1 (EGR1) kinase signaling, inducing Per2 transcription (Kim et al., 2013; Novakova et al., 2015). Lastly, the currently bipolar and unipolar depressed groups consisted of a much smaller sample size compared to controls and euthymics. Recruitment of a greater number of currently depressed subjects is a current short-term objective. In future, it will be of interest to explore non-linear, rest-activity state transition probabilities (Lim et al., 2011; Ortiz et al., 2016), which may shed more light on the sleep/wake architecture associated with mood disorders instead of actigraphic circadian variables.

In conclusion, subjective measures of sleep from the PSQI, and subjective measures of biological rhythm disturbance from the BRIAN detect group differences in mood compared to controls. Furthermore, objective sleep differences were found in WASO, where currently depressed BD, MDD, and euthymic BD displayed longer wake times compared to controls. Lastly, currently depressed BD displayed significantly lower levels of morning melatonin compared to controls and euthymic MDD. Our results suggest subjective reports of sleep and biological rhythm disturbance provide meaningful and valid context for affective symptoms in comparison to more time-consuming, expensive, variable and unfeasible measures in a clinical setting. These results attest to the clinical utility of subjective measurement of sleep and

biological rhythm disturbance in affective disorders, though further studies against objective

assessments of reliability and external validity are required.

References

- Arfken, C. L., Joseph, A., Sandhu, G. R., Roehrs, T., Douglass, A. B., & Boutros, N. N. (2014). The status of sleep abnormalities as a diagnostic test for major depressive disorder. *Journal of affective disorders*, 156, 36-45.
- Asaad, T., Sabry, W., Rabie, M., & El-Rassas, H. (2016). Polysomnographic characteristics of bipolar hypomanic patients: Comparison with unipolar depressed patients. *Journal of* affective disorders, 191, 274-279.
- Ashman, S. B., Monk, T. H., Kupfer, D. J., Clark, C. H., Myers, F. S., Frank, E., & Leibenluft, E. (1999). Relationship between social rhythms and mood in patients with rapid cycling bipolar disorder. *Psychiatry Research*, 86(1), 1-8.
- Baandrup, L., & Jennum, P. J. (2015). A validation of wrist actigraphy against polysomnography in patients with schizophrenia or bipolar disorder. *Neuropsychiatric disease and treatment*, 11, 2271.
- Benloucif, S., Burgess, H. J., Klerman, E. B., Lewy, A. J., Middleton, B., Murphy, P. J., ... & Revell, V. L. (2008). Measuring melatonin in humans. J Clin Sleep Med, 4(1), 66-69.
- Boland, E. M., & Alloy, L. B. (2013). Sleep disturbance and cognitive deficits in bipolar disorder: toward an integrated examination of disorder maintenance and functional impairment. *Clinical psychology review*, 33(1), 33-44.
- Boland EM, Stange JP, Molz Adams A et al. Associations between sleep disturbance, cognitive functioning and work disability in Bipolar Disorder. Psychiatry Res 2015;230:567–574.
- Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39(6):411–8.
- Bunney WE, Bunney BG. 2000. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. Neuropsychopharmacology, 22(4):335–345.
- Burton, C., McKinstry, B., Tătar, A. S., Serrano-Blanco, A., Pagliari, C., & Wolters, M. (2013). Activity monitoring in patients with depression: a systematic review. *Journal of affective disorders*, 145(1), 21-28.
- Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research 1989; 28:193-213, 1989.
- Buyukdura, J.S., McClintock, S.M., Croarkin, P.E., 2011. Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 395e409.

- Bullock B, Murray G. Reduced amplitude of the 24-hr activity rhythm: a biomarker of vulnerability to bipolar disorder? Clin Psychol Sci 2014;2: 86e98.
- Crasson M, Kjiri S, Colin A, et al. Serum melatonin and urinary 6-sulfatoxymelatonin in major depression. Psychoneuroendocrinology 2004;29(1):1–12.
- Cretu, J. B., Culver, J. L., Goffin, K. C., Shah, S., & Ketter, T. A. (2016). Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. *Journal of affective disorders*, 190, 162-166.
- Chang, Y. S., Lin, M. H., Lee, J. H., Lee, P. L., Dai, Y. S., Chu, K. H., ... & Yang, Y. H. (2016). Melatonin supplementation for children with atopic dermatitis and sleep disturbance: A randomized clinical trial. *JAMA pediatrics*, 170(1), 35-42.
- Ehlers, C.L., Frank, E., Kupfer, D.J., 1988. Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. Archives of General Psychiatry 45, 948–952.
- Faria, A. D., de Azevedo Cardoso, T., Mondin, T. C., de Mattos Souza, L. D., da Silva Magalhaes, P. V., Zeni, C. P., ... & Jansen, K. (2015). Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. *Journal of affective disorders*, 186, 145-148.
- Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 2004;65(Suppl 16):27–32.
- Folkard S, Monk TH, Lobban M. 1979. Towards a predictive test of adjustment to shift work. Ergonomics, 22(1): 79-91.
- Geoffroy, P. A., Boudebesse, C., Bellivier, F., Lajnef, M., Henry, C., Leboyer, M., ... & Etain, B. (2014). Sleep in remitted bipolar disorder: a naturalistic case-control study using actigraphy. *Journal of affective disorders*, 158, 1-7.
- Geoffroy PA, Scott J, Boudebesse C, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. Acta Psychiatr Scand 2015; 131(2):89–99.
- Gershon, A., Thompson, W. K., Eidelman, P., McGlinchey, E. L., Kaplan, K. A., & Harvey, A. G. (2012). Restless pillow, ruffled mind: Sleep and affect coupling in interepisode bipolar disorder. *Journal of abnormal psychology*, 121(4), 863.
- Giglio, L. M. F., da Silva Magalhães, P. V., Andreazza, A. C., Walz, J. C., Jakobson, L., Rucci, P., ... & Kapczinski, F. (2009). Development and use of a biological rhythm interview. *Journal of affective disorders*, 118(1), 161-165.
- Giglio, L. M., Magalhães, P. V., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of psychiatric research*, 44(4), 220-223.
- Harvey AG, Schmidt DA, Scarna A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am J Psychiatry 2005;162:50–57.

- Hasler BP, Buysse DJ, Kupfer DJ, Germain A. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depres- sion. Psychiatry Res 2010;178(1):205–7 [Research Support, NIH, Extramural Research Support, Non-US Gov't].
- Hori, H., Koga, N., Hidese, S., Nagashima, A., Kim, Y., Higuchi, T., & Kunugi, H. (2016). 24-h activity rhythm and sleep in depressed outpatients. *Journal of psychiatric research*, 77, 27-34.
- Horne JA & Ostberg O. 1976. A self-assessment questionnaire to determine morningnesseveningness in human circadian rhythms. International Journal of Chronobiology, 4(2):97-110.
- Jones, S. H., Hare, D. J., & Evershed, K. (2005). Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar disorders*, 7(2), 176-186.
- Kapczinski, F., Dias, V. V., Kauer-Sant'Anna, M., Frey, B. N., Grassi-Oliveira, R., Colom, F., & Berk, M. (2009). Clinical implications of a staging model for bipolar disorders. *Expert review of neurotherapeutics*, 9(7), 957-966.
- Kaplan, K. A., Talbot, L. S., Gruber, J., & Harvey, A. G. (2012). Evaluating sleep in bipolar disorder: comparison between actigraphy, polysomnography, and sleep diary. *Bipolar disorders*, 14(8), 870-879.
- Kennedy, S. H., Kutcher, S. P., Ralevski, E., & Brown, G. M. (1996). Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. *Psychiatry research*, 63(2), 219-222.
- Kim SH, Yu HS, Park HG et al. Egr1 regulates lithium- induced transcription of the Period 2 (PER2) gene. Bio- chim Biophys Acta 2013; 1832: 1969–1979.
- Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. Proc Natl Acad Sci USA 1996; 93: 8455–8459.
- Konno M. 2013. Circadian rhythm and mood disorder. Nihon Rinsho, 71(12):2171-2178.
- Krane-Gartiser, K., Steinan, M. K., Langsrud, K., Vestvik, V., Sand, T., Fasmer, O. B., ... & Morken, G. (2016). Mood and motor activity in euthymic bipolar disorder with sleep disturbance. *Journal of affective disorders*, 202, 23-31.
- Lai, Y. C., Huang, M. C., Chen, H. C., Lu, M. K., Chiu, Y. H., Shen, W. W., ... & Kuo, P. H. (2014). Familiality and clinical outcomes of sleep disturbances in major depressive and bipolar disorders. *Journal of psychosomatic research*, 76(1), 61-67.
- Lewy, A. J. (2009). Circadian misalignment in mood disturbances. *Current psychiatry reports*, 11(6), 459-465.
- Lewy, A. (2010). Clinical implications of the melatonin phase response curve. *The Journal of Clinical Endocrinology & Metabolism*, 95(7), 3158-3160.
- Lewy, A. J., Lefler, B. J., Emens, J. S., & Bauer, V. K. (2006). The circadian basis of winter depression. *Proceedings of the National Academy of Sciences*, 103(19), 7414-7419.

- Lewy, A. J., Nurnberger, J. I., Wehr, T. A., Pack, D., Becker, L. E., Powell, R. L., & Newsome, D. A. (1985). Supersensitivity to light: possible trait marker for manic-depressive illness. *Am J Psychiatry*, 142(6), 725-727.
- Lim, A. S., Yu, L., Costa, M. D., Buchman, A. S., Bennett, D. A., Leurgans, S. E., & Saper, C. B. (2011). Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. *Sleep*, 34(11), 1569.
- Millar, A., Espie, C. A., & Scott, J. (2004). The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *Journal of affective disorders*, 80(2), 145-153.
- Molina, T. A., & Burgess, H. J. (2011). Calculating the dim light melatonin onset: the impact of threshold and sampling rate. *Chronobiology international*, 28(8), 714-718.
- Montgomery, S. A., & Asberg, M. A. R. I. E. (1979). A new depression scale designed to be sensitive to change. *The British journal of psychiatry*, 134(4), 382-389.
- Ng, T. H., Chung, K. F., Ho, F. Y. Y., Yeung, W. F., Yung, K. P., & Lam, T. H. (2015). Sleepwake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. *Sleep medicine reviews*, 20, 46-58.
- Nováková, M., Praško, J., Látalová, K., Sládek, M., & Sumová, A. (2015). The circadian system of patients with bipolar disorder differs in episodes of mania and depression. *Bipolar disorders*, *17*(3), 303-314.
- Nowak, R., McMillen, I. C., Redman, J., & Short, R. V. (1987). The correlation between serum and salivary melatonin concentrations and urinary 6-hydroxymelatonin sulphate excretion rates: two non-invasive techniques for monitoring human circadian rhythmicity. *Clinical endocrinology*, *27*(4), 445-452.
- Nurnberger, J. I., Adkins, S., Lahiri, D. K., Mayeda, A., Hu, K., Lewy, A., ... & Smiley, C. (2000). Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archives of general psychiatry*, 57(6), 572-579.
- Ortiz, A., Bradler, K., Radu, L., Alda, M., & Rusak, B. (2016). Exponential state transition dynamics in the rest–activity architecture of patients with bipolar disorder. *Bipolar disorders*.
- Ritter PS, Marx C, Lewtschenko N, Pfeiffer S, Leopold K, Bauer M, et al. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. J Neural Transm 2012;119:1173e84.
- Robillard, R., Naismith, S. L., Rogers, N. L., Scott, E. M., Ip, T. K. C., Hermens, D. F., & Hickie, I. B. (2013). Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *European Psychiatry*, 28(7), 412-416.
- Rocha, P. M. B., Neves, F. S., & Corrêa, H. (2013). Significant sleep disturbances in euthymic bipolar patients. *Comprehensive psychiatry*, 54(7), 1003-1008.
- Rock, P., Goodwin, G., Harmer, C., & Wulff, K. (2014). Daily rest-activity patterns in the bipolar phenotype: A controlled actigraphy study. *Chronobiology international*, *31*(2), 290-296.

- Roenneberg T, Wirz-Justice A, Merrow M. 2003. Life between clocks: daily temporal patterns of human chronotypes. Journal of Biological Rhythms, 18(1):80-90.
- Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, Comes M, Colom F, Van Riel W, Ayuso-Mateos JL, Kapczinski F, Vieta E. 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health, 3:5.
- Ryves WJ, Harwood AJ. Lithium inhibits glycogen syn- thase kinase-3 by competition for magnesium. Biochem Biophys Res Commun 2001; 280: 720–725.
- Rumble, M. E., White, K. H., & Benca, R. M. (2015). Sleep disturbances in mood disorders. *Psychiatric Clinics of North America*, 38(4), 743-759.
- Salvatore P, Ghidini S, Zita G, De Panfilis C, Lambertino S, Maggini C, Baldessarini RJ. 2008. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disorders, 10(2):256-265.
- Samalin, L., Reinares, M., De Chazeron, I., Torrent, C., Bonnin, C. M., Hidalgo-Mazzei, D., ... & Llorca, P. M. (2016). Course of residual symptoms according to the duration of euthymia in remitted bipolar patients. *Acta Psychiatrica Scandinavica*, 134(1), 57-64.
- Sheehan DV, Lecrubier Y, Sheehan KH, Janavs AM, Weiller E, Hergueta T, Baker R, Dunbar GC. 1998. The Mini-International Neurospychiatric Invteriw (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-iV and ICD-10. Journal of Clinical Psychiatry, 59:22-33.
- Shen, G. H., Alloy, L. B., Abramson, L. Y., & Sylvia, L. G. (2008). Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. *Bipolar disorders*, 10(4), 520-529.
- Srinivasan, V., Smits, M., Spence, W., Lowe, A. D., Kayumov, L., Pandi-Perumal, S. R., ... & Cardinali, D. P. (2006). Melatonin in mood disorders. *The World Journal of Biological Psychiatry*, 7(3), 138-151.
- Sturgeon, S. R., Doherty, A., Reeves, K. W., Bigelow, C., Stanczyk, F. Z., Ockene, J. K., ... & Neuhouser, M. L. (2014). Urinary levels of melatonin and risk of postmenopausal breast cancer: women's health initiative observational cohort. *Cancer Epidemiology Biomarkers* & *Prevention*, 23(4), 629-637.
- Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry*, 133(5), 429-435.
- Yin L, Wang J, Klein PS, Lazar MA. Nuclear receptor Rev-erbalpha is a critical lithium-sensitive component of the circadian clock. Science 2006; 311: 1002–1005.

	НС	MDDE	MDDC	BDE	BDC
N (%F)	40 (55.0)	23 (69.5)	9 (55.5)	21 (61.9)	10 (50.0)
Psychotropic Meds (%, range)	N/A	56.5 (1-5)	77.8 (1-3)	90.4 (1-6)	80.0 (1-4)
Employment Status (% employed)	97.5	78.3	55.5	76.2	60.0
			M (SD)		
Age (years)	34.5 (12.5)	38.3 (13.8)	42.6 (13.7)	33.7 (10.2)	40.6 (10.9)
Education (years)	17.5 (3.8)	15.9 (1.87)	14.0 (2.40)	15.7 (2.70)	16.0 (3.09)
BMI	24.6 (4.5)	26.8 (5.07)	28.7 (5.53)	26.6 (4.96)	30.5 (6.28)
Age Onset	N/A	21.6 (10.3)	21.4 (13.6)	16.7 (7.06)	13.3 (5.61)
MADRS	1.76 (1.71)	6.13 (4.40)	16.3 (8.36)	8.09 (5.92)	9.75 (6.27)
YMRS	1.61 (1.26)	1.35 (1.43)	2.11 (2.15)	2.14 (2.24)	2.30 (2.11)
PSQI	3.84 (1.49)	6.88 (4.01)	12.1 (4.52)	6.47 (4.77)	6.60 (4.40)
ESS	3.59 (4.86)	7.07 (4.25)	8.57 (6.07)	7.76 (4.03)	7.22 (3.63)

Figures and Tables

Table 1. Demographic and clinical characteristics. BMI: Body Mass Index; MADRS: Montgomery-AsbergDepression Rating Scale; YMRS: Young Mania Rating Scale; PSQI: Pittsburgh Sleep Quality Index; ESS:Epworth Sleepiness Scale. Note: MADRS, YMRS, PSQI, ESS are completed at Visit 2. Diagnosis and moodstate were determined by MINI.

			M (SD)			
Subjective	HC	MDDE	MDDC	BDE	BDC	Sig. Contrasts
PSQI	3.84 (1.49)	6.88 (4.01)	12.0 (4.93)	6.47 (4.77)	7.18 (4.60)	MDDC>HC
Objective (Actigraphy)						
TST (h)	6.63 (0.83)	6.95 (1.05)	6.24 (1.57)	7.16 (1.25)	6.94 (1.03)	
SE (%)	84.7 (4.28)	83.8 (6.04)	80.6 (4.64)	83.8 (5.22)	83.3 (8.07)	
WASO (min)	37.5 (12.8)	53.5 (19.1)	64.6 (25.2)	59.9 (20.7)	59.8 (27.7)	MDDC>HC BDE>HC BDC>HC
SOL	15.1 (10.6)	15.2 (8.96)	13.5 (6.01)	11.0 (7.26)	7.18 (4.60)	

Table 2. Mean and standard deviation of subjective and objective sleep parameters. MDDE: MDD euthymic;MDDC: MDD currently depressed; BDE: BD euthymic; BDC: BD currently depressed; PSQI: PittsburghSleep Quality Index; TST: Total Sleep Time; SE: Sleep Efficiency; WASO: Wake After Sleep Onset; SOL:Sleep Onset Latency.

			M (SD)			
Subjective	НС	MDDE	MDDC	BDE	BDC	Sig. Contrasts
BRIAN	30.7 (6.34)	41.1 (9.50)	48.3 (11.3)	41.4 (9.51)	46.6 (13.7)	MDDE>HC MDDC>HC BDE>HC BDC>HC
Objective (Actigraphy)						
IS Weekday	0.54 (0.13)	0.48 (0.11)	0.43 (0.18)	0.51 (0.15)	0.46 (0.14)	
IS Weekend	0.56 (0.15)	0.57 (0.15)	0.48 (0.20)	0.60 (0.14)	0.55 (0.19)	
IV Weekday	0.68 (0.26)	0.79 (0.18)	0.79 (0.14)	0.82 (0.18)	0.90 (0.28)	
IV Weekend	0.77 (0.20)	0.79 (0.23)	0.70 (0.27)	0.73 (0.19)	0.70 (0.26)	
Acrophase Weekday	10.6 (6.9)	12.2 (7.37)	9.21 (4.44)	11.9 (6.51)	11.1 (6.86)	
Acrophase Weekend	12.3 (7.6)	14.2 (5.93)	10.8 (5.71)	11.7 (6.31)	12.5 (7.42)	
CQ Weekday	0.77 (0.08)	0.81 (0.12)	0.72 (0.13)	0.81 (0.19)	0.80 (0.14)	
CQ Weekend	0.83 (0.18)	0.85 (0.21)	0.76 (0.21)	0.89 (0.17)	0.85 (0.19)	

Table 3. Mean and standard deviation of subjective and objective circadian parameters. MDDE: MDDeuthymic; MDDC: MDD currently depressed; BDE: BD euthymic; BDC: BD currently depressed; IS:Interdaily stability; IV: Intradaily variability; CQ: Circadian quotient.

			M (SD)			
Subjective	НС	MDDE	MDDC	BDE	BDC	Sig. Contrasts
6-SM	33.8 (14.2)	38.1 (25.5)	30.5 (19.6)	33.8 (26.4)	11.9 (6.2)	HC>BDC MDDE>BDC
DLMO	21.0 (0.68)	20.7 (1.14)	21.5 (1.51)	21.4 (1.61)	18.9 (1.22)	
PAD	5.70 (2.05)	7.14 (1.10)	7.16 (2.13)	5.95 (1.76)	8.98 (1.71)	

Table 4. Mean and standard deviation of objective circadian parameters (melatonin). 6-SM: 6-sulphatoxymelatonin; DLMO: Dim Light Melatonin Onset; PAD: Phase Angle Difference.



Figure 1. Healthy control sample actogram. This individual has a fairly consistent sleep/activity schedule. Periods of blue indicate inactivity (rest overnight). Areas outside dark blue bars at the beginning and end of sleep indicate sleep onset latency, and wake onset. Orange: White light exposure. Black: Motor activity throughout the day. Red indicates wake.



Figure 2. Hourly melatonin concentrations plotted by group. Melatonin is normalized over individual creatinine value (ng/mg). BD (N) = 11, MDD (N) = 10, HC (N) = 10.



Figure 3. Hourly activity means by group. BDC: Bipolar disorder current depression; BDE: Bipolar disorder euthymic; HC: Healthy control; MDDC: MDD currently depressed; MDDE: MDD euthymic. All five groups generally show the same activity curve throughout a 24h period, and similar peak times of activity (acrophase). Currently depressed MDD show the lowest levels of activity throughout the peak of the curve, while controls and euthymic bipolars show higher peak levels.

CHAPTER 3

An objective validation of the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN)

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Abstract

Background: Circadian disruptions are widely associated with acute episodes and the long-term course of mood disorders. Current questionnaires are not useful in the clinical setting, and external validity of these items must be investigated. The Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) scale is subjective rating scale assessing biological rhythm disturbance. The aim of this study is to validate the BRIAN against objective parameters in individuals with mood disorders and controls.

Methods: A total of 103 subjects (40 controls, 32 MDD, 31 BD) wore an actiwatch for fifteen days. Subjects also completed one evening of saliva sampling, and completed one first morning urine sample, both to be assessed for melatonin profile. BRIAN was completed at the end of the 15 days. Spearman's correlations were used to assess the association between circadian and sleep variables, and the BRIAN.

Results: Total BRIAN score correlated with WASO in the total sample ($\rho = 0.34$, 95% CI [0.11, 0.54], p < 0.01), but not with any other sleep/circadian measures (all p > 0.05). MDD group appeared to drive the correlation between total BRIAN and WASO ($\rho = 0.52$, 95% CI [-0.004, 0.19], p < 0.01), and sleep efficiency ($\rho = -0.53$, 95% CI [-0.72, -0.09], p = 0.005). BRIAN sleep domain correlated with WASO ($\rho = 0.58$, 95% CI [-0.83, -0.009], p < 0.01) and sleep efficiency ($\rho = 0.56$, 95% CI [-0.07, 0.75], p < 0.01) in BD. BRIAN scores did not correlate with any daily activity rhythms variables (p > 0.05). Total BRIAN scores correlated with 6-SM ($\rho = -0.24$, 95% CI [-0.43, -0.02], p < 0.03).

Conclusion: We found that the BRIAN correlated with WASO and 6-SM, indexes of night awakenings and nocturnal melatonin secretion. No agreement was observed between BRIAN scores and actigraphic daily activity rhythms. The BRIAN self-report questionnaire demonstrates some promising external validity when correlated with objective measures of sleep and circadian rhythmicity.

Introduction

Bipolar disorder (BD) and major depressive disorder (MDD) are chronic, debilitating psychiatric conditions that cause shifts in mood, energy, and sleep patterns and can severely impair daily functioning. It is thought that two major contributors to the pathophysiology of mood disorders involve sleep and biological rhythm disturbances (Leboyer & Kupfer, 2010). Biological rhythms are daily cycles of activity that include our sleep/wake, appetite, hormonal and social rhythms. While both BD and MDD patients display varying disturbances of sleep and circadian markers, BD subjects exhibit an even more pronounced irregularity of sleep times and durations, cortisol and melatonin secretion, and phase preferences (Boudebesse et al., 2014; Novakova et al., 2015). BD and MDD are considered multi-systemic disorders where sleep and biological rhythm disturbance are central in the pathology of the disease (Buysse et al., 2008; Franzen et al., 2008; Harvey et al., 2005). In light of this, there is a great need for the objective assessment of biological rhythms and sleep in patients with a mood disorders (Kapczinski et al., 2011).

There are well-validated objective measures of circadian rhythmicity. Objective measures include polysomnography, actigraphy and daily fluctuations in melatonin and cortisol. Polysomnography, which is the gold standard in studying sleep abnormalities, is more suited to assessing sleep disorders and is not readily available in all countries. Actigraphy is the use of wrist-worn piezoelectric devices with microprocessors that are able to measure motility and light levels thereby distinguishing sleep from waking, and allowing for the analysis of specific phases of sleep and activity. This is a validated measure for objectively and non-invasively assessing daily activity rhythms (DAR) in patients with mood disorders (Etain et al., 2011; Winkler et al., 2005). Sleep parameters obtained from actigraphy have also been shown to be highly correlated with measures in polysomnography (Kaplan et al., 2012). Despite its objective validity, actigraphy is more costly and time consuming to administer compared to subjective rating scales. The melatonin profile, tested specifically for the increase in evening melatonin production, is considered the most reliable measure of the timing of the biological clock (Molina & Burgess,

2011). Melatonin can be assayed in plasma or saliva. However, the cost of assaying samples is relatively high and may not be feasible for patients (Molina & Burgess, 2011). Considering the issue of cost, the rate of sampling is called into question. Samples are usually done hourly, or further, half-hourly depending on the research question, objectives, and preference of accuracy. Melatonin secretion profiles show disturbance in MDD and BD (Harris et al., 2015; Novakova et a., 2015).

Subjective measures include self-rated questionnaires, such as the Munich Chronotype Questionnaire (MCTQ) (Roenneberg et al., 2003), Circadian Type Inventory (CTI) (Folkard et al., 1979) and Horne-Ostberg morningness-eveningness scale (MEO) (Horne & Ostberg, 1976). The literature is scarce in regard to assessing external validity on measures of circadian rhythmicity with these subjective measurements, and even so only treats specific items pertaining to sleep parameters rather than evaluating a full measurement (Boudebesse et al., 2014). The Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) is another subjective assessment that has recently been validated in both bipolar disorder (BD) (Giglio et al., 2009) and has been shown to distinguish between mood states in both BD and major depressive disorder (MDD) (Faria et al., 2015). The BRIAN scale is a 21-item interview assessing biological rhythms segregated into 5 domains: sleep, activity, eating patterns, social activity and chronotype. All items are scored from 1 (no difficulty maintaining daily patterns) to 4 (serious difficulty). It has demonstrated excellent internal consistency (Cronbach's $\alpha = 0.93$) and has a test-retest reliability 0.98 (95% CI 0.96-0.99) (Giglio et al., 2009). Notably, shows high correlation with the Functioning Assessment Short Test (Giglio et al., 2010), which is of interest in bipolar disorder due to reduced functionality interepisodically (Huxley & Baldessari, 2007). Furthermore, the BRIAN scale is an independent predictor of functioning (Giglio et al., 2010) and quality of life (Cudney et al., 2016) in euthymic BD.

The studies presented above advocate the clinical utility of circadian rhythm assessments in patients with mood disorders. Although the BRIAN scale has excellent reliability and is highly

correlated with other rating scales used to assess patients with mood disorders, its external validity must be assessed before it can be used in clinical practice. The main goal of this study is to validate the BRIAN against objective parameters of circadian rhythms in healthy volunteers and in patients with mood disorders. We hypothesized that the BRIAN scale would correlate with objective parameters of sleep and circadian rhythms in individuals both with and without BD and MDD.

Methods

Participants

A total of 103 subjects were obtained for this study. 40 controls, 32 MDD and 31 BD were recruited from the Mood Disorders Program and Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton, Ontario, or from the community. All subjects gave written informed consent to participate in the study, as approved by the Hamilton Integrated Research Ethics Board (HIREB). The diagnosis and mood state of MDD or BD was confirmed with the Mini International Neuropsychiatric Interview (MINI) English Version 6.0.0. (Sheehan et al., 1998). Subjects distributed into the BD or MDD groups were enrolled if they met criteria for either a current or past mood episode according to the MINI. Subjects were enrolled in the healthy control group if they did not meet criteria for current or past history of any Axis I disorder. All subjects were excluded if they (1) had a current or lifetime history of a sleep disorder, (2) had a current or longstanding use of melatonin, (3) were employed in shiftwork, (4) were currently using medication specifically prescribed for sleep, (5) were currently using prescribed medication for pain relief with sedative effects, (6) were currently using recreational drugs such as marijuana as a sleep aid at any time throughout the day, (7) met criteria for current alcohol/substance abuse or dependence, and (8) if they were currently experiencing jetlag from a recent trip outside the Eastern Time Zone.

Study Design

Please refer to Chapter 2 for study design. Chapter 2 and 3 are separate analyses conducted from the same study.

Assessments

The BRIAN

Subjective biological rhythm disturbance was measured with the Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009). The BRIAN is a 21item self-report questionnaire that inquires about how often one feels they have experienced rhythm disruption over the last 15 days. The BRIAN can be broken down into 4 domains over 18 questions: sleep, general activity, social, and eating patterns. There is a 5th domain that is not included in the total score, questions 19-21, which gives a measure of chronotype. Items are scored on a Likert-type scale, ranging from 1-4. The higher the score, the greater the subjective biological rhythm disturbance.

Actigraphy

Objective measures of sleep and circadian rhythmicity were obtained with the Actiwatch 2 monitor, purchased from Philips Respironics Inc., (Biolynx, Montreal, Quebec, CA). An Actiwatch contains an accelerometer that detects motor activity from the wrist to detect intensity and timing of successive movements over 24h periods. Data collected includes periods of sleep (inactivity), rest and activity. Data was collected in one-minute epochs continuously for 15 days. Actiwatch data was retrieved and processed using Philips Actiware Version 6.0.

Sleep measures obtained from Actiware included total sleep time, sleep onset latency (SOL), sleep efficiency, and wake after sleep onset (WASO). Cosinor analysis was employed to further explore underlying circadian rhythmicity. This procedure fits time-series data to a single cosine wave. The measurements obtained from the cosinor analysis give a mean value over 15

days, fitted to the wave over a 24h period. The cosinor analysis generated the following parameters: (1) MESOR (midline-estimating statistic of the rhythm), (2) amplitude (a value indication ¹/₂ the variation in the data, or the activity range from mean level to the peak/trough of the cosine wave), (3) acrophase (a measure of when peak activity occurs, converted to 24h time). MESOR and amplitude are then computed to the (4) circadian quotient (CQ), which is the amplitude/MESOR ratio, providing a normalized measure of the strength of an individual rhythm.

Non-parametric measures of circadian function were also obtained from the cosinor analysis. (1) Intradaily variability (IV): This is a measure of rhythm fragmentation, and is calculated as the ratio of the mean square difference between successive measurements over the overall variance in the data. IV scores range from 0 - 2, with higher scores indicating greater rhythm fragmentation. (2) Interdaily stability (IS): This is a measure of the strength of coupling between endogenous daily activity rhythms and external zeitgebers, or how well internal activity is synchronized to external cues. IS is calculated as the normalized ratio of the variance of the mean 24h rhythm over the overall variance in the study duration. Scores range from 0 - 1, with higher scores indicated greater synchronization of daily activity rhythms to external cues.

Melatonin

The saliva samples were used to measure dim light melatonin onset (DLMO) as an objective biological measure of phase assessment. 2 mL of salivary melatonin was collected each hour from 6:00 pm until habitual bedtime using 15 mL presterilized conical centrifuge tubes (VWR, Radnor, Pennsylvania). Each sample was immediately frozen upon collection and returned to the laboratory. Saliva samples were later assayed using an ELISA salivary melatonin enzyme immunoassay kit (Salimetrics, State College, Pennsylvania, USA). Each subject's samples were analyzed in the same batch. The sensitivity of the assay was 1.42 pg/mL. The interassay coefficient of variation for low endogenous melatonin was 23.6%. The intra-assay coefficients of variation for the mean of low levels of endogenous melatonin were between 5.9%

and 6.5%.

The morning urine sample was used to measure urinary melatonin metabolite, 6sulphatoxymelatonin (6-SM). Morning urine was refrigerated until arrival to the laboratory for return. Urine samples were analyzed using ELISA for 6-SM (Buhlmann Diagnostics Corporation, Amherst, New Hampshire, USA). The sensitivity of the assay was 0.14 ng/mL. The inter-assay coefficient of variation was 11.9%. The intra-assay coefficient of variation was 7.1%. Urinary melatonin aliquots were also analyzed for creatinine levels by the Hamilton Regional Laboratory Medicine Program at St. Joseph's Healthcare Hamilton (Ministry of Health License #4037).

Statistical Analysis

For each evening melatonin profile, one DLMO time was derived. Due to the high interindividual variability in our sample, and relatively high levels of melatonin secretion, we chose a DLMO threshold of 10 pg/mL to fit our data (Benloucif et al., 2008; Lewy, 2009). The DLMO was therefore interpreted as the interpolated time that melatonin concentrations reached and exceeded 10 pg/mL for at least two hours thereafter. From this data, phase angle differences (PAD) were also calculated. PAD was calculated as the [midpoint of sleep – DLMO] (Lewy et al., 2006). Urinary melatonin measurement was normalized by calculating a melatonin-creatinine ratio [absolute melatonin/creatinine], which has proven to be a reliable standardized measure comparable to plasma melatonin levels (Chang et al., 2016; Nowak et al., 1987; Sturgeon et al., 2014).

All analyses were performed with R (Version 3.0.2, R Development Core Team, 2012). Spearman tests were employed for correlations since BRIAN scores were not normally distributed. Correlations were done in groups as a whole, and then broken down into BD, MDD and controls to further assess the driving cohort. BRIAN total scores were correlated with (1) objective sleep measures including total sleep time, WASO, SOL and sleep efficiency, (2) objective circadian parameters including weekend and weekday IS, IV, acrophase and CQ, and

Results

Demographic and clinical data are displayed in Table 1.

Correlations between BRIAN scores and objective sleep

Total BRIAN score significantly correlated with WASO in the total sample ($\rho = 0.34$, 95% CI [0.11, 0.54], p < 0.01), however it did not significantly correlate with any other objective sleep measures (p > 0.05). BRIAN sleep domain did not significantly correlate with objective sleep measures in the total sample. In BD, BRIAN total score did not significantly correlate with objective sleep parameters (p > 0.05). However, BRIAN sleep domain significantly correlate with wth WASO ($\rho = 0.58, 95\%$ CI [-0.83, -0.01], p < 0.002) and sleep efficiency ($\rho = 0.56, 95\%$ CI [-0.07, 0.76], p = 0.003) in BD. In MDD, total BRIAN score significantly correlated with WASO ($\rho = 0.53, 95\%$ CI [0.00, 0.19], p < 0.01) and sleep efficiency ($\rho = -0.53, 95\%$ CI [-0.72, -0.09], p < 0.01). BRIAN sleep domain also significantly correlated with SOL ($\rho = 0.40, 95\%$ CI [0.04, 0.67], p = 0.04) and sleep efficiency ($\rho = -0.47, 95\%$ CI [-0.69, 0.01], p < 0.02) in MDD. Total BRIAN score and BRIAN sleep domain did not significantly correlate with any objective sleep measures. Full results with Bonferroni adjustments are reported in Table 2.

Correlations between BRIAN scores and objective circadian

Total BRIAN score did not significantly correlate with any objective circadian parameters in the total sample (p > 0.05). Full results are reported in Table 3.

Correlation of phase markers assessed by melatonin

Total BRIAN scores significantly correlated with the total sample of 6-SM ($\rho = -0.24$,

95% CI [-0.43, -0.02], p < 0.03). When broken down by group, total BRIAN scores significantly correlated with bipolar 6-SM ($\rho = -0.42$, 95% CI [-0.77, 0.04], p < 0.04). Total BRIAN score did not significantly correlate with the MDD or control groups (p > 0.05). Total BRIAN score in total sample and by group did not significantly correlate with DLMO or PAD measures (Table 4).

Discussion

We found varying levels of agreement the BRIAN and objective measures of sleep and circadian rhythmicity. Total BRIAN scores correlated with WASO and sleep efficiency. No agreement was observed between BRIAN scores and actigraphic parameters of circadian rhythmicity. Lastly, morning urine melatonin levels showed mild agreement with BRIAN total score. These findings provide evidence of some external validity to support the use of subjective measurements of biological rhythm disturbance in the clinical setting.

It is understandable that there is hesitation about using subjective measurements of sleep in a clinical setting, due to the lack of defined relationships between accurate findings in how they relate to objective measurements. Several studies have reported discordance among objective and subjective measures of sleep, and our study adds to the mixed outcomes. Subjective reports tend to overestimate SOL and underestimate WASO and total sleep time when compared to objective measures (Conroy et al., 2006; Harvey et al., 2005). Mayers et al., (2003) showed that subjects with a diagnosis of MDD can perceive, or overestimate poor sleep quality, and feeling exhausted after a full night's sleep even if sleep disturbance estimates were no different from controls. These results are corroborated by another study that found the degree of wrongful estimation of sleep parameters is greater in depressed patients compared to controls (Rotenberg et al., 2000), suggesting MDD subjects experience more sleep distress. When comparing subjective measures of sleep and objective polysomnography measures, Armitage et al., (1997) found a strong correlation between time in bed, total sleep time and SOL in depressed patients and healthy controls, but no correlation with sleep quality. Interestingly, in our study, WASO and

MSc. Thesis: O. Allega, McMaster University, Neuroscience sleep efficiency significantly correlated with BRIAN total scores in both mood groups, indicating greater biological rhythm disturbance is associated with greater periods of wakeful activity throughout the night. Moreover, this relationship was not significant in controls.

The literature, however, is scarce when it comes to evaluating objective and subjective assessments of circadian rhythmicity in mood populations, or at all, for that matter. After performing a literature search, only one study by evaluated correlations between objective (actigraphy) and subjective (Pittsburgh Sleep Quality Index, Composite Scale of Morningness, and Circadian Type Inventory) measures of circadian rhythmicity in a sample of remitted bipolar subjects (Boudebesse et al., 2014). However, each questionnaire was not fully assessed; only certain items on each of these indices were matched to actigraphic parameters that corresponded by definition. Rhythm stability, sleep quality, sleep latency and sleep disturbance displayed modest correlation between objective and subjective measures. These results suggest there are varying levels of agreement between subjective and objective measures of rhythmicity. Though the BRIAN does not have criteria that specifically match with actigraphy parameters for sleep and circadian rhythmicity (TST, WASO, SOL, sleep efficiency, IS, IV, CQ), it does have items that could be considered proxy measures. For example, items (1) and (5) on the BRIAN ask about difficulty falling asleep at regular bedtimes, which could be equated to SOL. Item (4) on the BRIAN, which inquires about feeling rested with the quantity of sleep one receives, could be equated to sleep efficiency.

Total BRIAN scores showed agreement with levels of nocturnal melatonin secretion. When assessed by group, BD subjects appeared to be driving the correlation. This makes sense since BD subjects display significantly less 6-SM compared to controls (p > 0.05; Chapter 2). This finding suggests lower levels of melatonin secretion are associated with higher levels of selfreported biological rhythm disturbance, which is a very promising measure for external validity of the BRIAN. Melatonin levels have been identified as a trait marker in bipolar disorder where

which provides insight into the pathophysiological mechanisms at the crux of mood disorders. This could potentially be related to a phase shift in the nocturnal melatonin peak, which further corroborates evidence of sleep disturbance, cognitive and psychosocial impairment persisting into remission in BD (Boland et al., 2015; Harvey et al., 2015; Russo et al., 2015). These findings encourage the need for therapeutic intervention more specifically targeted at the melatonin secretion pathway.

The limitations of this study must be discussed. A limitation of this study was the lack of comparative data between the social, activity and eating pattern domains of the BRIAN. Future studies should include objective measures of these domains. A feasible example of such for the social domain might include the smartphone-based tracker developed from the Social Rhythm Metric (Monk et al., 1990; Monk et al., 1991), *MoodRhythm* (Matthews et al., 2016), which uses smartphone sensors and accelerometers to detect social rhythms and social interaction levels. Self-report options are also available on this application. Comparing parameters from *MoodRhythm* to BRIAN might provide further external validation to the tool as a whole. Lastly, compliance levels from saliva collection to assess DLMO were quite low. Please refer to Chapter 2 (Discussion) for further detail.

In conclusion, the BRIAN self-report questionnaire demonstrates some promising external validity when correlated with objective measures of sleep and circadian rhythmicity. Objective sleep parameters, mainly WASO and sleep efficiency, showed variability in significant correlations with total BRIAN score and BRIAN sleep domain. The BRIAN scale and biological measure 6-SM showed significant correlation in bipolar disorder, further adding to the body of literature asserting that lower levels of melatonin are associated with greater rhythm disturbance. The BRIAN scale showed no accordance with objective circadian parameters as determined by

actigraphy. These results provide evidence that the BRIAN is a useful tool in the clinical setting

to measure biological rhythm disturbance.

References

- Armitage, R., Trivedi, M., Hoffmann, R., & Rush, A. J. (1997). Relationship between objective and subjective sleep measures in depressed patients and healthy controls. *Depression and anxiety*, 5(2), 97-102.
- Boland, E. M., Stange, J. P., Adams, A. M., LaBelle, D. R., Ong, M. L., Hamilton, J. L., ... & Alloy, L. B. (2015). Associations between sleep disturbance, cognitive functioning and work disability in Bipolar Disorder. *Psychiatry research*, 230(2), 567-574.
- Boudebesse, C., Geoffroy, P. A., Bellivier, F., Henry, C., Folkard, S., Leboyer, M., & Etain, B. (2014). Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiology international*, 31(5), 698-704.
- Buysse, D. J., Angst, J., Gamma, A., Ajdacic, V., Eich, D., & Rossler, W. (2008). Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep*, *31*(4), 473.
- Conroy, D. A., Todd Arnedt, J., Brower, K. J., Strobbe, S., Consens, F., Hoffmann, R., & Armitage, R. (2006). Perception of sleep in recovering alcohol-dependent patients with insomnia: Relationship with future drinking. *Alcoholism: Clinical and Experimental Research*, 30(12), 1992-1999.
- Cudney, L. E., Frey, B. N., Streiner, D. L., Minuzzi, L., & Sassi, R. B. (2016). Biological rhythms are independently associated with quality of life in bipolar disorder. *International journal of bipolar disorders*, 4(1), 1.
- Dallaspezia, S., & Benedetti, F. (2009). Melatonin, circadian rhythms, and the clock genes in bipolar disorder. *Current psychiatry reports*, 11(6), 488-493.
- De Dios, C., Ezquiaga, E., Agud, J. L., Vieta, E., Soler, B., & García-López, A. (2012). Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. *Journal of affective disorders*, 143(1), 160-165.
- Etain B, Milhiet V, Bellivier F, Leboyer M. 2011. Genetics of circadian rhythms and mood spectrum disorders. European Neuropsychopharmacology, 21(4):S676-682.
- Faria, A. D., de Azevedo Cardoso, T., Mondin, T. C., de Mattos Souza, L. D., da Silva Magalhaes, P. V., Zeni, C. P., ... & Jansen, K. (2015). Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. *Journal of affective disorders*, 186, 145-148.
- Folkard S, Monk TH, Lobban M. 1979. Towards a predictive test of adjustment to shift work. Ergonomics, 22(1): 79-91.

Franzen, P. L., & Buysse, D. J. (2008). Sleep disturbances and depression: risk relationships for

subsequent depression and therapeutic implications. *Dialogues in clinical neuroscience*, 10(4), 473.

- Gallagher, P., Watson, S., Smith, M.S., Young, A.H., Ferrier, I.N., 2007. Plasma corti- soldehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar dis- order. Schizophr. Res. 90 (1-3), 258–265.
- Giglio, L. M. F., da Silva Magalhães, P. V., Andreazza, A. C., Walz, J. C., Jakobson, L., Rucci, P., ... & Kapczinski, F. (2009). Development and use of a biological rhythm interview. *Journal of affective disorders*, 118(1), 161-165.
- Giglio, L. M., Magalhães, P. V., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of psychiatric research*, 44(4), 220-223.
- Harris, A., Reme, S. E., Tangen, T., Hansen, Å. M., Garde, A. H., & Eriksen, H. R. (2015). Diurnal cortisol rhythm: Associated with anxiety and depression, or just an indication of lack of energy?. *Psychiatry research*, 228(2), 209-215.
- Harvey, A. G., Schmidt, D. A., Scarnà, A., Semler, C. N., & Goodwin, G. M. (2005). Sleeprelated functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry*, 162(1), 50-57.
- Harvey, A. G., Soehner, A. M., Kaplan, K. A., Hein, K., Lee, J., Kanady, J., ... & Buysse, D. J. (2015). Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: A pilot randomized controlled trial. *Journal of consulting and clinical psychology*, 83(3), 564.
- Horne JA & Ostberg O. 1976. A self-assessment questionnaire to determine morningnesseveningness in human circadian rhythms. International Journal of Chronobiology, 4(2):97-110.
- Huxley, N., & Baldessarini, R. J. (2007). Disability and its treatment in bipolar disorder patients. *Bipolar disorders*, 9(1-2), 183-196.
- Judd, L. L., Schettler, P. J., Akiskal, H. S., Coryell, W., Leon, A. C., Maser, J. D., & Solomon, D. A. (2008). Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Archives of general psychiatry*, 65(4), 386-394.
- Kalsbeek, A., Van der Spek, R., Lei, J., Endert, E., Buijs, R. M., & Fliers, E. (2012). Circadian rhythms in the hypothalamo-pituitary-adrenal (HPA) axis. *Molecular and cellular endocrinology*, 349(1), 20-29.
- Kapczinski, F., Frey, B. N., & Vieta, E. (2011). Sleep and circadian rhythm disturbances in bipolar disorder: an urgent need for objective assessment and systematic follow-up. *The Journal of clinical psychiatry*, 72(5), 724-724.
- Kaplan, K. A., Talbot, L. S., Gruber, J., & Harvey, A. G. (2012). Evaluating sleep in bipolar disorder: comparison between actigraphy, polysomnography, and sleep diary. *Bipolar disorders*, 14(8), 870-879.

- Kennedy, S. H., Kutcher, S. P., Ralevski, E., & Brown, G. M. (1996). Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. *Psychiatry research*, 63(2), 219-222.
- Lam, R. W., Berkowitz, A. L., Berga, S. L., Clark, C. M., Kripke, D. F., & Gillin, J. C. (1990). Melatonin suppression in bipolar and unipolar mood disorders. *Psychiatry research*, 33(2), 129-134.
- Leboyer M, Kupfer DJ. (2010). Bipolar disorder: New perspectives in health care and prevention. J Clin Psychiatr. 71:1689–95.
- Linkowski, P., Kerkhofs, M., Van Onderbergen, A., Hubain, P., Copinschi, G., L'Her- mite-Baleriaux, M., Leclercq, R., Brasseur, M., Mendlewicz, J., Van Cauter, E., 1994. The 24hour profiles of cortisol, prolactin, and growth hormone secretion in mania. Arch. Gen. Psychiatry 51 (8), 616–624.
- Matthews, M., Abdullah, S., Murnane, E., Voida, S., Choudhury, T., Gay, G., & Frank, E. (2016). Development and Evaluation of a Smartphone-Based Measure of Social Rhythms for Bipolar Disorder. *Assessment*, 1073191116656794.
- Mayers, A.G., van Hooff, J.C., Baldwin, D.S., 2003. Quanti- fying subjective assessment of sleep and life-quality in antidepressant-treated depressed patients. Human Psychopharmacology 18, 21–27.
- Molina, T. A., & Burgess, H. J. (2011). Calculating the dim light melatonin onset: the impact of threshold and sampling rate. *Chronobiology international*, *28*(8), 714-718.
- Monk, T. K., Flaherty, J. F., Frank, E., Hoskinson, K., & Kupfer, D. J. (1990). The Social Rhythm Metric: An instrument to quantify the daily rhythms of life. *Journal of Nervous* and Mental Disease.
- Monk, T. H., Kupfer, D. J., Frank, E., & Ritenour, A. M. (1991). The Social Rhythm Metric (SRM): measuring daily social rhythms over 12 weeks. *Psychiatry research*, 36(2), 195-207.
- Nováková, M., Praško, J., Látalová, K., Sládek, M., & Sumová, A. (2015). The circadian system of patients with bipolar disorder differs in episodes of mania and depression. *Bipolar disorders*, *17*(3), 303-314.
- Nurnberger, J. I., Adkins, S., Lahiri, D. K., Mayeda, A., Hu, K., Lewy, A., ... & Smiley, C. (2000). Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archives of general psychiatry*, 57(6), 572-579.
- Rock, P., Goodwin, G., Harmer, C., & Wulff, K. (2014). Daily rest-activity patterns in the bipolar phenotype: A controlled actigraphy study. *Chronobiology international*, *31*(2), 290-296.
- Roenneberg T, Wirz-Justice A, Merrow M. 2003. Life between clocks: daily temporal patterns of human chronotypes. Journal of Biological Rhythms, 18(1):80-90.

- Rotenberg, V. S., Indursky, P., Kayumov, L., Sirota, P., & Melamed, Y. (2000). The relationship between subjective sleep estimation and objective sleep variables in depressed patients. *International Journal of Psychophysiology*, 37(3), 291-297.
- Russo, M., Mahon, K., Shanahan, M., Ramjas, E., Solon, C., Purcell, S. M., & Burdick, K. E. (2015). The relationship between sleep quality and neurocognition in bipolar disorder. *Journal of affective disorders*, 187, 156-162.
- Shehean DV, Lecrubier Y, Sheehan KH, Janavs AM, Weiller E, Hergueta T, Baker R, Dunbar GC. 1998. The Mini-International Neurospychiatric Invteriw (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-iV and ICD-10. Journal of Clinical Psychiatry, 59:22-33.
- Winkler D, Pjrek E, Praschak-Rieder N, Willeit M, Pezawas L, Konstantinidis A, Stastny K, Kasper S. 2005. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. Biological Psychiatry, 58(4):331-336.

Figures and Tables

	НС	MDD	BD
N (%F)	40 (55.0)	32 (65.6)	31 (58.1)
Current MDE (%)	0	31.3	29.0
Psychotropic Meds (%, range)	N/A	62.5 (1-5)	87.0 (1-6)
Employment Status (% employed)	97.5	75.0	67.7
		M (SD)	
Age (years)	34.5 (12.5)	39.5 (13.5)	35.7 (10.9)
Education (years)	17.5 (3.8)	15.5 (2.17)	15.8 (2.82)
BMI	24.6 (4.5)	27.1 (5.17)	28.1 (5.57)
Age Onset	N/A	15.5 (6.83)	21.4 (11.2)
MADRS	1.76 (1.71)	8.30 (6.90)	8.80 (5.97)
YMRS	1.61 (1.26)	1.51 (1.66)	2.32 (2.16)
PSQI	3.84 (1.49)	8.17 (4.90)	6.73 (4.50)
ESS	3.59 (4.86)	7.45 (4.75)	7.68 (3.88)

Table 1. Demographic and clinical characteristics. BMI: Body Mass Index; MADRS: Montgomery-AsbergDepression Rating Scale; YMRS: Young Mania Rating Scale; PSQI: Pittsburgh Sleep Quality Index; ESS:Epworth Sleepiness Scale. Note: MADRS, YMRS, PSQI, ESS are completed at Visit 2. Diagnosis andmood state were determined by MINI.

	Group	TST	WASO	SOL	Sleep Efficiency
	Total N	$\rho = 0.016, p = 0.887$	$\rho = 0.346, p = 0.002 **$	$\rho = 0.058, p = 0.619$	$\rho = -0.145, p = 0.214$
BRIAN Total	HC	$\rho = -0.294, p = 0.154$	$\rho = 0.253, p = 0.256$	$\rho = -0.278, p = 0.211$	$\rho = -0.071, p = 0.754$
10181	MDD	$\rho = 0.229, p = 0.230$	$\rho = 0.528, p = 0.006 **$	$\rho = 0.365, p = 0.067$	$\rho = -0.534, p = 0.005 **$
	BD	$\rho = -0.017, p = 0.937$	ρ = -0.209, p = 0.316	$\rho = 0.066, p = 0.752$	$\rho = 0.199, p = 0.340$
	Total N	$\rho = 0.057, p = 0.622$	$\rho = -0.042, p = 0.722$	$\rho = 0.005, p = 0.964$	$\rho = 0.090, p = 0.445$
BRIAN	НС	$\rho = 0.093, p = 0.659$	$\rho = -0.253, p = 0.257$	$\rho = -0.266, p = 0.232$	$\rho = 0.337, p = 0.125$
Domain	MDD	$\rho = -0.142, p = 0.463$	$\rho = 0.296, p = 0.141$	$\rho = 0.401, p = 0.042*$	$\rho = -0.470, p = 0.015 **$
2 cmum	BD	$\rho = 0.268, p = 0.195$	$\rho = 0.580, p = 0.002 **$	$\rho = -0.169, p = 0.420$	$\rho = 0.569, p = 0.003 **$

Table 2. Objective measures of sleep correlated with BRIAN total scores and BRIAN sleep domains.

* Significant at p < 0.05

** Significant after Bonferroni adjustment

	Total N	НС	MDD	BD
IS Weekday	$\rho = -0.109, p = 0.335$	$\rho = -0.314, p = 0.127$	$\rho = -0.061, p = 0.757$	$\rho = 0.098, p = 0.636$
IS Weekend	$\rho = 0.047, p = 0.678$	$\rho = -0.171, p = 0.424$	$\rho = 0.082, p = 0.684$	$\rho = 0.153, p = 0.456$
IV Weekday	$\rho = 0.099, p = 0.377$	$\rho = 0.085, p = 0.686$	$\rho = -0.098, p = 0.621$	$\rho = 0.048, p = 0.818$
IV Weekend	$\rho = -0.105, p = 0.357$	$\rho = 0.240, p = 0.258$	$\rho = -0.288, p = 0.145$	$\rho = -0.076, p = 0.711$
Acrophase Weekday	$\rho = 0.017, p = 0.882$	$\rho = 0.159, p = 0.458$	$\rho = -0.310, p = 0.123$	$\rho = 0.057, p = 0.787$
Acrophase Weekend	$\rho = 0.019, p = 0.866$	$\rho = 0.002, p = 0.992$	$\rho = -0.315, p = 0.109$	$\rho = 0.159, p = 0.437$
CQ Weekday	ρ = -0.006, <i>p</i> = 0.958	$\rho = -0.366, p = 0.094$	$\rho = -0.124, p = 0.546$	$\rho = 0.168, p = 0.433$
CQ Weekend	$\rho = -0.002, p = 0.983$	$\rho = -0.300, p = 0.155$	ρ = -0.096, <i>p</i> = 0.635	$\rho = 0.213, p = 0.297$

Table 3. Objective measures of circadian rhythmicity correlated with BRIAN total scores. IS: Inter-daily stability; IV: Intra-daily variability; CQ: Circadian quotient.

* Significant at p < 0.05** Significant after Bonferroni adjustment

Melatonin Measure	Group as whole	НС	MDD	BD
6-SM	$\rho = -0.247, p = 0.024*$	$\rho = -0.028, p = 0.159$	$\rho = -0.076, p = 0.687$	$\rho = -0.426, p = 0.033*$
DLMO	$\rho = -0.161, p = 0.452$	$\rho = 0.162, p = 0.728$	$\rho = -0.033, p = 0.932$	$\rho = -0.381, p = 0.352$
PAD	$\rho = 0.193, p = 0.354$	$\rho = -0.180, p = 0.670$	$\rho = 0.025, p = 0.949$	$\rho = 0.310, p = 0.456$

Table 4. Correlations between BRIAN total scores and melatonin measurements. No Bonferroni adjustments were required. 6-SM: 6-sulphatoxymelatonin; DLMO: Dim light melatonin onset; PAD: Phase angle difference.

* Significant at p < 0.05



AMT6s vs. BRIAN Scores

Figure 1. 6-sulphatoxymelatonin levels negatively correlate with total BRIAN score ($\rho = -0.24$, 95% CI [-0.43, -0.02], p < 0.03), suggesting lower levels of melatonin secretion are associated with greater biological rhythm disturbance.

CHAPTER 4

The impact of circadian rhythms on cognitive function: A review of the clinical and preclinical research

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Abstract

Brain arousal and neurocognitive function are modulated in a rhythmic manner by a complex interaction involving homeostatic sleep/wake regulation and the endogenous circadian oscillator. While it is clear that temporal variations modulate the interplay between circadian processes and homeostatic mechanisms for a variety of neurobehavioural events, the impact of circadian rhythms on cognitive performance is an area that warrants further investigation. Evidence demonstrating varying resiliencies to circadian disruption supports the hypothesis that distinct cognitive subdomains are differentially affected by disruptions in circadian rhythms. The aim of this present review is to (1) provide an update on the existing literature regarding preclinical and clinical studies on the impact of 24-hour circadian variation, circadian misalignment, and sleep deprivation (SD) on cognitive performance, and (2) critically review agreements/disagreements between human and animal studies from a translational approach. Current preclinical and clinical research on the impact of circadian rhythms on cognitive performance reveals that across species, vulnerability to circadian fluctuations exists within cognitive domains, and that this vulnerability is also influenced by factors such as inter-individual differences in daily functioning, chronotype and prior amount of wakefulness. Several domains demonstrate variations in arousal that are synchronized to the sleep/wake cycle. What distinguishes each of these parameters from the other is the degree to which they are influenced by circadian variations and the degree to which they are impacted by circadian disturbances. Further investigation is warranted in seeking out consistent, standardized rhythmicity in cognitive domains across individuals, which will critically contribute to providing better avenues for intervention in treating neuropsychological disorders.

KEYWORDS: Animal models; Circadian rhythms; Circadian misalignment; Cognition; Cognitive function; Neuropsychological tests; Sleep deprivation

Introduction

A regulator of many physiological processes, the main circadian pacemaker, or suprachiasmatic nucleus (SCN) is responsible for the 24 hour temporal fluctuations observed in several domains from gene expression and body temperature (Valdez et al., 2012), to metabolic homeostasis (Jha et al., 2010; Rutter et al., 2002), eating patterns (Mistlberger et al., 2011), sleep/wake cycles and brain arousal (Wright et al., 2012). The underlying mechanisms by which circadian rhythms influence cognition were first postulated by Kleitman (1933), a pioneer in the sleep and circadian rhythm investigation. Features of "simple mental performances" such as speed and accuracy showed diurnal variation, fluctuation throughout the day, and these variations were associated with core body temperature (CBT) (Kleitman, 1933; Kleitman et al., 1938). While there is a large body of literature clearly delineating periodicity in these homeostatic parameters, empirical evidence provided by temporal isolation studies support the theory that both homeostatic and circadian components interact with one another to produce time-of-day (TOD) variations in neurophysiological activity involved in brain arousal (Chee et al., 2006; Gunzelmann et al., 2012; Harrison et al., 2007; Vandewalle et al., 2011). The essential nature of this interplay is demonstrated by exogenous cues, or "zeitgebers", which trigger entrainment of biological rhythms, that are omitted from or desynchronized in a controlled environment. This elicits a free-running state driven by the circadian oscillator. However, these rhythms can be re-entrained most notably by implementation of a controlled light/dark cycle that optimally coincides with the pacemaker's cyclical performance. Disruptions in circadian cycles and, in turn, homeostatic mechanisms, result in maladaptive consequences for the body's physiological and behavioural processes that can emerge as significant cognitive deficits that affect one's daily functioning. This is observed as reduced vigilance, reduced accuracy, lower levels of attention and deficits in overall executive function.

While it is clear that temporal variations in the interplay between circadian processes and homeostatic mechanisms exist for a variety of neurobehavioural events, the mechanisms by which circadian rhythms impact cognitive performance are not yet fully understood. Early
clinical studies performed on healthy subjects elucidated a preference in TOD of the circadian system for optimal cognitive performance dependent upon arousal and sleepiness on the 24-hour clock, as evaluated primarily with subjective ratings (Gillooly et al., 1990; Gordon et al., 1995; Whitton, 1978). These early findings were later supported by evidence from animal studies showing that cognitive domains such as learning and memory in reward-associated contexts are subject to circadian variation (Ralph et al., 2002; Ruby et al., 2008), which suggests that TOD may act as a discriminative cue. These and other studies set a precedent for further investigation in the area of circadian variation on cognition: *Which higher order cognitive functions are sensitive to time-of-day variables? Are temporal fluctuations uniform for all cognitive functions, or are there phase differences throughout the day for performance rhythms? Is there a selectivity involved in specific subdomains of cognition that have a greater vulnerability to be impacted by circadian disruption?*

Evidence demonstrating varying resiliencies to circadian disruption supports the hypothesis that distinct cognitive subdomains are differentially affected by disruptions in circadian rhythms (Horowitz et al., 2003; Jennings et al., 2003; Palchykova et al., 2005). By controlling TOD influences on cognitive processes, it is possible to directly observe the endogenous circadian oscillator as the driving force behind fluctuations in human and animal cognitive performance. There are several chronobiologic study designs that, when compared, can offer insight into the physiological mechanisms that ultimately influence cognitive outcomes. Some of these designs have simply implemented observation of 24-hour circadian variation on cognitive performance, while others studied the impact of circadian misalignment. These paradigms employ a number of designs such as forced desynchrony (FD) protocols, in which subjects follow a non-24 hour sleep/wake schedule (i.e. 20h or 28h) separating circadian and sleep homeostasis (Blatter et al., 2007), constant routine (CR) protocols in which subjects are observed under free-running conditions intended to unmask endogenous rhythmicity, or even mismatch designs monitoring morning and evening types tested at their respective day time nadir

of performance. Finally, some studies implemented sleep deprivation (SD) paradigms by inducing a disruption or shift in circadian phase. Each of these study designs allows a clear comparison and contrast between the superimposition of sleep homeostasis onto circadian lineation, versus the driving force of each individual component behind cognitive performance.

Three reviews have been previously published in this area (Blatter et al. 2007; Kyriacou & Hastings, 2010; Schmidt et al. 2007). However, to our knowledge, none of these reviews compared agreements and disagreements between human and animal studies. The aim of this present review is to (1) provide an update on the existing literature regarding preclinical and clinical studies on the impact of 24-hour circadian variation, circadian misalignment, and sleep deprivation (SD) on cognitive performance, and (2) critically review agreements/disagreements between human and animal studies from a translational perspective.

Methods

We performed a literature search using the databases MEDLINE, PsycINFO and Embase on OVID using the following search terms: *circadian rhythms, biological rhythms, cognition, neuropsychological tests, cognitive tests* and *cognitive function*. The search was limited to the English language, and set with search years from 1806-present. The list was deduplicated. Studies involving observation of circadian variations, circadian misalignment, and sleep deprivation were included. We excluded papers that reported on studies of shift work, jet lag, any form of treatment or intervention, or studies that evaluated psychiatric or circadian/sleep disorders (Figure 1).

Though "sleep deprivation" was not included in our initial search, it became clear upon screening references of reviews that papers following this design provided valuable information relevant to our objective. While our search yielded many sleep deprivation studies in human populations, preclinical sleep deprivation studies were lacking from our outline. In light of this, a second search was performed on preclinical studies involving the effects of sleep deprivation on

cognition. We performed this search using MEDLINE, PsycINFO and Embase on OVID using the following search terms: *sleep deprivation, mice, rats, monkey, cognition, cognitive tests,* and *neuropsychological tests*. The search was limited to the English language, and set with search years from 1806-present. The list was deduplicated. The same inclusion criteria as mentioned above were applied. Studies involving treatment were excluded. Additionally, from both literature searches, case studies, letters, editorials, commentaries, and reviews were also excluded (Figure 2). Upon identification of relevant articles, full manuscripts were reviewed and data was extracted on a spreadsheet using Microsoft Excel.

Results

Preclinical Studies of 24-hour Circadian Variation

Five studies that experimentally observed 24h circadian variation in animals were reviewed (Table 1). Overall, studies evaluating the sensitivity of sustained attention and memory to TOD differences have yielded equivocal results. Furthermore, there is evidence that TOD and/or time of training is encoded as an external cue for retrieval and plays a confounding role in elucidating patterns of rhythmicity across studies. For instance, in tasks of sustained attention, it has been reported that rats trained outside their naturally occurring active period demonstrate poorer rates of acquisition and performance, however this is not the case for spatial memory (Gritton et al., 2012; McDonald et al., 2002). This indicates that acquisition rate during training on a task requiring attentional effort is TOD-dependent across groups, suggesting a difference in vulnerability of cognitive parameters to daily performance fluctuations. Martin-Fairey & Nunez (2014) also found that acquisition during a spatial memory task was not affected by TOD, however better memory retention was seen during the active phase. Effects of time of training implied that rodents observed TOD as a discriminatory cue. In contrast, steeper acquisition curves during the rodent active phase in tasks of spatial memory have been observed (Valentinuzzi et al., 2004). Another study reported that TOD had an effect on learning and memory, but time of MSc. Thesis: O. Allega, McMaster University, Neuroscience *training* did not, where groups trained both during the night and during the day showed peak recall times during the day. Rodents generally displayed peak times for acquisition at 09:00 and retention at 09:00 and 15:00 (Chaudry & Colwell, 2002).

Interestingly, tasks of sustained attention, but not spatial memory, encouraged a dynamic shift in entrainment toward the time of daily training, promoting diurnality synchronized to the time of training rather than the rats' endogenous active phase. This alignment indicates that tasks requiring attentional demand are heavily influenced by daily distribution of the sleep/wake rhythm. Additionally, the rhythmicity of hippocampal *PER1* and *PER2* gene expression in diurnal grass rats was associated with an optimal phase for learning in a hippocampal-dependent task using the Morris water maze (MWM), more specifically for acquisition and retention (Martin-Fairey & Nunez, 2014). It has been suggested that spatial learning and memory may be TOD insensitive because of utilization of different neural networks for attention and memory (Gritton et al., 2012). Tasks of sustained attention are proposed to be dependent, in part, on the cortical cholinergic system (Sarter et al., 2001) as increases in acetylcholine are correlated with increased demands of directed orientation to behaviourally relevant information from the environment sustained over a longer period of time (Himmelheber et al., 2000). This component is not required for acquisition or performance. Moreover, Paolone et al. (2014) reported that fixed-timed daily sustained attention task (SAT) practice in rats produced the same fixed-timed corresponding increases in prefrontal cholinergic transmission that continued even after SAT training concluded. Spatial learning tasks such as the MWM require brief, ~60 second uses of hippocampaldependent cognitive effort that may not necessarily rely on circadian effects for optimal performance throughout free-running conditions, particularly when animals have been trained over long periods of time.

Clinical Studies of 24-hour Circadian Variation

In our search, the five studies investigating 24h circadian variations in cognitive performance in humans primarily focused on aspects of executive function. Evidence from earlier

MSc. Thesis: O. Allega, McMaster University, Neuroscience prospective studies showed significant inter-individual differences and sustained periodicities in subjective ratings on general mental clarity, specifically *clearness of thinking* and *creativity* (Whitton et al., 1978). Spatial localization was reported to have a significant period of 96 minutes (Gordon & Stoffer, 1995) and demonstrate a peak performance time around $\phi = 1916$ (ϕ representing acrophase, or peak activity time) (Gillooly et al., 1990). While Gordon & Stoffer (1995) reported a similar period of 80 minutes for verbal fluency, conflicting findingslater reported no TOD preference (Bennet et al., 2008), challenging whether periodicity influences cognitive performance. Peak performance times in early evening have also been reported for reaction time (ϕ =2032), choice reaction time (ϕ =1832), logical reasoning (ϕ =1932), and sustained attention (ϕ =1912) (Gillooly et al., 1990). Evidence of cognitive flexibility and inhibition imposing an interaction between circadian typology and TOD (Bennett et al., 2008) has also been observed to be modulated by time on task (Ramirez et al., 2012), which indicates that circadian oscillations throughout the waking day are influenced by complex integrated processes. Other studies have simply found no interaction between TOD and circadian typology for sustained attention and memory (Bennett et al., 2008; Hidalgo et al., 2004). The absence of optimal TOD performance on certain executive functions in this study are in partial disagreement with other findings supporting rhythms of mental performance influenced by chronotype and TOD (Bodenhausen, 1990; Dickinson & McElroy, 2012; Intons-Peterson et al., 1998; Lawrence & Stanford, 1999; Valdez et al., 2010).

In summary, within the domain of executive function, it is apparent that cognitive flexibility is influenced by 24h circadian variation in humans. A robust period in flexibility implies that performance at the circadian nadir may render one vulnerable to the complex and changing circumstances of environmental demands. Lower performance in the ability to shift between cognitive tasks could appear as functional deficits in adjusting behaviour rapidly and adaptably. Only one of five studies in our search (Bennett et al., 2008) took circadian typology into account when observing circadian variation throughout the day. This factor could have also

contributed to the absence of any TOD interactions in these observational studies. As the results of investigations of 24h circadian variation were contingent upon the daily routine of each subject (circadian typology, hours slept previous night, longer/shorter work days, eating patterns, etc.), each of these individual differences could have influenced the outcomes. When comparing human and animal studies, the fact that different cognitive domains have been evaluated for each species prevent an in-depth comparison. Although both sets of data offer insight into TOD dependencies on cognitive performance, animal studies have focused on attention and memory while human studies evaluated executive function. Bennett et al. (2008) did perform a cross-sectional continuous performance task (CPT) with young adults, however no interaction between attentional performance and circadian typology or TOD were seen. Conversely, Gritton et al. (2012) performed a SAT on rodents that involved discriminatory cues. A comparative study of these cognitive domains using validated cross-species tasks between animals and humans would provide valuable insight as to whether studies employing animal models ultimately correspond to human functional outcomes.

Preclinical Studies of Circadian Misalignment

Thirteen preclinical studies investigated the impact of circadian misalignment on cognitive outcomes, and the majority of these evaluated learning and memory. These studies generally found deficits in retention, but not acquisition, indicating a potential impairment in consolidation of learned behaviours as a consequence of circadian shifts. Retrieval deficits were observed from six-hour phase shifts onward, suggesting a threshold imposed on reorganizing the temporal distribution of sleep. The debate as to whether animals encode TOD as a discriminative cue for testing and training times is also illuminated by some of these studies. Hoffman & Balschun (1992) observed a clear daily activity rhythm in maze learning, peaking between 5-7 hours after "lights off", or during the rodent active phase. More recently, evidence shows that wild-type hamsters display a synchronized daily activity rhythm in working memory that peaks every 3 hours during the active phase, with the initial rise in activity beginning 1 hour before the

onset of the active phase (Muller et al., 2015). A chronic phase advance of 3h over six days caused deficits in retention of a hidden platform on a MWM task (Devan et al. 2001; Craig & McDonald, 2008). Notably, impairment in spatial memory persisted even after re-entrainment. Craig & McDonald (2008) expanded their own findings by evaluating an experimental group subjected to an acute phase advance who, when trained and recovered, did not display impairments in acquisition or memory. In another study, a 12h phase advance did not impair acquisition of fear-conditioned freezing behaviour during or after training, but did impair recall of the fear conditioning in both scenarios (Loh et al., 2010). Together, these results suggest that acute modifications to exogenous circadian cues, in this case the temporal distribution of sleep, selectively impacts recall but not acquisition. This is consistent with extensive evidence asserting sleep on a synchronized schedule is essential for memory consolidation of fear conditioning among other learned behaviours (Menz et al., 2013; Pace-Schott et al., 2009; Spoormaker et al., 2012). When testing for the minimum magnitude of phase shift required to produce a deficit in learning and memory (3, 6 and 12h), acquisition was similar among all groups including controls (Loh et al., 2010). Recall of fear conditioning was impaired among the 6 and 12h phase-advance groups compared to the non-shifted group, however the 3h phase advance was no different from controls. In another study, a 6h phase advance significantly impaired learning and memory for female hamsters who performed a conditioned place preference (CPP) task (Gibson et al., 2010). Control animals demonstrated a preference for the chamber previously containing the probe, dwelling three times longer in this chamber compared to phase shifted hamsters. Phase-shifted hamsters spent similar amounts of time in both chambers upon recall. Additionally, phase shifted rats experienced a reduction in hippocampal cell proliferation by $\sim 50\%$, while the effect of a phase shift on hippocampal neurogenesis was completely abolished in adrenalectomized animals. These findings not only indicate that circadian disruptions are involved in suppression of hippocampal neurogenesis and impaired learning and memory, but also support a role of hypothalamic-pituitary-adrenal (HPA) axis activation in mediating mnemonic mechanisms

MSc. Thesis: O. Allega, McMaster University, Neuroscience associated with proliferation (Gibson et al., 2010). Impairments of similar magnitude in learning and memory have also been detected between arrhythmic and sleep deprived rodents (Ruby et al., 2008).

Housing nocturnal rodents under chronic constant light (CCL) at various levels produces robust memory impairment. For instance, exposure to \sim 5 lux through to \sim 100 lux produced increased latencies to target, higher error rates, and reduced times in target quadrant in spatial navigation tasks (Fonken et al., 2012; Ma et al., 2007). Ma and colleagues (2007) reported that short-term, but not long-term plasticity was influenced by CCL exposure, as demonstrated by the reduction in short-term synaptic depression in CCL rats compared to controls about 30 minutes after low frequency stimulation. Although diurnality was maintained, arrhythmic activity suggests CCL exposure whether at lower or higher intensities of light impair circadian rhythmicity and spatial memory. Another study with a protocol similar to the one employed by Ma and colleagues only found impairments in learning and working memory when mice were subjected to constant darkness, while mice exposed to ~25 lux CCL did not display impaired performance (Ramos et al., 2013). Hamsters with complete ablation of the SCN subjected to a 2h light pulse separated by 5h darkness could not discriminate between novel and familiar objects during an object recognition task (ORT) (Ruby et al., 2008), suggesting a sleep-independent influence of circadian rhythms on memory formation. Although the temporal distribution of the sleep pattern was reorganized, the animals were not sleep deprived and experienced the same amount of NREM and REM sleep as controls. Rather, the difference lay on the fact that the hamsters were not experiencing consolidated hours of wakefulness and sleep as per their habitual rhythmicity (Ruby et al., 2008). In another study, animals housed in both a 14:10 LD cycle and constant light condition (~40-50 lux) showed preference for a reward-associated context during the time of training (Ralph et al., 2002). These results further corroborate with the notion that preference for learned behaviours, such as a reward-associated context, depend on whether testing and training occur at the same TOD, suggesting that animals encode TOD as a discriminative cue.

Evidence exists for cognitive performance operating as a zeitgeber to reorganize circadian activity. For instance, cognitive training with a SAT was demonstrated to modify circadian entrainment in male Sprague-Dawley rats (Gritton et al., 2009). In this study, phase advanced rodents (6h) displayed lower vigilance scores, however more interestingly, daily SAT training at zeitgeiber time (ZT) 4 (4 hours into light phase) produced a robust diurnal activity pattern (average activity during the light phase compared to the dark phase) in otherwise nocturnal animals. Diurnal activity was also present when daily SAT was shifted to ZT 10, showing an advance in activity onset relative to training time. These results suggest that entrainment is possible for a range of times throughout the day, and, more importantly, that a task requiring attentional demand can modify circadian activity rhythms. These findings were later supported by another study showing that oscillators outside the SCN can drive entrainment during cognitive training (Gritton et al., 2013). In that study, SCN-ablated animals had the highest light/dark ratios and displayed the strongest anticipatory behaviour for the SAT when compared to other groups. However, under free-running conditions, lesioned animals only showed a marginal amount of activity after training ended. These findings suggest that cognitive oscillators entrained by a task requiring sustained attention are only able to maintain synchrony for a short period in SCN-ablated animals.

In summary, preclinical studies investigating the effects of circadian misalignment on cognition were predominantly focused on learning and memory. Both constant low-light conditions and irregular light/dark cycles had a robust effect on learning and memory. It also appears that hippocampal-dependent memory rather than learning is particularly affected by the magnitude of the phase shift One study indicated a minimum of 6h phase advance is necessary to impair retention in mice (Loh et al., 2010), however empirical evidence examining the impact of the magnitude of a phase delay is still lacking. Gritton et al. (2009; 2013), using a SAT, provided evidence that cognitive training may act as a *zeitgeiber in male Sprague-Dawley rats*. This body of work indicates that cognitive training not only reorganizes circadian activity, but also *drives*

entrainment even in the absence of the SCN, which would otherwise induce desynchrony. These studies also provide evidence in support of the arousal theory, which postulates that circadian variations in cognitive performance reflect an underlying rhythm in basal arousal level (Colguhoun, 1971; Blatter et al., 2007). Time awake and circadian processes directly influence cognitive performance, and so it is plausible that a circadian rhythm exists for generalized baseline behavioural alertness. Moreover, inter-task phase differences could reflect rhythms in domain performance, which suggests that multioscillatory control outside the SCN exists to regulate different cognitive rhythms (Folkard et al., 1983). This could also explain why circadian misalignment did not produce a robust deficit in performance on the sustained attention task. It is possible that attentional processes are less vulnerable to phase shifts, or that the amplitude of attentional rhythms is truncated compared to memory rhythms. It is also possible that because the majority of phase shift studies had memory tests performed at the same time for all groups, significant changes were not recorded over treatments. Further insight provided by exposure of all groups to testing at different times throughout the day, or even hourly, would test the theory that free-running circadian variations exist in learning and memory regardless of re-entrainment to a different light dark and therefore sleep/wake cycle.

Clinical Studies of Circadian Misalignment

Sixteen studies of circadian misalignment found a negative impact on a variety of executive functions in humans. In a 40h CR protocol followed by a 28h FD paradigm, Dijk et al. (1992) observed alertness and performance to steadily increase and remain fairly constant for the first 16h, trailed by temporal fluctuations in both variables during FD. Although time awake impacted alertness and performance, outcomes were heavily dependent on circadian phase, where time awake had the strongest effect at the minimum of CBT rhythms and the least effect at the maximum. Although circadian effects on cognitive performance are observed throughout the waking day, a constant and gradual performance decline is typically seen after the first day in

both misalignment and SD protocols (Couvoumdjian et al., 2010; Tucker et al., 2009, Van Dongen et al., 2003), implying that circadian effects do not fully counteract the build up of homeostatic sleep drive. Other studies also report cognitive performance varying independently in processing speed and accuracy (Wright et al. 2006), throughput (Darwent et al. 2010) and components of sustained attention (Harrison et al., 2007)as a function of circadian phase. One study specifically reported a 100-min phase delay with respect to CBT displayed in performance time for inhibition, while errors in inhibition exhibited no correlation (Ramirez et al., 2012), suggesting it is only speed of inhibition performance that displays rhythmicity, and not accuracy. Simulated nighttime shiftwork conditions were implemented in a case control investigation performed by Van Dongen et al. (2011). Lapses in psychomotor vigilance were revealed in an interaction involving condition, number of days into night shifts, and time of day within shift. A condition by TOD interaction revealed that cognitive throughput gradually declines with progressing time awake. Another high-order function that is influenced by temporal rhythmicity is decision making/strategic reasoning. Depletion of cognitive resources at "off-peak" times tend to modulate high-level decision-making (Bodenhausen, 1990, Rock et al., 2013). Additionally, Dickinson & McElrov (2012) showed that circadian mismatch of chronotype and optimal TOD for performance produced lower levels of reasoning in the first rounds of decision making on a strategic reasoning task, which was not seen on an easier level of the task. This suggests that different brain/cognitive demands are differentially affected by circadian misalignment. Higherlevel prefrontal cortex (PFC)-controlled processes involved in decision-making and strategic reasoning, such as anticipatory thought, are influenced by the reduced alertness associated with performance at a TOD not harmonized with chronotype. The impact of homeostatic and circadian processes on cognition cannot be simply split between endogenous and exogenous components; rather, there is a complex interaction between these two constituents that produces rhythms in function. In addition, factors such as the sleep/wake and TOD effects known to modulate frontal lobe function suggest that there is a state-dependency with regard to performance that can

MSc. Thesis: O. Allega, McMaster University, Neuroscience potentially induce sub-clinical impairment (Harrison et al., 2007; Manly et al., 2002). A major behavioral component of PFC function is novel, goal-directed behaviour. Therefore, tests of executive function that repeat assessments at different TOD, or hourly, should be interpreted carefully due to practice effects.

Current literature is mixed as to whether or not circadian variation exists in specific timeof-day protocols when evaluating working memory, likely due to the inconsistency of protocols used (i.e. test time in morning versus afternoon, different tasks used to assess cognitive domains, and different components of memory i.e. short-term versus long-term memory, varying storage components). Distinct components of working memory have been found to have their own rhythms relative to CBT. Several studies proposed that working memory performance rhythms parallel CBT (Monk et al., 1996; Cajochen et al., 1999, Ramirez et al., 2006, Wright et al., 2002). Ramirez et al. (2006) reported lower global memory performance occurring at the minimum of CBT rhythms. However more specifically, phonological storage displayed a 1hr phase delay and visuospatial storage displayed a 3hr phase delay with respect to the peak of CBT in a 30hr CR protocol. Control of task demands involved in a working memory load have shown an interaction with TOD under "fractional desynchronization" CR conditions independent of CBT (Folkard et al., 1983), which suggests an autonomous working memory period of ~21h.

In summary, preclinical studies of circadian desynchrony largely focused on learning and memory, while human studies assessed desynchrony on both memory and executive processes. In both humans and animals, alertness and performance increases and remains fairly constant throughout the "active period", or waking day, thereafter tending to decrease as cognitive effort is extended into the biological night. Many studies report daily rhythmicity and optimal performance times in accuracy, throughput, strategic reasoning, decision-making and attentional processes in humans. Performance times in inhibition are reported to specifically display rhythmicity with a delay of 100 minutes with respect to CBT, while components of working memory show parallelism to CBT (Cajochen et al., 1999; Wright et al., 2002) and 1-3 hour phase

delays in humans (Ramirez et al., 2006). Circadian misalignment in animals causes deficits in retention, while the literature is inconsistent as to whether acquisition is implicated. Although inconsistent, rhythmicity in working memory seem to exist independently of these impairments, peaking cyclically throughout the active phase (Hoffman & Balschun, 1992; Mueller et al., 2015). Attentional deficits that occur as a consequence of desynchrony between internal physiological processes and exogenous cues offer some notable similarities and contrasts between humans and animals as well. In tasks of sustained attention, rodents, but not humans, with more stable circadian activity display higher vigilance scores after distracter blocks. Humans display more errors of commission with increasing wake duration, and discernable modulation of activity by circadian variation with shorter wakefulness durations compared to animals, while errors of omission and reaction times remain unaffected in both species (Gritton et al., 2009; Harrison et al., 2007). These findings suggest that certain endogenous circadian oscillator pathways involved in attention and memory may operate in a comparable manner between species.

Preclinical Studies of Sleep Deprivation

Most preclinical studies of SD also focused on its impact on learning and memory. Fifteen studies meeting our criteria evaluated cognitive performance as a function of TOD as pressure to sleep escalates. Sportiche et al. (2010) investigated whether suppression of neurogenesis by sustained sleep fragmentation (SF) can impact hippocampal-dependent cognitive function. Not only was hippocampal cell count in the dentate gyrus reduced by 32% in SF rats, but they also had more search attempts compared to controls. In addition, SF rats had lengthier escape latencies when testing occurred 14 days after termination of training compared to controls. Learning was not affected by SF. These findings are consistent with other reports, including deficit in recall of platform location in other maze tasks, longer time to enter target quadrant, and less time spent in target quadrant (Leenaars et al. 2012a; McCoy et al., 2007). Other studies also found that acute SF or SD produced deficits in set-shifting abilities (McCoy et al., 2007) and

accuracy of task-switching (Leenaars et al. 2012b). Contrary to previous studies, Zielinski et al. (2013) did find impairments in acquisition during the learning phase along with longer latencies during recall, however this result was most likely is due to the extreme SD conditions implemented where mice were subjected to SD for eleven weeks, twelve hours per day, seven days a week during their inactive period. Empirical evidence also exists of sex differences with regard to the effect of SD on learning and memory, where females are more susceptible to the deleterious effects of SD (Koehl et al., 2006). After 72h of SD, ovariectomized female rats demonstrated increased latency to find platform and spent less time in the target quadrant compared to male rats in the MWM (Hajali et al., 2012). No sex differences were found with regard to discrimination index or exploration time in a NOR in a study conducted by Ruby et al., (2013), however males displayed greater motivation denoted by 14% more arm entries upon arrhythmic-induction.

Three studies investigated the impact of a 96h SD paradigm on performance in an inhibitory avoidance task in rats (Dubeila et al., 2005; Esumi et al., 2011; Perry et al., 2008). While all studies found impairments in retention (significantly reduced latencies when confronted with aversive stimulus), only one found deficits in both acquisition and retention (Perry et al., 2008). Adolescent, but not adult rats, also displayed deficits in retention while subjected to a mild sleep restriction paradigm from 08:00 – 12:00 by manipulating stages of NREM and REM sleep (Yang et al., 2012). This result is indicative of a critical window present in adolescent rats that involves REM and NREM sleep, required for memory consolidation that is perhaps non-essential for adult rats.

It is well known that chronic SD can trigger inflammatory processes. Ramesh et al. (2010) found that SD *TNF-a* knockout (KO) mice displayed less impairment on a MWM task during learning relative to *wild-type* mice. *TNF-a* KO mice were also spared in reference memory tests showing that SD mice without the KO also had impairments in retention for latency and path length compared to *TNF-a* KO mice. These findings suggest that TNF-a-related inflammatory

MSc. Thesis: O. Allega, McMaster University, Neuroscience pathways may modulate the effects of SD on spatial memory in mice. Notably, peripheral administration of cytokines such as interleukin-1 and 6, which show rhythmic expression, have been implicated in cognitive impairments (Li et al., 2002; Rada et al., 1991).

Sleep, and the timing of sleep, hold a pivotal role in memory consolidation. SD occurring immediately after acquisition during an object recognition task (ORT) impaired memory retrieval, whereas delayed SD (7-12h later) did not (Palchykova et al., 2006), suggesting that delayed SD allowed time for consolidation. Hagewoud et al. (2010), however, found that SD produced a significant deficit in spatial working memory in a novel arm recognition task after 12h, but not 6h of SD. From a neurobiological standpoint, these results are consistent with empirical evidence showing that the formation rate of dendritic spines in rodents steadily increases within the first 6h of training and progressively continues within the first day (Yang et al., 2014). Interestingly, non-REM sleep, but not REM sleep, was sufficient for proper memory consolidation suggesting that the underlying mechanisms implicated in long-term memory storage involve sleep promoting learning-induced synapse growth/formation (Euston & Steenland, 2014; Yang et al., 2014).

A recent study examined whether time on task and response stimulus interval (RSI) timing effects on a rat PVT (rPVT) were analogous to those of the human PVT (hPVT) following SD (Oonk et al., 2015). Rats showed a reduction in number of correct responses and an increase in lapses and premature responses after 24h SD, which was comparable to attention lapses and false starts on the hPVT. Humans, but not rodents, displayed increases in time on task and response times, comparable to human studies of sustained attention in time on task for correct responses and lapses (Doran et al., 2001; Horowitz et al., 2003).

Clinical Studies of Sleep Deprivation

The homeostatic diurnal sleep/wake cycle and endogenous circadian oscillator are thought to act in synchrony with each other as a compensatory mechanism with opposing progressions (Aschoff & Wever, 1976). Human studies have shown that processes of learning and memory exhibit peak performance times throughout the day that are modulated by circadian

MSc. Thesis: O. Allega, McMaster University, Neuroscience oscillators, while homeostatic sleep drive increases with time awake. The net result is a decrease in arousal and alertness as the day continues, complimented by increased pressure to sleep. Throughout the night, or rest phase, homeostatic sleep drive dissipates most prominently during non-REM or slow-wave sleep (Schmidt et al., 2007, Blatter et al., 2007), promoting wakefulness and arousal in the morning hours. Clinical investigations of SD on cognitive performance aimed to separate these two processes, providing inquiry as to whether performance rhythms exist with increased pressure to sleep, and whether either process is more heavily relied upon.

Several studies have reported deficits in executive function after SD in humans. Paradigms ranging from one night of complete SD up to 88h report deficits in verbal learning (Drummond et al., 2000), greater lapses on SAT, longer latencies on recognition and reduced accuracy (Wimmer et al., 1992; Nilsson et al., 2005; Gunzelmann et al., 2012), increased errors of omission on word fluency (Harrison & Horne 1998; Tucker et al., 2009), slower reaction times and more lapses in recall (Tucker et al., 2009) and impaired cognitive flexibility (Drummond et al., 2001; Thomas et al., 2000). Restriction to 6h or less of sleep per night for two weeks produced deficits in throughput in a study conducted by Van Dongen et al. (2003). Blagrove et al. (1995) investigated the effects of chronic SD and sleep-restriction (SR) on reasoning. SD subjects showed impairments in accuracy in an auditory vigilance task, and measures of non-verbal reasoning compared to controls. Chronic SR groups restricted to 5.2h sleep per night for three weeks, however, displayed subjective sleepiness but not objective impairments on either of those measures. These results are indicative that subjective sleepiness is not always accompanied by cognitive impairment. It also suggests that different facets of executive function (e.g. throughput, vigilance, reasoning) might be more vulnerable to sleep loss than others. Later findings reported by Loh et al. (2012) implicate sustained SR as having a much greater global impact on sustained attention, subjective alertness, and working memory on a task with high executive load, however when participants were subsequently subjected to total acute SD, only sustained attention and alertness were impacted. Also, circadian phase modulated the effects of sleep loss, specifically

impacting alertness and attention. These findings suggest not only that circadian variation plays a role in performance for alertness and attention under sleep loss, but also that alertness and attention are more sensitive to sleep loss, whereas working memory displays a greater reserve against SD. Thomas et al. (2000) reported deficits in accuracy, speed and throughput in an executive function battery after 85h SD. In this study, SD individuals displayed an 8% decrease in global glucose cerebral metabolic rate compared to baseline, and this reduction coincided with reduced metabolic activity both in the dorsal and ventral PFC and thalami. One study specifically assessing verbal fluency as a measure of executive function found more errors and longer latencies after 36h SD, but no changes in response initiation in a sentence completion task (Harrison & Horne 1998). Together these findings suggest that acute SD impairs verbal fluency and, more broadly, disruption of prefrontal cortical functions as shown by a deficit in inhibiting strong word associations.

Studies evaluating both acute and extended SD over a number of days have consistently found impairments in overall executive function, however conflicting results emerged as to the degree that working memory is impaired (Table 1). A few studies reported no working memory impairment after 24h (Chee et al., 2006; Nilsson et al., 2005; Wimmer et al., 1992), whereas one study found an overall performance decline after 24 and 35h SD (Chee et al., 2006). Greater activation in the left fronto-parietal regions was associated with performance decline at both times. Furthermore, activation in these regions after one night of normal sleep was associated with higher resistance to impairment following SD. Although homeostatic sleep drive is less at SD24 than 35, the drive for waking at SD24 is at a lower circadian phase compared to SD35 (Chee et al., 2006). This interaction could account for the insignificant differences observed between the two time points. Using blood oxygenation level dependent (BOLD) fMRI, Mu et al. (2005), showed that individuals with greater vulnerability to memory impairment after SD display greater global brain activation before SD, and overall reduced activation following SD. While the parietal region has been linked to phonological storage (Chee et al., 2006; Ravizza et

al., 2011; Smith et al., 1998), its concomitant ties to attentional processes (Chee et al., 2006; Kastner & Ungerleider, 2000; Fan et al., 2005) implicate inter-individual differences in baseline neural activation as a strong predictor of performance outcomes. Yoo et al. (2007) supported these findings when showing impairments in working memory performance during an encoding task. Interestingly, two functionally distinguished patterns of encoding were observed for SD and controls. SD subjects showed stronger connectivity for basic alertness networks in the brainstem and thalamus, but less activity in the left and right hippocampal regions, posterior cingulate cortex, medial temporal lobe and inferior parietal lobule during fMRI, a network associated with memory processing. This study suggests that decreased functional connectivity in the hippocampal complex is part of the neural basis for SD-induced impairments in memory encoding. These results are consistent with the role of sleep in both learning and memory consolidation (Siegel, 2001; Stickgold, 2005; Stickgold et al., 2007).

Small but pertinent effects have been found for WM impairments after SD in *PER3* 5/5 individuals, with larger effects on alertness and attention (Lo et al., 2012). The effect of genotype on SD-induced cognitive deficits was more robustly observed in tasks of executive function (Dijk & Archer, 2010), which tends to be most sensitive to SD. Although SD-induced performance decline is observed in *PER3* 5/5 individuals, the two genotypes do not differ with respect to circadian phase (Groeger et al., 2008) and no variations in circadian parameters have been seen in CR protocols (Viola et al., 2007).

Working memory following SD has been also investigated under the impact of acute variations in light. Following one night SD, Vandewalle et al. (2011) reported that blue light relative to green light produced increased activity during the auditory "n-back test", a working memory task employed in fMRI, in the left thalamo-fronto-parietal circuit including the premotor cortex, thalamus and intraparietal sulcus in individuals with the *PER3* 5/5 polymorphism, a sleep-loss vulnerable phenotype, compared to controls who possess the *PER3* 4/4 phenotype. Exposure to wavelengths in the blue light range (450-495 nm) therapeutically maintained memory

MSc. Thesis: O. Allega, McMaster University, Neuroscience processes during adversity to homeostatic sleep processes in *PER3* 5/5 individuals. These results suggest that working memory function is partially dependent on genetically determined susceptibility to homeostatic and circadian changes.

It has been well established that circadian disruption from SD compromises an individual's ability to maintain the complex processes of psychomotor vigilance for extended periods of time. Attentional processes become progressively impaired with increased time awake into the circadian rest period, however only a handful of studies investigated circadian variation persisting through SD, in conjunction with deficits in performance with increased hours awake. Early reports proposed the number of days of SD and TOD impacted subjective attention and slowness of thought, indicating an existing circadian component (Mikulincer et al., 1989). After one night of SD, Drummond et al. (2001) reported that participants experienced reduced concentration on a divided attention task in fMRI. The superior frontal gyrus, middle/inferior frontal gyri, anterior cingulate gyrus, insula and inferior parietal lobe showed enhanced activity after SD on the divided attention task compared to a normal night of sleep. Although acute SD did not disrupt the ability to complete a divided attention set, increased reaction times in SD patients who were subjected to a compatible preparatory bias on a choice reaction time task were observed compared to incompatible-preparatory-biased SD individuals and controls (Jennings et al., 2003). The compatible preparatory bias involved pressing a button on the right side of the control pad when an arrow presented on the screen pointing in the right direction, whereas the incompatible preparatory bias presented an arrow pointed to the left on the screen with a right button response. These results provided evidence of attentional processes being selectively impaired by SD, particularly reaction time, and in turn aggravating the ability to optimize preparatory strategies when under physiological stress.

Many studies have found higher response errors and increased reaction times with time awake on the PVT (Doran et al., 2001; Horowitz et al., 2003; Valdez et al., 2010). Valdez et al. (2010) reported variations in performance regarding the stability of correct responses, while Horowitz et

al. (2003) extended these findings by showing reaction times were slowest at the peak of the melatonin curve. Circadian phase was also seen to marginally interact with target presence/absence accuracy on a visual search task. These results indicate a dissociation of processes such that the circadian pacemaker and sleep drive effects on global vigilance and alertness differ from their impact on selective attention. Inter-subject variability on reaction times in SD groups support the "state instability hypothesis" (Blatter et al., 2007; Doran et al., 2001), which affirms that SD impacts those cognitive processes vulnerable to state instability, where lapses in performance are a result of variability in attention and alertness. Moderate SR and, therefore, alterations in circadian phase contribute to an increase in number and length of lapses in the PVT. One study showed 6h or less of sleep restriction per night significantly impaired PVT performance, demonstrating deficits comparable to two nights of SD as determined by cumulative sleep loss over duration of participation (Van Dongen et al., 2003). Other studies of attentional processes simply discuss the deficits sustained as a result of disruption of the sleep/wake cycle. Increased reaction times and response errors have also been observed on simple sustained attention tasks (Sagaspe et al., 2006) and task-switching paradigms (Couyoumdjian et al., 2010). Increasing levels of difficulty on a simple visual attention task have also been associated with reduced binding of dopamine antagonists in the striatum and thalamus (Volkow et al., 2008). Correlated with reduced performance after SD, these results suggest a compensatory increase in dopamine upon extended wakefulness. In summary, animal studies focused primarily on learning, memory and attention in SD, whereas human studies focus on executive processes, memory and attention. Deficits in recall, but not learning during working memory tasks were generally seen in animals (Sportiche et al., 2010; Leenaars et al., 2012a; McCoy et al., 2007) and humans (Yoo et al., 2007). Some experimental paradigms designed to assess working memory are speciesspecific, which may make it challenging to compare results between species. For instance, working memory tasks for animals typically involve a spatial component in object or arm recognition, which make perception of environmental stimuli a much larger component of their

task than what would be employed in clinical populations, which is typically signal detection in the form of a shape, light, digit, or letter on a screen whether assessed by fMRI or not. Moreover, the methodology and paradigm of SD used depend entirely on the "testable" and "interpretable" characteristics/behaviours of each species. For instance, methods of sustained wakefulness in animal studies generally include "paradoxical" SD, where the researcher relies on muscle atonia of a rodent, for example, that attempts to stay on a small platform otherwise falling into water if falling asleep. The magnitude of sleepiness throughout this protocol must be quite large, and a confound in some ways, due to the increased level of muscle tone required to stay on the platform; a factor human SD studies lack. Another paradigm involves mild, gentle tapping or shaking of a housing cage, disturbing rest if necessary, whereas human studies of SD generally include lights on at all hours, with a researcher coming in to "refresh" the subject if need be.

Two studies directly compared the impact of SD on cognition in both animals and humans. Oonk et al. (2015) evaluated how similar outcomes of time on task were in the rat PVT following SD compared to humans. An initial increase, then decrease of premature responses with time on task was seen in rats. In humans, false starts increase with time on task (Doran et al., 2001), reflective of the theory of the time-on-task effect. The time-on-task effect implies a performance decline with increased time on task, which requires more effort in using cognitive resources (Van Dongen et al., 2011a). As task time progresses, vulnerability to sleep increases in humans, and therefore one may postulate that the effect would be amplified especially during the biological night. However, this effect was not seen in this particular preclinical evaluation.

Animal models are useful in exploring potential molecular pathways associated with cognitive dysfunction. However, when comparing human and animal studies, it is important to keep in mind that the underlying brain networks associated with tasks of sustained attention are distinct across species. More specifically, humans display greater top-down control modulated by the frontoparietal system compared to rodents, which if disturbed, show exacerbated deficits in meeting attentional demands (Demeter et al., 2008). van Enkhuizen et al. (2014) compared

similarities between humans and animals on a five-choice continuous performance task (5C-CPT) after 36h SD. Reduced correct response rates and vigilance were observed in humans, while accuracy impairments showed a trend. Mice showed both reduced accuracy, correct response rates and trending effects on vigilance. These findings suggest the 5C-CPT may be a useful translational task demonstrating sensitivity for similar cognitive deficits in both humans and animals. Importantly, before making inferences between species in other domains, cross-species translational task validation is imperative. Together, these cross-species investigations indicate that SD-induced cognitive impairment is domain and task-selective, and is partly dependent on time awake. Oonk et al. (2015) and van Enkhuizen et al. (2014) also provided the perspective that SD implements a selectivity in that it can differentially affect the same cognitive domains in animals and humans, specifically components of attention involving accuracy, response rates and overall vigilance (i.e. detection of a peripheral target).

Discussion

Current preclinical and clinical research on the impact of circadian rhythms on cognitive performance reveals that across species, vulnerability to circadian fluctuations exists within various cognitive domains. Importantly, this vulnerability is influenced by factors such as interindividual differences in daily functioning, chronotype, prior amount of wakefulness and even sex. Brain arousal and cognitive function seem to be modulated in a rhythmic manner by a complex interaction involving homeostatic sleep/wake regulation and the endogenous circadian oscillator, which both contribute to overall cognitive outcomes. Clinical and preclinical studies investigating the impact of 24-hour circadian variation, circadian misalignment, and SD on cognitive function revealed that most cognitive parameters are affected by disturbances in the sleep/wake cycle. What remains to be determined is the degree to which different cognitive domains are impacted by circadian rhythm disruption. Overall, alertness and attention tend to follow a linear increase in performance for the first 16h of the waking day, and a progressive decline thereafter as the waking day continues. A rhythmic pattern recognized in attention, as well as memory, is that highly practiced paradigms during training do not show vulnerability to TOD effects, which could be the cause of many studies dismissing rhythmicity in performance measures. However, studies are inconsistent as to whether performance rhythmicity exists and what periodicity those rhythms display in the domain of memory. Some studies assert that performance rhythmicity exists in working, declarative and procedural memory that parallels CBT, with a performance decline with increased hours awake, whereas no rhythmicity is found in working memory. The component of executive function that seems most readily observable to circadian variation is mental flexibility. As with all other parameters, a performance decline is seen with increased hours awake, with peaks reported in early afternoon. Lastly, it is clear that chronotype is a major contributor to the performance of individuals in any cognitive domain and, therefore, it is a characteristic that needs to be considered in human studies.

The majority of animal studies involving the investigation of circadian rhythms and cognitive function evaluated attention, and learning and memory. Overall 24h circadian variation in rodents revealed "peak" times, or rhythmicity for learning and attention, but not memory. Information is generally maintained over a long period of time once it is consolidated. In addition, it seems that memory processing and encoding are vulnerable to TOD variations in working memory, however once the information is stored for long-term or semantic recall, retrieval outputs are unaffected by circadian parameters. Most animal studies in our search recorded cross-sectional data, after extended periods of circadian disruption. This may be problematic because cognitive impairments observed at a specific time point do not necessarily reflect extended temporal impairment. Testing on a sequence of subsequent time points would shed more light on rhythmicity persisting through performance, similar to CR or FD protocols in humans. It would be useful to record data hourly, or at several time points throughout the day, which would provide a clearer picture of TOD-vulnerable impairments, entrainment, and optimal times for learning and/or recall. Animal studies of circadian misalignment showed robust findings of memory impairments such as increase latency to target and longer latencies during exploration.

Acute SD had only mild to moderate effects on visuospatial learning, whereas learning on visual and working memory were highly sensitive to the impact of SD (Hagewoud et al., 2010, McCoy et al., 2013; Sportiche et al., 2010; Zielinski et al., 2013). Studies inducing SD after learning suggest that impairment in memory retrieval is either caused by deficits in consolidation, or by the lack of consolidation at the proper circadian timing of sleep. Conversely, studies implementing SD prior to learning are unclear as to whether the deficits in memory retrieval are attributable to impaired acquisition or impaired consolidation.

Clinical SD studies found daily variations in throughput, vigilance, alertness and attention in the wake of increased homeostatic sleep pressures. Interestingly, short-term/working memory neither yields significant impairments after SD nor robust rhythms of performance as seen in preclinical studies. The amount of information being kept active, or stored, for the short-term seems to partially contribute to the level of complexity of a WM task. Folkard et al. (1976) proposed that rhythms in WM efficiency are determined by the activities one is performing throughout the day, the complexity of those activities, and arousal levels throughout the day. WM tasks of greater complexity however, show task-specific variations in performance (Folkard et al., 1976; Schmidt et al., 2007). Moreover, preliminary evidence of genetic influences on resiliency to sleep loss shows differences in sleep-loss vulnerable phenotypes (*PER3* 5/5) performing worse on cognitive tasks compared to sleep-resilient phenotypes (*PER3* 4/4) (Lo et al., 2012, Viola et al., 2007). Genetic vulnerability for circadian-induced cognitive impairment is a promising area for future research. These inconsistencies are likely associated with the many potential adaptive mechanisms associated with the preservation of basic brain functions in light of stress on the sleep/wake cycle.

At the cellular level, aside from the hypothalamus, rhythmic levels of expression of clock genes have also been detected in the prefrontal (Chun et al., 2015), parietal and cingulate cortex, (Chun et al., 2015; Li et al., 2013), amygdala (Moriya et al., 2015), and hippocampus (Wright et al., 2012; Wakamatsu et al., 2001). Brain arousal and cognitive function is promoted by

ascending projections from brain stem, forebrain and hypothalamic to the cerebral cortex and midbrain (Wright et al., 2012). Along with direct projections from the SCN, indirect projections from the dorsomedial hypothalamus not only modulate arousal, but also indirectly regulate the ventrolateral preoptic area of the hypothalamus, a sleep promoting system (Wright et al., 2012) also involved in temperature regulation (Szymusiak et al., 2007). In addition the SCN sends signals to the pineal gland via an indirect path via the brain stem and cervical sympathetic output that regulates the output of melatonin during darkness. In turn melatonin acts as a hormonal message to regulate MT1 and MT2 peptidergic receptors that are widespread in the brain, thus providing a humoral circadian signal (Monti et al., 2013).

The length of recovery time required following circadian misalignment or SD in humans has received less attention. Additionally, there do not seem to be standardized procedures to determine proper length of time for recovery required, which raises ethical issues regarding cognitive capacity following circadian disruption. FD studies set at 20 or 28h or studies evaluating acute (one night) SD generally assign a minimum of 8h rest period directly after protocol end times (Couyoumdjian et al., 2010; Darwent et al., 2010; Wright et al., 2006), suggesting that this short amount of time acts as a rapid and sufficient recovery function. Extended FD studies ranging multiple days have implemented anywhere from 12 - 30h recovery period in the laboratory before subjects are sent home (Harrison et al., 2007; Lo et al., 2012). Extended SD periods ranging anywhere from 58 - 85h have allotted 12 - 16h recovery sleep (Elmenhorst et al., 2014; Thomas et al., 2000; Tucker et al., 2010). Notably, Belenky et al. (2003) showed that subjects in a sleep restriction paradigm who spent either 3, 5, 7, or 9h daily time in bed for one week followed by 3 days of 8h per night sleep recovery did not fully restore cognitive capacity to baseline levels. Moderate to severe sleep restricted subjects did perform at reduced, however stable levels, suggesting that the brain undergoes adaptive changes to maintain a level of cognitive capacity even into the recovery period. Interestingly, in order for cognitive restitution to take place after sleep loss, less hours of sleep are needed than the number of hours previously lost

MSc. Thesis: O. Allega, McMaster University, Neuroscience (Blatter et al., 2007). It has been suggested that loss of NREM sleep is what largely contributes to decrements in cognitive performance after sleep loss (Miccoli et al., 2008; Darwent et al., 2010; Van Dongen et al., 2003).

The main limitations of clinical studies include small sample sizes, and lack of hourly testing in FD and SD studies, as seen in the CR protocols. A progressive curve at each hour, rather than at every "three or more" hours, would provide a clearer model for the fluctuations suspected in each cognitive domain in the absence of exogenous cues. In addition, it may have been useful for studies to also measure objective parameters of sleep and circadian rhythms such as nocturnal melatonin levels, dim light melatonin onset, or employed actigraphy to monitor sleep and daily activity rhythms. Another limitation, mainly seen in animal studies, is the use of male-only samples. Meta-analytic assessment of sex differences in rodents in learning and memory show that certain rodent species such as Sprague-Dawley, Fisher and Long Evans strains display male advantage, while Wistar rats show much smaller effects of male advantage (Jonasson, 2005).

In terms of potential clinical implications, given the evidence that changes in biological rhythms can impact cognitive performance, it is conceivable that this relationship may be relevant in certain psychiatric conditions such as major depression and bipolar disorder (McClung, 2013). In fact, Vanderlind et al. (2014) found that poorer overall sleep quality was associated with greater difficulty of cognitive control (disengaging from negative stimuli), which predicted greater increases in depressive symptoms in healthy volunteers. Evidence also suggests that poor cognitive function in depressed subjects is associated with poor functional outcomes even during periods of clinical remission (Robinson et al., 2006). This is consistent with studies showing that self-reported changes in daily rhythms were correlated with poor psychosocial functioning and worse performance on executive function tests in individuals with bipolar disorder (Giglio et al., 2010; Pinho et al., 2016). Thus, biological rhythms may be a major target for interventions aiming at improving cognitive function in individuals with mood disorders, a promising area for future research. In addition, the development of validated and reliable translational models is also

MSc. Thesis: O. Allega, McMaster University, Neuroscience a fruitful area of research into the neurobiological mechanisms behind the association between circadian rhythms and cognitive function.

In conclusion, there is an increasing body of evidence delineating the effects of circadian variation on cognition, and the specific cognitive parameters susceptible to variations throughout the 24h day in both animals and humans. Unfortunately, only few studies have conducted cross-species validation of cognitive tasks in order to further study the complexity that is inherently human by applying animal models, which makes it challenging at this stage to draw major conclusions regarding cross-species cognitive parameters that are distinctly vulnerable to fluctuations throughout the 24h day and whether those variations display phase differences in performance rhythms. The research performed thus far provides a promising framework for a challenging, yet fascinating investigations to seek out standardized criteria involved in TOD fluctuations in cognitive performance. Cross-species translational validation experiments have the potential to refine how we assess neuropsychological disorders and subsequently provide the most suitable interventions.

References

- Aschoff, J., & Wever, R. (1976). Human circadian rhythms: a multioscillatory system. In *Federation proceedings* (Vol. 35, No. 12, pp. 236-232).
- Adrien, J. (2002). Neurobiological bases for the relation between sleep and depression. *Sleep medicine reviews*, 6(5), 341-351.
- An, M., Huang, J., Shimomura, Y., & Katsuura, T. (2009). Time-of-day-dependent effects of monochromatic light exposure on human cognitive function. *Journal of physiological anthropology*, 28(5), 217-223.
- Antunes, L. C., Levandovski, R., Dantas, G., Caumo, W., & Hidalgo, M. P. (2010). Obesity and shift work: chronobiological aspects. *Nutrition research reviews*, 23(01), 155-168.
- Arble, D. M., Bass, J., Laposky, A. D., Vitaterna, M. H., & Turek, F. W. (2009). Circadian timing of food intake contributes to weight gain. *Obesity*, 17(11), 2100-2102.
- Barch, D. M., Braver, T. S., Nystrom, L. E., Forman, S. D., Noll, D. C., & Cohen, J. D. (1997). Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia*, 35(10), 1373-1380.
- Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., ... & Balkin, T. J. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: A sleep dose-response study. *Journal of sleep research*, 12(1), 1-12.
- Bennett, C. L., Petros, T. V., Johnson, M., & Ferraro, F. R. (2008). Individual differences in the influence of time of day on executive functions. *The American journal of psychology*, 349-361.
- Blagrove, M., Alexander, C., & Horne, J. A. (1995). The effects of chronic sleep reduction on the performance of cognitive tasks sensitive to sleep deprivation. *Applied Cognitive Psychology*, 9(1), 21-40.
- Blatter, K., & Cajochen, C. (2007). Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. *Physiology & behavior*, *90*(2), 196-208.
- Bodenhausen, G. V. (1990). Stereotypes as judgmental heuristics: Evidence of circadian variations in discrimination. *Psychological Science*, 1, 319–322.
- Bonnet, M. H. (2000). Sleep deprivation. In W. C. Dement (Ed.), Principles and practice of sleep medicine (3rd ed., pp. 53 71). Philadelphia: Saunders.
- Burgess, P. W. and Shallice, T. Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia, 1996, 34: 263–272.
- Cajochen, C., Khalsa, S. B. S., Wyatt, J. K., Czeisler, C. A., & Dijk, D. J. (1999). EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 277(3), R640-R649.
- Chaudhury, D., & Colwell, C. S. (2002). Circadian modulation of learning and memory in fearconditioned mice. *Behavioural brain research*, 133(1), 95-108.
- Chee, M. W., Chuah, L. Y., Venkatraman, V., Chan, W. Y., Philip, P., & Dinges, D. F. (2006). Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *Neuroimage*, 31(1), 419-428.

- Chun, L. E., Woodruff, E. R., Morton, S., Hinds, L. R., & Spencer, R. L. (2015). Variations in Phase and Amplitude of Rhythmic Clock Gene Expression across Prefrontal Cortex, Hippocampus, Amygdala, and Hypothalamic Paraventricular and Suprachiasmatic Nuclei of Male and Female Rats. *Journal of biological rhythms*, 0748730415598608.
- Colquhoun WP. Circadian variations in mental efficiency. In: Colquhoun WP, editor. Biological rhythms and human performance. London: Academic Press; 1971.
- Couyoumdjian, A., Sdoia, S., Tempesta, D., Curcio, G., Rastellini, E., De Gennaro, L., & Ferrara, M. (2010). The effects of sleep and sleep deprivation on task-switching performance. *Journal of sleep research*, 19(1-Part-I), 64-70.
- Craig, L. A., & McDonald, R. J. (2008). Chronic disruption of circadian rhythms impairs hippocampal memory in the rat. *Brain research bulletin*, *76*(1), 141-151.
- Darwent, D., Ferguson, S. A., Sargent, C., Paech, G. M., Williams, L., Zhou, X., ... & Roach, G. D. (2010). Contribution of core body temperature, prior wake time, and sleep stages to cognitive throughput performance during forced desynchrony. *Chronobiology International*, 27(5), 898-910.
- Devan, B. D., Goad, E. H., Petri, H. L., Antoniadis, E. A., Hong, N. S., Ko, C. H., ... & McDonald, R. J. (2001). Circadian phase-shifted rats show normal acquisition but impaired long-term retention of place information in the water task. *Neurobiology of learning and memory*, 75(1), 51-62.
- Dickinson, D. L., & McElroy, T. (2012). Circadian effects on strategic reasoning. *Experimental Economics*, 15(3), 444-459.
- Dijk, D. J., & Archer, S. N. (2010). PERIOD3, circadian phenotypes, and sleep homeostasis. *Sleep medicine reviews*, 14(3), 151-160.
- Dijk, D. J., Duffy, J. F., & Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *Journal of sleep research*, 1(2), 112-117.
- Doran, S. M., Van Dongen, H. P. A., & Dinges, D. F. (2001). Sustained attention performance during sleep deprivation: evidence of state instability. *Archives italiennes de biologie*, 139(3), 253-267.
- Drummond, S., Gillin, J. C., & Brown, G. G. (2001). Increased cerebral response during a divided attention task following sleep deprivation. *Journal of sleep research*, *10*(2), 85-92.
- Dubiela, F. P., de Oliveira, M. G. M., Moreira, K. D. M., Nobrega, J. N., Tufik, S., & Hipólide, D. C. (2005). Learning deficits induced by sleep deprivation and recovery are not associated with altered [3 H] muscimol and [3 H] flunitrazepam binding. *Brain research*, 1037(1), 157-163.
- Elmenhorst, D., Elmenhorst, E. M., Aeschbach, D., Kroll, T., Matusch, A., & Bauer, A. (2014). Impact of recovery sleep after sleep deprivation on cerebral A1 adenosine receptor density. In 10th International Symposium on Functional NeuroReceptor Mapping of the Living Brain (No. FZJ-2015-00683). Molekulare Organisation des Gehirns.
- Esumi, L. A., Palma, B. D., Gomes, V. L., Tufik, S., & Hipolide, D. C. (2011). Inflammatory markers are associated with inhibitory avoidance memory deficit induced by sleep deprivation in rats. *Behavioural brain research*, 221(1), 7-12.
- Fan, J., McCandliss, B.D., Fossella, J., Flombaum, J.I., Posner, M.I., 2005. The activation of attentional networks. NeuroImage 26, 471 – 479.
- Folkard, S., Knauth, P., & Monk, T. H. (1976). The effect of memory load on the circadian variation in performance efficiency under a rapidly rotating shift system. Ergonomics, 19,

479-488.

- Folkard S, Wever RA, Wildgruber CM. Multi-oscillatory control of circadian rhythms in human performance. Nature 1983;305:223–6.
- Fonken, L. K., Kitsmiller, E., Smale, L., & Nelson, R. J. (2012). Dim nighttime light impairs cognition and provokes depressive-like responses in a diurnal rodent. *Journal of biological rhythms*, 27(4), 319-327.
- Gibson, E. M., Wang, C., Tjho, S., Khattar, N., & Kriegsfeld, L. J. (2010). Experimental 'jet lag'inhibits adult neurogenesis and produces long-term cognitive deficits in female hamsters. *PLoS One*, 5(12), e15267-e15267.
- Giglio, L. M., Magalhães, P. V., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of psychiatric research*, 44(4), 220-223.
- Gillooly, P. B., Smolensky, M. H., Albright, D. L., Hsi, B., & Thorne, D. R. (1989). Circadian variation in human performance evaluated by the Walter Reed performance assessment battery. *Chronobiology international*, 7(2), 143-153.
- Gordon, H. W., Stoffer, D. S., & Lee, P. A. (1995). Ultradian rhythms in performance on tests of specialized cognitive function. *International Journal of Neuroscience*, 83(3-4), 199-211.
- Gritton, H. J., Stasiak, A. M., Sarter, M., & Lee, T. M. (2013). Cognitive performance as a zeitgeber: cognitive oscillators and cholinergic modulation of the SCN entrain circadian rhythms. *PloS one*, *8*(2).
- Gritton, H. J., Sutton, B. C., Martinez, V., Sarter, M., & Lee, T. M. (2009). Interactions between cognition and circadian rhythms: attentional demands modify circadian entrainment. *Behavioral neuroscience*, 123(5), 937.
- Groeger, J. A., Viola, A. U., Lo, J. C., von Schantz, M., Archer, S. N., & Dijk, D. J. (2008). Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. *Sleep*, 31(8), 1159.
- Gunzelmann, G., Gluck, K. A., Moore, L. R., & Dinges, D. F. (2012). Diminished access to declarative knowledge with sleep deprivation. *Cognitive Systems Research*, 13(1), 1-11.
- Hajali, V., Sheibani, V., Esmaeili-Mahani, S., & Shabani, M. (2012). Female rats are more susceptible to the deleterious effects of paradoxical sleep deprivation on cognitive performance. *Behavioural brain research*, 228(2), 311-318.
- Hagewoud, R., Havekes, R., Novati, A., Keijser, J. N., VAN DER, Z. E. E., & Meerlo, P. (2010). Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. *Journal of sleep research*, 19(2), 280-288.
- Harrison, Y., Jones, K., & Waterhouse, J. (2007). The influence of time awake and circadian rhythm upon performance on a frontal lobe task. *Neuropsychologia*, 45(8), 1966-1972.
- Henderson, V. W., Paganini-Hill, A., Emanuel, C. K., Dunn, M. E., & Buckwalter, J. G. (1994). Estrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. *Archives of Neurology*, 51(9), 896-900.
- Hidalgo, M. P., Zanette, C. B., Pedrotti, M., Souza, C. M., Nunes, P. V., & Chaves, M. L. (2004). Performance of chronotypes on memory tests during the morning and the evening shifts. Psychological Report, 95, 75–85.
- Himmelheber, A. M., Sarter, M., & Bruno, J. P. (2000). Increases in cortical acetylcholine release during sustained attention performance in rats. *Cognitive Brain Research*, 9(3), 313-325.

- Horowitz, T. S., Cade, B. E., Wolfe, J. M., & Czeisler, C. A. (2003). Searching Night and Day A Dissociation of Effects of Circadian Phase and Time Awake on Visual Selective Attention and Vigilance. *Psychological Science*, 14(6), 549-557.
- Intons-Peterson, M. J., Rocchi, P., West, T., McLellan, K., & Hackney, A. (1999). Age, testing at preferred or non- preferred times (testing optimality), and false memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 25, 23–40.
- Jennings, J. R., Monk, T. H., & Van der Molen, M. W. (2003). Sleep deprivation influences some but not all processes of supervisory attention. *Psychological Science*, *14*(5), 473-486.
- Jha, P. K., Challet, E., & Kalsbeek, A. (2015). Circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. *Molecular and cellular endocrinology*.
- Jonasson, Z. (2005). Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. *Neuroscience & Biobehavioral Reviews*, 28(8), 811-825.
- Karlsson, B., Knutsson, A., & Lindahl, B. (2001). Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27 485 people. Occupational and environmental medicine, 58(11), 747-752.
- Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. 23, 315–341.
- Keeler, J. F., & Robbins, T. W. (2011). Translating cognition from animals to humans. *Biochemical pharmacology*, *81*(12), 1356-1366.
- Kleitman, N. (1933). Studies on the physiology of sleep: VIII. Diurnal variation in performance. *Am J Physiol*, 104, 449-456.
- Kleitman, N., Titelbaum, S., & Feiveson, P. (1938). The effect of body temperature on reaction time. *American Journal of Physiology--Legacy Content*, *121*(2), 495-501.
- Kyriacou, C. P., & Hastings, M. H. (2010). Circadian clocks: genes, sleep, and cognition. Trends in cognitive sciences, 14(6), 259-267.
- Lawrence, J. B., & Stanford, M. S. (1998). Impulsivity and time of day: Effects on performance and cognitive tempo. *Personality and Individual Differences*, *26*(2), 199-207.
- Leproult, R., Holmbäck, U., & Van Cauter, E. (2014). Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*, *63*(6), 1860-1869.
- Leenaars, C. H., Joosten, R. N., Kramer, M., Post, G., Eggels, L., Wuite, M., ... & Van Someren, E. J. (2012a). Spatial reversal learning is robust to total sleep deprivation. *Behavioural brain research*, 230(1), 40-47.
- Leenaars, C. H., Joosten, R. N., Zwart, A., Sandberg, H., Ruimschotel, E., Hanegraaf, M. A., ... & van Someren, E. J. (2012b). Switch-task performance in rats is disturbed by 12 h of sleep deprivation but not by 12 h of sleep fragmentation. *Sleep*, 35(2), 211.
- Li, J. Z., Bunney, B. G., Meng, F., Hagenauer, M. H., Walsh, D. M., Vawter, M. P., ... & Schatzberg, A. F. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proceedings of the National Academy of Sciences*, 110(24), 9950-9955.
- Li, Y., Liu, L., Kang, J., Sheng, J. G., Barger, S. W., Mrak, R. E., & Griffin, W. S. T. (2000). Neuronal-glial interactions mediated by interleukin-1 enhance neuronal

acetylcholinesterase activity and mRNA expression. *The Journal of Neuroscience*, 20(1), 149-155.

- Loh, D. H., Navarro, J., Hagopian, A., Wang, L. M., Deboer, T., & Colwell, C. S. (2010). Rapid changes in the light/dark cycle disrupt memory of conditioned fear in mice. *PloS one*, 5(9), e12546.
- Ma, W. P., Cao, J., Tian, M., Cui, M. H., Han, H. L., Yang, Y. X., & Xu, L. (2007). Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats. *Neuroscience research*, 59(2), 224-230.
- Marquié, J. C., Tucker, P., Folkard, S., Gentil, C., & Ansiau, D. (2014). Chronic effects of shift work on cognition: findings from the VISAT longitudinal study. *Occupational and environmental medicine*, oemed-2013.
- Martin-Fairey, C. A., & Nunez, A. A. (2014). Circadian modulation of memory and plasticity gene products in a diurnal species. *Brain research*, *1581*, 30-39.
- McCoy, J. G., Christie, M. A., Kim, Y., Brennan, R., Poeta, D. L., McCarley, R. W., & Strecker, R. E. (2013). Chronic sleep restriction impairs spatial memory in rats. *Neuroreport*, 24(2), 91.
- McDonald, R. J., Hong, N. S., Ray, C., & Ralph, M. R. (2002). No time of day modulation or time stamp on multiple memory tasks in rats. *Learning and Motivation*, *33*(2), 230-252.
- Menz, M. M., Rihm, J. S., Salari, N., Born, J., Kalisch, R., Pape, H. C., ... & Büchel, C. (2013). The role of sleep and sleep deprivation in consolidating fear memories. *Neuroimage*, 75, 87-96.
- Miccoli, L., Versace, F., Koterle, S., & Cavallero, C. (2008). Comparing Sleep-Loss Sleepiness and Sleep Inertia: Lapses Make the Difference. *Chronobiology international*, 25(5), 725-744.
- Mikulincer, M., Babkoff, H., Caspy, T., & Sing, H. (1989). The effects of 72 hours of sleep loss on psychological variables. *British Journal of Psychology*, 80(2), 145-162.
- Mistlberger, R. E. (2011). Neurobiology of food anticipatory circadian rhythms. *Physiology & behavior*, 104(4), 535-545.
- Monk, T. H. (1997). Circadian rhythms in human performance and mood under constant conditions. Journal of Sleep Research, 6, 9–18.
- Monti, J. M., Bahammam, A. S., Pandi-Perumal, S. R., Bromundt, V., Spence, D. W., Cardinali, D. P., & Brown, G. M. (2013). Sleep and circadian rhythm dysregulation in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 43, 209–216.
- Moriya, S., Tahara, Y., Sasaki, H., Ishigooka, J., & Shibata, S. (2015). Housing under abnormal light–dark cycles attenuates day/night expression rhythms of the clock genes Per1, Per2, and Bmal1 in the amygdala and hippocampus of mice. *Neuroscience research*, *99*, 16-21.
- Mu, Q., Mishory, A., Johnson, K.A., Nahas, Z., Kozel, F.A., Yamanaka, K., Bohning, D.E., George, M.S., 2005. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep 28, 433–436.
- Müller, L., Fritzsche, P., & Weinert, D. (2015). Novel object recognition of Djungarian hamsters depends on circadian time and rhythmic phenotype. *Chronobiology international*, *32*(4), 458-467.

Nilsson, J. P., Söderström, M., Karlsson, A. U., Lekander, M., Åkerstedt, T., Lindroth, N. E., &

Axelsson, J. (2005). Less effective executive functioning after one night's sleep deprivation. *Journal of sleep research*, 14(1), 1-6.

- Oonk, M., Davis, C. J., Krueger, J. M., Wisor, J. P., & Van Dongen, H. P. (2014). Sleep Deprivation and Time-on-Task Performance Decrement in the Rat Psychomotor Vigilance Task. *Sleep*, 38(3), 445-451.
- Pace-Schott, E. F., Milad, M. R., Orr, S. P., Rauch, S. L., Stickgold, R., & Pitman, R. K. (2009). Sleep promotes generalization of extinction of conditioned fear. *Sleep*, *32*(1), 19.
- Palchykova, S., Winsky-Sommerer, R., Meerlo, P., Dürr, R., & Tobler, I. (2006). Sleep deprivation impairs object recognition in mice. *Neurobiology of learning and memory*, 85(3), 263-271.
- Perry, J. C., D'Almeida, V., Lima, M. M., Godoi, F. R., Vital, M. A. B., Oliveira, M. G. M., & Tufik, S. (2008). Intermittent hypoxia and sleep restriction: motor, cognitive and neurochemical alterations in rats. *Behavioural brain research*, 189(2), 373-380.
- Pike CJ, Carroll JC, Rosario ER, Barron AM. Protective actions of sex steroid hormones in Alzheimer's disease. Front Neuroendocrinol 2009;30:239–58.
- Pinho, M., Sehmbi, M., Cudney, L. E., Kauer-Sant'anna, M., Magalhães, P. V., Reinares, M., ... & Vieta, E. (2015). The association between biological rhythms, depression, and functioning in bipolar disorder: a large multi-center study. *Acta Psychiatrica Scandinavica*.
- Puttonen, S., Härmä, M., & Hublin, C. (2010). Shift work and cardiovascular disease—pathways from circadian stress to morbidity. *Scandinavian journal of work, environment & health*, 96-108.
- Rada, P., Mark, G. P., Vitek, M. P., Mangano, R. M., Blume, A. J., Beer, B., & Hoebel, B. G. (1991). Interleukin-1β decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain research*, 550(2), 287-290.
- Ralph, M. R., Ko, C. H., Antoniadis, E. A., Seco, P., Irani, F., Presta, C., & McDonald, R. J. (2002). The significance of circadian phase for performance on a reward-based learning task in hamsters. *Behavioural brain research*, 136(1), 179-184.
- Ramesh, V., Nair, D., Zhang, S. X., Hakim, F., Kaushal, N., Kayali, F., ... & Gozal, D. (2012). Disrupted sleep without sleep curtailment induces sleepiness and cognitive dysfunction via the tumor necrosis factor-α pathway. *J Neuroinflammation*, 9, 91.
- Ramirez, C., Garcia, A., & Valdez, P. (2012). Identification of circadian rhythms in cognitive inhibition and flexibility using a Stroop task. *Sleep and Biological Rhythms*, 10(2), 136-144.
- Ramírez, C., Talamantes, J., García, A., Morales, M., Valdez, P., & Menna-Barreto, L. (2006). Circadian rhythms in phonological and visuospatial storage components of working memory. *Biological Rhythm Research*, 37(5), 433-441.
- Ramos, S. E., Murgas, L. D. S., Rodrigues, M., & Ferreira, C. A. M. J. Learning and Working Memory In Mice Under Different Lighting Conditions.
- Ravizza, S. M., Hazeltine, E., Ruiz, S., & Zhu, D. C. (2011). Left TPJ activity in verbal working memory: implications for storage-and sensory-specific models of short term memory. *Neuroimage*, 55(4), 1836-1846.
- Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of affective disorders*, 93(1), 105-115.

- Ruby, N. F., Fernandez, F., Garrett, A., Klima, J., Zhang, P., Sapolsky, R., & Heller, H. C. (2013). Spatial memory and long-term object recognition are impaired by circadian arrhythmia and restored by the GABA A antagonist pentylenetetrazole. *PloS one*, 8(8), e72433.
- Ruby, N. F., Hwang, C. E., Wessells, C., Fernandez, F., Zhang, P., Sapolsky, R., & Heller, H. C. (2008). Hippocampal-dependent learning requires a functional circadian system. *Proceedings of the National Academy of Sciences*, 105(40), 15593-15598.
- Rutter, J., Reick, M., & McKnight, S. L. (2002). Metabolism and the control of circadian rhythms. *Annual review of biochemistry*, 71(1), 307-331.
- Rouch I, Wild P, Ansiau D, et al. Shift work experience, age and cognitive performance. Ergonomics 2005;48:1282–93.
- Sagaspe, P., Sanchez-Ortuno, M., Charles, A., Taillard, J., Valtat, C., Bioulac, B., & Philip, P. (2006). Effects of sleep deprivation on Color-Word, Emotional, and Specific Stroop interference and on self-reported anxiety. *Brain and cognition*, 60(1), 76-87.
- Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain research reviews*, *35*(2), 146-160.
- Schmidt, C., Collette, F., Cajochen, C., & Peigneux, P. (2007). A time to think: circadian rhythms in human cognition. *Cognitive Neuropsychology*, 24(7), 755-789.
- Siegel, J. M. (2001). The REM sleep-memory consolidation hypothesis. *Science*, 294(5544), 1058-1063.
- Stickgold, R. (2005). Sleep-dependent memory consolidation. Nature, 437(7063), 1272-1278.
- Stickgold, R., & Walker, M. P. (2007). Sleep-dependent memory consolidation and reconsolidation. *Sleep medicine*, 8(4), 331-343.
- Smith, E.E., Jonides, J., Marshuetz, C., Koeppe, R.A., 1998. Components of verbal working memory: evidence from neuroimaging. Proc. Natl. Acad. Sci. U. S. A. 95, 876–882.
- Spoormaker, V. I., Schröter, M. S., Andrade, K. C., Dresler, M., Kiem, S. A., Goya-Maldonado, R., ... & Czisch, M. (2012). Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Human brain mapping*, 33(10), 2362-2376.
- Szosland, D. (2010). Shift work and metabolic syndrome, diabetes mellitus and ischaemic heart disease. *International journal of occupational medicine and environmental health*, 23(3), 287-291.
- Szymusiak, R., Gvilia, I., & McGinty, D. (2007). Hypothalamic control of sleep. *Sleep medicine*, 8(4), 291-301.
- Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., ... & Redmond, D. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of sleep research*, 9(4), 335-352.
- Tucker, A. M., Whitney, P., Belenky, G., Hinson, J. M., & Van Dongen, H. P. (2010). Effects of sleep deprivation on dissociated components of executive functioning. *Sleep*, 33(1), 47.
- Valdez, P., Ramírez, C., García, A., Talamantes, J., & Cortez, J. (2010). Circadian and homeostatic variation in sustained attention. *Chronobiology international*, 27(2), 393-416.

- Valentinuzzi, V. S., Menna-Barreto, L., & Xavier, G. F. (2004). Effect of circadian phase on performance of rats in the Morris water maze task. *Journal of biological rhythms*, 19(4), 312-324.
- Vanderlind, M.W., Beevers, C.G., Sherman, S.M., Trujillo, L.T., McGeary, J.E., Matthews, M.D. et al., 2014. Sleep and sadness: exploring the relation among sleep, cognitive control and depressive symptoms in young adults. Sleep Med. 15: 144-149.
- Vandewalle, G., Archer, S. N., Wuillaume, C., Balteau, E., Degueldre, C., Luxen, A., ... & Maquet, P. (2011). Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *Journal of biological rhythms*, 26(3), 249-259.
- Van Dongen, H. P., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. SLEEP-NEW YORK THEN WESTCHESTER-, 26(2), 117-129.
- Van Dongen, H. P., Belenky, G., & Krueger, J. M. (2011a). A local, bottom-up perspective on sleep deprivation and neurobehavioral performance. *Current topics in medicinal chemistry*, 11(19), 2414.
- Van Dongen, H. P., Belenky, G., & Vila, B. J. (2011b). The efficacy of a restart break for recycling with optimal performance depends critically on circadian timing. *Sleep*, 34(7), 917.
- van Enkhuizen, J., Acheson, D., Risbrough, V., Drummond, S., Geyer, M. A., & Young, J. W. (2014). Sleep deprivation impairs performance in the 5-choice continuous performance test: similarities between humans and mice. *Behavioural brain research*, 261, 40-48.
- Viola, A. U., Archer, S. N., James, L. M., Groeger, J. A., Lo, J. C., Skene, D. J., ... & Dijk, D. J. (2007). PER3 polymorphism predicts sleep structure and waking performance. *Current Biology*, 17(7), 613-618.
- Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Wong, C., ... & Jayne, M. (2008). Sleep deprivation decreases binding of [11C] raclopride to dopamine D2/D3 receptors in the human brain. *The Journal of Neuroscience*, 28(34), 8454-8461.
- Wakamatsu, H., Yoshinobu, Y., Aida, R., Moriya, T., Akiyama, M., and Shibata, S. (2001). Restricted- feeding-induced anticipatory acti- vity rhythm is associated with a phase-shift of the expression of mPer1 and mPer2 mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. *Eur. J. Neurosci.* 13, 1190–1196.
- Wang, L. M., Dragich, J. M., Kudo, T., Odom, I. H., Welsh, D. K., O'Dell, T. J., & Colwell, C. S. (2009). Expression of the circadian clock gene Period2 in the hippocampus: possible implications for synaptic plasticity and learned behaviour. *Asn Neuro*, 1(3), AN20090020.
- Whitton, J. L. (1978). Periodicities in self-reports of health, sleep and mood variables. *Journal of psychosomatic research*, 22(2), 111-115.
- Wimmer, F., Hoffman, R. F., Bonato, R. A., & Moffitt, A. R. (1992). The effects of sleep deprivation on divergent thinking and attention processes. *Journal of sleep research*, 1(4), 223-230.
- Wise, P. M. (2002). Estrogens and neuroprotection. *Trends in Endocrinology & Metabolism*, 13(6), 229-230.
- Wise, P. M., Dubal, D. B., Wilson, M. E., Rau, S. W., Böttner, M., & Rosewell, K. L. (2001). Estradiol is a protective factor in the adult and aging brain: understanding of mechanisms

derived from in vivo and in vitro studies. Brain Research Reviews, 37(1), 313-319.

- Wright, K. P., Hull, J. T., & Czeisler, C. A. (2002). Relationship between alertness, performance, and body temperature in humans. *American Journal of Physiology-Regulatory*, *Integrative and Comparative Physiology*, 283(6), R1370-R1377.
- Wright, K. P., Hull, J. T., Hughes, R. J., Ronda, J. M., & Czeisler, C. A. (2006). Sleep and wakefulness out of phase with internal biological time impairs learning in humans. *Journal of Cognitive Neuroscience*, 18(4), 508-521.
- Wright, K. P., Lowry, C. A., & LeBourgeois, M. K. (2012). Circadian and wakefulness-sleep modulation of cognition in humans. *Frontiers in molecular neuroscience*, *5*.
- Yang, S. R., Sun, H., Huang, Z. L., Yao, M. H., & Qu, W. M. (2012). Repeated sleep restriction in adolescent rats altered sleep patterns and impaired spatial learning/memory ability. *Sleep*, 35(6), 849.
- Yoo, S. S., Hu, P. T., Gujar, N., Jolesz, F. A., & Walker, M. P. (2007). A deficit in the ability to form new human memories without sleep. *Nature neuroscience*, *10*(3), 385-392.
- Zielinski, M. R., Davis, J. M., Fadel, J. R., & Youngstedt, S. D. (2013). Influence of chronic moderate sleep restriction and exercise training on anxiety, spatial memory, and associated neurobiological measures in mice. *Behavioural brain research*, 250, 74-80.


Figure 1. Initial record selection. The total number of records included is added to the total number of records included in search #2 for the final number of records (n = 78).



Figure 2. Search #2 on preclinical studies of sleep deprivation. The total number of records included is added to the total number of records included in search #1 for the final number of records (n = 78).

	Stroop and CRTT used, one study actively assessed circadian rhythmicity while the other did not, no cross-species translation	Literature divided on whether or not ability to complete a task-shifting set disrupted with increased hours awake ^{14,19,20} , phase of performance time parallels CBT ⁸	×	```		<	Shifting/Flextbility
	Stroop and CRTT used, one study actively assessed circadian rhythmicity while other did not, no cross-species translation	Generally no impairment with increased hours awake, performance decline seen in afternoon with regard to response time ^{19, 20} , performance time displays 100- min phase delay with respect to CBT ²¹	z		``		Inhibition
	Consistency among throughput tasks detecting rhythm, no known cross-species translation	Circadian effects operating in early afternoon ^{16,17} , peaking every 21-27 hours with a decline in performance into biological night ¹⁸	Y	``			Throughput
	Consistency among divided attention tasks, no cross-species translation	SD slows performance on task-switching for accuracy ¹⁴ , performance decline with hours awake, performance better in early hours ¹⁵ , no circadian variation observed	Y	٢		٢	Multi-task/dual processing
		Executive Function					
	Serial reaction time task ¹² only known task to be performed, no cross-species validation	Very scarce literature on circadian rhythm detection in procedural memory; sequence learning possible under low and high sleep pressure conditions, where memory improved following naps after circadian peak of REM sleep ¹³	Y			٩	Procedural memory
	Parallelism to CBT consistent in recognition tasks, word/letter pairs, picture memorization, no cross-species task validation completed	Earlier papers denote rhythms in episodic memory parallel to CBT ^{11,12} , performance decline with increased hours awake, no known literature evaluating semantic memory rhythms	Y	<	<	۲	Declarative memory
Recall dependent on WM load ¹⁰ , tasks of grater complexity show greater variation in performance	Variations in rhythmicity seen with different tasks assessing phonological WM, visual WM, spatial WM, no cross-species task validation completed	Literature divided on whether or not performance rhythmicity exists, performance decline seen with hours awake into biological night. Parallelism to CBT seen ⁷ , as well as 1-3hr phase delays with respect to CBT ⁸ , other studies cite no TOD effects ⁹	γ	٢		<	Working memory
		Memory		-			
	Visual search does not seem to readily detect rhythms as CPT and PVT do, stability of correct responses declines with time awake, no "selective attention"- specific cross-species task validation complete	Literature divided on whether or not robust rhythm exists, performance decline seen with hours awake, possible that homeostatic and circadian factors modulate performance downstream from locus of selective attention, of which effects on global vigilance and alertness are strikingly different ⁶	Y	< <u> </u>		< <u> </u>	Selective attention
Performance on tasks modulated by TOT; greater performance variability seen with increased time awake	No task differences seen for detection. CPT translational task validation completed ⁴ , rodent analog of human PVT completed ⁵ : similar in global performance outcomes but outcomes of TOT and RSI differ in SD- induced impairments	Lowest errors of commission at 1h after CBT min and 16h after CBT max ¹ , generally mirroring CBT, no TOD sensitivity seen for RT, errors of omission; 1hr delay for RT and 3hr delay for % correct responses with respect to CBT ^{2,3}	Y	٩	< <u> </u>	<	Sustained attention/vigilance
	KSS & SSS mainly used for alertness measure, consistency in rhythm detection, no translational task validation	Generally stable through first 16h of waking day, decline as time awake increases, "after lunch" midday dip	Y	<u>م</u>	<	٩	Alertness
		Attention		Ċ	t		
				SD	FD	CR	
Other	Task-sensitivity/Cross-species Translation?	Rhythm Detection (TOD)?	Impairments	Used	radigms	Pa_i	Domain

Table 1. A summary of the findings of circadian rhythmicity in cognitive performance in humans and cross-species translational validity. *CBT: Core body temperature; CPT: Continuous performance test; CRTT: Choice reaction time task; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor vigilance task; REM: Rapid eye movement; RSI: Response-stimulus interval; RT: Reaction time; SSS: Subjective Sleepiness Scale; TOD: Time of day; TOT: Time on task; WM: Working memory.* ¹Harrison et al., 2007; ³Valdez et al., 2010; ⁴Van Enkuizen et al., 2014; ⁵Oonk et al., 2015; ⁶Horowitz et al., 2006; ⁷Wright et al., 2002; ⁸Ramirez et al., 2012; ⁹Hidalgo et al., 2004; ¹⁰Folkard et al., 1976; ¹¹Johnson et al., 1992; ¹²Cajochen et al., 1999; ¹³Cajochen et al., 2004; ¹⁴Drummond et al., 2001; ¹⁵Couyoumidjan et al., 2010; ¹⁶Gordon et al., 1995; ¹⁷Van Dongen et al., 2010; ²⁰Thomas et al., 2000.

Chapter 5

Concluding Statements/Future Directions

Overview

In the study addressed in chapters 2 and 3, we aimed to examine the relationship between biological rhythm disruption and mood disorders, and to compare several parameters that measure circadian rhythmicity. We first did this by investigating group differences between objective and subjective measures of sleep and circadian rhythmicity, followed by an objective validation of the BRIAN. While the exact causal mechanisms involved in development of depression and bipolar disorder may never be fully understood, studies of its major determinants will provide valuable insight that will lead to improved clinical assessments, prevention methods and intervention.

Objective and Subjective Measures of Sleep and Biological Rhythm Disruption, and focus on the BRIAN

In chapter 2 we investigated group differences in objective and subjective measurements of sleep and circadian rhythm disruption in mood disorders and controls. In chapter 3 we provided a preliminary objective validation of the BRIAN against sleep and circadian variables. Our results revealed that objective and subjective sleep parameters show moderate agreement with each other, while objective and subjective measures of biological rhythm disturbance show mild agreement. While the majority of the mood sample was euthymic, participants in all four mood groups reported greater biological rhythm disruption compared to controls, whereas objective actigraphic measures of circadian rhythmicity did not detect differences. However, objective melatonin profiling obtained via urine sampling did show agreement with the BRIAN with regard to currently depressed BD displaying lowest melatonin levels, and highest BRIAN scores. The BRIAN also showed moderate correlation with mood groups between the sleep domain, actigraphic sleep parameters and urinary melatonin. This information provides some

promising external validity to the usefulness of questionnaires in the clinical setting for episode prediction, maintenance, and prevention.

Biological rhythms constitute a wide range of physiological and psychosocial functions that are assessed on the BRIAN, that were not addressed in this study. Further assessment of the activity, eating pattern and social domains with objective measures is imperative. As mentioned in chapter 3, the BRIAN social domain could be objectively assessed with the newly developed smartphone application, *MoodRhythm* (Matthews et al., 2016), which detects social rhythms from sensory activity monitored by the accelerometer in a cell phone, a factor that is based on the assumption that the phone is on the individual's person at all times. Although the BRIAN assesses overall biological rhythm disruption, an objective validation of each domain would provide clinicians with unequivocal data shedding light on which parameters of biological rhythms may be affected to a greater degree in patients, and how those domains contribute to inter-individual symptom severity. Furthermore, it may be of interest to test the BRIAN in populations with different psychiatric conditions if it is to be used as a clinical screening tool, so as to detect discriminant validity of the questionnaire (Moro et al., 2014). In our analyses conducted in chapter 2, the BRIAN did not detect differences between MDD and BD subjects, which could mean one of two things. Depression and bipolar disorder display similar pathophysiological mechanisms, and can be assessed for circadian disturbance using the same constructs, or, the BRIAN items require refining so to dissociate biological rhythm disruption in depression from mania.

It must be taken into consideration that the BRIAN questionnaire assesses biological rhythm disturbance over the last 15 days by means of self-report. The point of validating this questionnaire is to enable a quick, accurate, cost-efficient and feasible method of assessing disruption, however patients are likely subject to recall biases. While our actiwatches were monitoring subjects in one-minute epochs continuously for 15 days, the measurement the BRIAN

records is at one time point, asking subjects to recall events accurately for the two weeks prior, which could potentially be contributing to why we did not see greater group differences and correlations with circadian variables. In future it might be of interest to consider using the BRIAN weekly, or even have subjects complete the questionnaire once per day as part of a diagnostic assessment. This would also add insight into whether subjective biological rhythm disruption is a state or trait feature of affective disorders.

Circadian rhythms and cognition

In chapter 4 we looked at preclinical and clinical studies investigating the impact of circadian disturbance on cognition. Although the literature within and between species is inconsistent as to whether similar rhythmicity exists in cognitive domains, there are a few conclusions to address. The degree to which cognitive domains are affected by circadian disturbances varies. Alertness and attention tend to steadily increase and maintain a high level of performance throughout the waking day, displaying a decline around the 16h mark. In memory, both humans and animals have been reported to display rhythmicity that shows a 1-4h phase delay with respect to the CBT. Executive functions are more widely tested in humans than animals. Inhibition has been reported to act in a phase delay of about 100 minutes with respect to CBT and flexibility peaks early in the morning, as CBT is rising. To assess the robustness of these results, we are in the process of calculating effect sizes for both human and animal studies.

A major finding noted in the chapter 4 discussion is the lack of methodological harmony between human and animal studies. These are issues that must be addressed prior to assessing rhythmicity in cognitive variables. There are very few studies that begin with hypothesis-driven preclinical results that end with affirmative clinical results in neuropsychiatric disorders (Talpos & Steckler, 2013). Different tasks are used to assess the same parameter in humans (i.e. continuous performance test versus psychomotor vigilance task to assess aspects of sustained

attention and reaction time), and animals (i.e. Barnes Maze versus Morris Water Maze to evaluate spatial learning and memory), which are usually chosen at the investigator's discretion. It is difficult to make conclusions about deficits associated with circadian rhythm dysregulation in each species alone due to differences that may involve task sensitivity to rhythmicity. Moreover, a question is raised of task translation between species in order to provide feasible animal models that bear some approximation to higher complexities seen in humans (for example, episodic memory is thought to be unique to humans) (Keeler & Robbins, 2011). One approach researchers are taking involves "back-translation" from human models to animal models. Keeler & Robbins (2011) discuss the CANTAB Paired Associates Learning (PAL) task that evaluates features of visual memory and learning using a touch screen. Patients will recall several abstract visual objects with short delays between probe and recall, with increasing levels of difficulty. Several studies have modeled a PAL in rodents after the human CANTAB task (Bartko et al., 2011, Kim et al., 2015; Talpos et al., 2009), where similar effects of hippocampal deficits in humans have been observed in rodents. Translational models such as this will allow researchers to engage in a priori hypothesis testing in preclinical representations and provide meaningful clinical results, rather than making post hoc conclusions generalized between species (Talpos & Steckler, 2013).

Conclusion

The ultimate goal of this thesis was to investigate the relationship between objective and subjective circadian rhythm disturbances and mood disorders. This was done by comparing several measurements both self-reported and objectively that are known to be sensitive to dysregulation in mood. It is of importance to highlight the finding that BRIAN scores detect group differences similar to that of urinary melatonin measurements between controls and BD, suggesting lower levels of melatonin secretion are associated with greater subjective biological rhythm disturbance, a finding that was further corroborated by a significant correlation. Our results provide meaningful evidence of the use of subjective ratings in the clinical setting,

however further systematic objective validations are warranted. These findings further corroborate theories that circadian disturbance may be at core of mood disorders, which are an important target of intervention and prevention. We also investigated the impact of circadian rhythm dysregulation on cognitive performance. The results of this review provide promising evidence of using translational models to identify patterns of rhythmicity in cognitive domains of attention, memory and executive function, however much work still has to be done. This was of interest due to the known interaction between reduced cognitive capacity associated with circadian disturbance, and its involvement in mood (Boland & Alloy, 2013; McKenna & Tyler, 2012).

Additional References

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C: American Psychiatric Association.
- Bakish D. New standard of depression treatment: remission and full recovery. J Clin Psychiatry. 2001;62 Suppl 26: 5-9.
- Bartko, S. J., Romberg, C., White, B., Wess, J., Bussey, T. J., & Saksida, L. M. (2011). Intact attentional processing but abnormal responding in M 1 muscarinic receptor-deficient mice using an automated touchscreen method. *Neuropharmacology*, 61(8), 1366-1378.
- Betchel, W. (2015). Circadian rhythms and mood disorders: are the phenomena and mechanisms causally related? *Frontiers in psychiatry*, 6.
- Becker, C., Zeau, B., Rivat, C., Blugeot, A., Hamon, M., & Benoliel, J. J. (2008). Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. *Molecular psychiatry*, 13(12), 1079-1092.
- Benson, K. L., & Zarcone, V. P. (1993). Rapid eye movement sleep eye movements in schizophrenia and depression. *Archives of General Psychiatry*, 50(6), 474-482.
- Boivin, D. B., Czeisler, C. A., Dijk, D. J., Duffy, J. F., Folkard, S., Minors, D. S., ... & Waterhouse, J. M. (1997). Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Archives of General Psychiatry*, 54(2), 145-152.
- Boland, E. M., & Alloy, L. B. (2013). Sleep disturbance and cognitive deficits in bipolar disorder: toward an integrated examination of disorder maintenance and functional impairment. *Clinical psychology review*, 33(1), 33-44.
- Boudebesse, C., Geoffroy, P. A., Bellivier, F., Henry, C., Folkard, S., Leboyer, M., & Etain, B. (2014). Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiology international*, 31(5), 698-704
- Burgess, H. J., Trinder, J., Kim, Y., & Luke, D. (1997). Sleep and circadian influences on cardiac autonomic nervous system activity. *American Journal of Physiology-Heart and Circulatory Physiology*, 273(4), H1761-H1768.
- Cagampang, F. R., & Bruce, K. D. (2012). The role of the circadian clock system in nutrition and metabolism. *British Journal of Nutrition*, 108(03), 381-392.
- Cajochen, C., Khalsa, S. B. S., Wyatt, J. K., Czeisler, C. A., & Dijk, D. J. (1999). EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 277(3), R640-R649.
- Coque L, Mukherjee S, Cao JL, Spencer S, Marvin M, Falcon E, et al. (2011): Specific role of VTA dopamine neuronal firing rates and morphology in the reversal of anxiety-related, but not depression- related behavior in the ClockDelta19 mouse model of mania. Neuropsychopharmacology 36:1478–1488.
- Charmandari, E., Chrousos, G. P., Lambrou, G. I., Pavlaki, A., Koide, H., Ng, S. S. M., & Kino, T. (2011). Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man. *PLoS One*, 6(9), e25612.
- Chaudhury, D., & Colwell, C. S. (2002). Circadian modulation of learning and memory in fearconditioned mice. *Behavioural brain research*, 133(1), 95-108.

- Chung, S., Lee, E. J., Yun, S., Choe, H. K., Park, S. B., Son, H. J., ... & Son, G. H. (2014). Impact of circadian nuclear receptor REV-ERBα on midbrain dopamine production and mood regulation. *Cell*, *157*(4), 858-868.
- Depp CA, Strassnig M, Mausbach BT, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. Bipolar Disord. 2014;16(4):422-431.
- Devan, B. D., Goad, E. H., Petri, H. L., Antoniadis, E. A., Hong, N. S., Ko, C. H., ... & McDonald, R. J. (2001). Circadian phase-shifted rats show normal acquisition but impaired long-term retention of place information in the water task. *Neurobiology of learning and memory*, 75(1), 51-62.
- Dijk, D. J., Duffy, J. F., & Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *Journal of sleep research*, 1(2), 112-117.
- Dockray, G. J. (2012). Cholecystokinin. Current Opinion in Endocrinology, Diabetes and Obesity, 19(1), 8-12.
- Duffy, A., Grof, P., & Alda, M. (2000). The implications of genetic studies of major mood disorders for clinical practice. *The Journal of clinical psychiatry*, 61(9), 630-637.
- Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. J Clin Psychiatry. 2009;70 (suppl 3):22-29.
- Faria, A. D., de Azevedo Cardoso, T., Mondin, T. C., de Mattos Souza, L. D., da Silva Magalhaes, P. V., Zeni, C. P., ... & Jansen, K. (2015). Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. *Journal of affective disorders*, 186, 145-148.
- Geoffroy PA, Boudebesse C, Bellivier F et al. Sleep in remitted bipolar disorder: a naturalistic case-control study using actigraphy. J Affect Disord 2014;158:1–7.
- Giglio, L. M., Magalhães, P. V., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of psychiatric research*, 44(4), 220-223.
- Gnam W., S.-H.A., Mustard C., Rush B., Lin E., 2006. The economic costs of mental disorders and alcohol, tobacco, and illicit drug abuse in Ontario, 2000: a cost-of-illness study. Centre for Addiction and Mental Health Toronto.
- Gooley, J. J., Lu, J., Chou, T. C., Scammell, T. E., & Saper, C. B. (2001). Melanopsin in cells of origin of the retinohypothalamic tract. *Nature neuroscience*, 4(12), 1165-1165.
- Gritton, H. J., Kantorowski, A., Sarter, M., & Lee, T. M. (2012). Bidirectional interactions between circadian entrainment and cognitive performance. *Learning & Memory*, 19(3), 126-141.
- Gulevich, G. D., Dement, W. C., & Zarcone, V. P. (1967). All-night sleep recordings of chronic schizophrenics in remission. *Comprehensive psychiatry*, 8(3), 141-149.
- Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W. A., & Beekman, A. T. F. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica*, 122(3), 184-191.
- Harrington, M. E., & Rusak, B. (1988). Ablation of the geniculo-hypothalamic tract alters circadian activity rhythms of hamsters housed under constant light. *Physiology & behavior*, 42(2), 183-189.

- Henry C, van den Bulke D, Bellivier F et al. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. Psychiatry Res 2008;159:1–6.
- Hinton, J. M. (1963). Patterns of insomnia in depressive states. Journal of Neurology, Neurosurgery & Psychiatry, 26(2), 184-189.
- Hidalgo, M. P. L., Zanette, C. B., Pedrotti, M., Souza, C. M., Nunes, P. V., & Chaves, M. L. F. (2004). Performance of chronotypes on memory tests during the morning and the evening shifts. *Psychological reports*, 95(1), 75-85.
- Hirschfeld RM, Dunner DL, Keitner G, Klein DN, Koran LM, Kornstein SG, et al. Does psychosocial functioning improve independent of depressive symptoms? A compari- son of nefazodone, psychotherapy, and their combination. Biol Psychiatry 2002;51:123-133.
- Hong, C. J., Huo, S. J., Yen, F. C., Tung, C. L., Pan, G. M., & Tsai, S. J. (2003). Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology*, 48(4), 186-189.
- Horowitz, T., & Wolfe, J. (2003). Memory for rejected distractors in visual search?. Visual Cognition, 10(3), 257-298.
- Huang N, Chelliah Y, Shan Y, Taylor CA, Yoo SH, Partch C, Green CB, Zhang H, Takahashi JS. Crystal structure of the heterodimeric CLOCK:BMAL1 transcriptional activator complex. Science. 2012;337:189–194.
- Judd, L. L., Schettler, P. J., Akiskal, H. S., Coryell, W., Leon, A. C., Maser, J. D., & Solomon, D. A. (2008). Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Archives of general psychiatry*, 65(4), 386-394.
- Keeler, J. F., & Robbins, T. W. (2011). Translating cognition from animals to humans. *Biochemical pharmacology*, *81*(12), 1356-1366.
- Kim, C. H., Heath, C. J., Kent, B. A., Bussey, T. J., & Saksida, L. M. (2015). The role of the dorsal hippocampus in two versions of the touchscreen automated paired associates learning (PAL) task for mice. *Psychopharmacology*, 232(21-22), 3899-3910.
- Krawczak, E. M., Minuzzi, L., Hidalgo, M. P., & Frey, B. N. (2016). Do changes in subjective sleep and biological rhythms predict worsening in postpartum depressive symptoms? A prospective study across the perinatal period. *Archives of women's mental health*, 1-8.
- Kripke, D. F., Mullaney, D. J., Atkinson, M., & Wolf, S. (1978). Circadian rhythm disorders in manic-depressives. *Biological psychiatry*.
- Lewy, A. J., Sack, R. L., Singer, C. M., & White, D. M. (1987). The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. *Psychopharmacology Bulletin*, 23(3), 349.
- Lopez AD, Murray CC (1998) The global burden of disease, 1990–2020. Nat Med 4: 1241–1243. pmid:9809543. doi: 10.1038/3218
- Magalhaes PV, Kapczinski F, Nierenberg AA, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012;125(4):303-308.
- Manning, J. S. (2015). Bipolar disorder, bipolar depression, and comorbid illness. Journal of Family Practice, 64(6), S10-S10.
- Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., ... & Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and

euthymic states in bipolar disorder. American Journal of Psychiatry, 161(2), 262-270.

- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, Kessler RC (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 64:543–552.
- Miller, T. H. (2016). Bipolar Disorder. Primary Care: Clinics in Office Practice, 43(2), 269-284.
- Miller, I. W., Keitner, G. I., Schatzberg, A. F., Klein, D. N., Thase, M. E., Rush, A. J., ... & Davis, S. M. (1998). The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *The Journal of clinical psychiatry*, 59(11), 608-619.
- Mondin, T. C., de Azevedo Cardoso, T., Jansen, K., da Silva, G. D. G., de Mattos Souza, L. D., & da Silva, R. A. (2015). Long-term effects of cognitive therapy on biological rhythms and depressive symptoms: A randomized clinical trial. *Journal of affective disorders*, 187, 1-9.
- Morin, L. P. (2013). Neuroanatomy of the extended circadian rhythm system. *Experimental neurology*, 243, 4-20.
- Morin, L. P., & Allen, C. N. (2006). The circadian visual system, 2005. *Brain research reviews*, 51(1), 1-60.
- Moro, M. F., Carta, M. G., Pintus, M., Pintus, E., Melis, R., Kapczinski, F., ... & Colom, F. (2014). Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): Some Considerations on its Screening Usefulness. *Clinical practice and epidemiology in mental health: CP & EMH*, 10, 48.
- Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remis- sion of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol Med 2010;40(1):41–50.
- Patten, S. B., Williams, J. V., Lavorato, D. H., Wang, J. L., McDonald, K., & Bulloch, A. G. (2015). Descriptive epidemiology of major depressive disorder in Canada in 2012. *The Canadian Journal of Psychiatry*, 60(1), 23-30.
- Patton, D. F., & Mistlberger, R. E. (2013). Circadian adaptations to meal timing: neuroendocrine mechanisms. *Frontiers in neuroscience*, 7, 185.
- Phan, T. H., Chan, G. C. K., Sindreu, C. B., Eckel-Mahan, K. L., & Storm, D. R. (2011). The diurnal oscillation of MAP (mitogen-activated protein) kinase and adenylyl cyclase activities in the hippocampus depends on the suprachiasmatic nucleus. *The Journal of Neuroscience*, 31(29), 10640-10647.
- Price, A. L., & Marzani-Nissen, G. R. (2012). Bipolar disorders: a review. *Am Fam Physician*, 85(5), 483-493.
- Ramírez, C., Talamantes, J., García, A., Morales, M., Valdez, P., & Menna-Barreto, L. (2006). Circadian rhythms in phonological and visuospatial storage components of working memory. *Biological Rhythm Research*, 37(5), 433-441.
- Refinetti, R. (2010). Entrainment of circadian rhythm by ambient temperature cycles in mice. *Journal of biological rhythms*, 25(4), 247-256.
- Rosenthal, N. E., Joseph-Vanderpool, J. R., Levendosky, A. A., Johnston, S. H., Allen, R., Kelly, K. A., ... & Starz, K. E. (1990). Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep*, 13(4), 354-361.

- Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatr Serv. 2009;60(2): 147-156.
- Rumble, M. E., White, K. H., & Benca, R. M. (2015). Sleep disturbances in mood disorders. *Psychiatric Clinics of North America*, 38(4), 743-759.
- Schaffer, A., Cairney, J., Cheung, A., Veldhuizen, S., & Levitt, A. (2006). Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics. *The Canadian Journal of Psychiatry*, 51(1), 9-16.
- Schmidt, C., Collette, F., Cajochen, C., & Peigneux, P. (2007). A time to think: circadian rhythms in human cognition. *Cognitive neuropsychology*, 24(7), 755-789.
- Silver, R., & Kriegsfeld, L. J. (2014). Circadian rhythms have broad implications for understanding brain and behavior. *European Journal of Neuroscience*, 39(11), 1866-1880.
- Snider, K. H., Dziema, H., Aten, S., Loeser, J., Norona, F. E., Hoyt, K., & Obrietan, K. (2016). Modulation of learning and memory by the targeted deletion of the circadian clock gene Bmal1 in forebrain circuits. *Behavioural brain research*, 308, 222-235.
- Sollars, P. J., Pickard, G. E., & Sprouse, J. S. (2010). Serotonin and the regulation of mammalian circadian rhythms. In *Elsevier Ltd*.
- Souêtre, E., Salvati, E., Belugou, J. L., Pringuey, D., Candito, M., Krebs, B., ... & Darcourt, G. (1989). Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry research*, 28(3), 263-278.
- St-Amand, J., Provencher, M. D., Bélanger, L., & Morin, C. M. (2013). Sleep disturbances in bipolar disorder during remission. *Journal of affective disorders*, 146(1), 112-119.
- Pearson, Caryn, Teresa Janz and Jennifer Ali. (2013). "Mental and substance use disorders in Canada" *Health at a Glance*. September. Statistics Canada Catalogue no. 82-624-X.
- Ratnasingham, S., Cairney, J., Manson, H., Rehm, J., Lin, E., & Kurdyak, P. (2013). The burden of mental illness and addiction in Ontario. *The Canadian Journal of Psychiatry*, 58(8), 529-537.
- Robillard, R., Naismith, S. L., Rogers, N. L., Scott, E. M., Ip, T. K. C., Hermens, D. F., & Hickie, I. B. (2013). Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *European Psychiatry*, 28(7), 412-416.
- Suarez, E. C., Krishnan, R. R., & Lewis, J. G. (2003). The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosomatic medicine*, 65(3), 362-368.
- Sylvia LG, Dupuy JM, Ostacher MJ et al. Sleep disturbance in euthymic bipolar patients. J Psychopharmacol 2012;26:1108–1112.
- Talpos, J., & Steckler, T. (2013). Touching on translation. *Cell and tissue research*, 354(1), 297-308.
- Talpos, J. C., Winters, B. D., Dias, R., Saksida, L. M., & Bussey, T. J. (2009). A novel touchscreen-automated paired-associate learning (PAL) task sensitive to pharmacological manipulation of the hippocampus: a translational rodent model of cognitive impairments in neurodegenerative disease. *Psychopharmacology*, 205(1), 157-168.

- Thase, M. E. (1998). Depression, sleep, and antidepressants. *The Journal of clinical psychiatry*, *59*(suppl 4), 55-65.
- Turek, F. W., Joshu, C., Kohsaka, A., Lin, E., Ivanova, G., McDearmon, E., ... & Eckel, R. H. (2005). Obesity and metabolic syndrome in circadian Clock mutant mice. *Science*, 308(5724), 1043-1045.
- Tye, K. M., Mirzabekov, J. J., Warden, M. R., Ferenczi, E. A., Tsai, H. C., Finkelstein, J., ... & Gunaydin, L. A. (2013). Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*, 493(7433), 537-541.
- Ulbricht, C. M., Rothschild, A. J., & Lapane, K. L. (2015). The association between latent depression subtypes and remission after treatment with citalopram: a latent class analysis with distal outcome. *Journal of affective disorders*, *188*, 270-277.
- Valdez, P., Ramírez, C., García, A., Talamantes, J., Armijo, P., & Borrani, J. (2005). Circadian rhythms in components of attention. *Biological rhythm research*, *36*(1-2), 57-65.
- Van Dongen, H. P., & Dinges, D. F. (2000). Circadian rhythms in fatigue, alertness, and performance. *Principles and practice of sleep medicine*, *20*, 391-9.
- Van Cauter, E. (1990). Diurnal and ultradian rhythms in human endocrine function: a minireview. *Hormone Research in Paediatrics*, 34(2), 45-53.
- Vujovic, N., Gooley, J. J., Jhou, T. C., & Saper, C. B. (2015). Projections from the subparaventricular zone define four channels of output from the circadian timing system. *Journal of Comparative Neurology*, 523(18), 2714-2737.
- Wardlaw, S. M., Phan, T. X., Saraf, A., Chen, X., & Storm, D. R. (2014). Genetic disruption of the core circadian clock impairs hippocampus-dependent memory. *Learning & Memory*, 21(8), 417-423.
- Welsh DK, Takahashi JS, Kay SA. Suprachiasmatic nucleus: cell autonomy and network properties. Annu Rev Physiol. 2010;72:551–577.
- Winokur, A., Gary, K. A., Rodner, S., Rae-Red, C., Fernando, A. T., & Szuba, M. P. (2001). Depression, sleep physiology, and antidepressant drugs. *Depression and anxiety*, 14(1), 19-28.
- Woo, Y. S., Rosenblat, J. D., Kakar, R., Bahk, W. M., & McIntyre, R. S. (2016). Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clinical Psychopharmacology and Neuroscience*, 14(1), 1.
- Wright, K. P., Hull, J. T., & Czeisler, C. A. (2002). Relationship between alertness, performance, and body temperature in humans. *American Journal of Physiology-Regulatory*, *Integrative and Comparative Physiology*, 283(6), R1370-R1377.
- Wyatt, J. K., Ritz-De Cecco, A., Czeisler, C. A., & Dijk, D. J. (1999). Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 277(4), R1152-R1163.
- Zelinski, E. L., Deibel, S. H., & McDonald, R. J. (2014). The trouble with circadian clock dysfunction: multiple deleterious effects on the brain and body. *Neuroscience & Biobehavioral Reviews*, 40, 80-101.
- Zhu, C. B., Blakely, R. D., & Hewlett, W. A. (2006). The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology*, 31(10), 2121-2131.

Zwanzger, P., Domschke, K., & Bradwejn, J. (2012). Neuronal network of panic disorder: the role of the neuropeptide cholecystokinin. *Depression and anxiety*, *29*(9), 762-774.

	Stroop and CRTT used, one study actively assessed circadian rhythmicity while the other did not, no cross-species translation	Literature divided on whether or not ability to complete a task-shifting set disrupted with increased hours awake ^{14,19,20} , phase of performance time parallels CBT ⁸	×	```		<	Shifting/Flexibility
	Stroop and CRTT used, one study actively assessed circadian rhythmicity while other did not, no cross-species translation	Generally no impairment with increased hours awake, performance decline seen in afternoon with regard to response time ^{19, 20} , performance time displays 100- min phase delay with respect to CBT ²¹	z		``		Inhibition
	Consistency among throughput tasks detecting rhythm, no known cross-species translation	Circadian effects operating in early afternoon ^{16,17} , peaking every 21-27 hours with a decline in performance into biological night ¹⁸	Y	``			Throughput
	Consistency among divided attention tasks, no cross-species translation	SD slows performance on task-switching for accuracy ¹⁴ , performance decline with hours awake, performance better in early hours ¹⁵ , no circadian variation observed	Y	٢		٢	Multi-task/dual processing
		Executive Function					
	Serial reaction time task ¹² only known task to be performed, no cross-species validation	Very scarce literature on circadian rhythm detection in procedural memory; sequence learning possible under low and high sleep pressure conditions, where memory improved following naps after circadian peak of REM sleep ¹³	Y			٩	Procedural memory
	Parallelism to CBT consistent in recognition tasks, word/letter pairs, picture memorization, no cross-species task validation completed	Earlier papers denote rhythms in episodic memory parallel to CBT ^{11,12} , performance decline with increased hours awake, no known literature evaluating semantic memory rhythms	Y	<	<	۲	Declarative memory
Recall dependent on WM load ¹⁰ , tasks of grater complexity show greater variation in performance	Variations in rhythmicity seen with different tasks assessing phonological WM, visual WM, spatial WM, no cross-species task validation completed	Literature divided on whether or not performance rhythmicity exists, performance decline seen with hours awake into biological night. Parallelism to CBT seen ⁷ , as well as 1-3hr phase delays with respect to CBT ⁸ , other studies cite no TOD effects ⁹	γ	٢		<	Working memory
		Memory		-			
	Visual search does not seem to readily detect rhythms as CPT and PVT do, stability of correct responses declines with time awake, no "selective attention"- specific cross-species task validation complete	Literature divided on whether or not robust rhythm exists, performance decline seen with hours awake, possible that homeostatic and circadian factors modulate performance downstream from locus of selective attention, of which effects on global vigilance and alertness are strikingly different ⁶	Y	< <u> </u>		< <u> </u>	Selective attention
Performance on tasks modulated by TOT; greater performance variability seen with increased time awake	No task differences seen for detection. CPT translational task validation completed ⁴ , rodent analog of human PVT completed ⁵ : similar in global performance outcomes but outcomes of TOT and RSI differ in SD- induced impairments	Lowest errors of commission at 1h after CBT min and 16h after CBT max ¹ , generally mirroring CBT, no TOD sensitivity seen for RT, errors of omission; 1hr delay for RT and 3hr delay for % correct responses with respect to CBT ^{2,3}	Y	٩	< <u> </u>	<	Sustained attention/vigilance
	KSS & SSS mainly used for alertness measure, consistency in rhythm detection, no translational task validation	Generally stable through first 16h of waking day, decline as time awake increases, "after lunch" midday dip	Y	<u>۲</u>	<	٩	Alertness
		Attention		Ċ	t		
				SD	FD	CR	
Other	Task-sensitivity/Cross-species Translation?	Rhythm Detection (TOD)?	Impairments	Used	radigms	Pa_i	Domain

Table 1. A summary of the findings of circadian rhythmicity in cognitive performance in humans and cross-species translational validity. *CBT: Core body temperature; CPT: Continuous performance test; CRTT: Choice reaction time task; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor vigilance task; REM: Rapid eye movement; RSI: Response-stimulus interval; RT: Reaction time; SSS: Subjective Sleepiness Scale; TOD: Time of day; TOT: Time on task; WM: Working memory.* ¹Harrison et al., 2007; ³Valdez et al., 2010; ⁴Van Enkuizen et al., 2014; ⁵Oonk et al., 2015; ⁶Horowitz et al., 2006; ⁷Wright et al., 2002; ⁸Ramirez et al., 2012; ⁹Hidalgo et al., 2004; ¹⁰Folkard et al., 1976; ¹¹Johnson et al., 1992; ¹²Cajochen et al., 1999; ¹³Cajochen et al., 2004; ¹⁴Drummond et al., 2001; ¹⁵Couyoumidjan et al., 2010; ¹⁶Gordon et al., 1995; ¹⁷Van Dongen et al., 2010; ²⁰Thomas et al., 2000.

Chapter 5

Concluding Statements/Future Directions

Overview

In the study addressed in chapters 2 and 3, we aimed to examine the relationship between biological rhythm disruption and mood disorders, and to compare several parameters that measure circadian rhythmicity. We first did this by investigating group differences between objective and subjective measures of sleep and circadian rhythmicity, followed by an objective validation of the BRIAN. While the exact causal mechanisms involved in development of depression and bipolar disorder may never be fully understood, studies of its major determinants will provide valuable insight that will lead to improved clinical assessments, prevention methods and intervention.

Objective and Subjective Measures of Sleep and Biological Rhythm Disruption, and focus on the BRIAN

In chapter 2 we investigated group differences in objective and subjective measurements of sleep and circadian rhythm disruption in mood disorders and controls. In chapter 3 we provided a preliminary objective validation of the BRIAN against sleep and circadian variables. Our results revealed that objective and subjective sleep parameters show moderate agreement with each other, while objective and subjective measures of biological rhythm disturbance show mild agreement. While the majority of the mood sample was euthymic, participants in all four mood groups reported greater biological rhythm disruption compared to controls, whereas objective actigraphic measures of circadian rhythmicity did not detect differences. However, objective melatonin profiling obtained via urine sampling did show agreement with the BRIAN with regard to currently depressed BD displaying lowest melatonin levels, and highest BRIAN scores. The BRIAN also showed moderate correlation with mood groups between the sleep domain, actigraphic sleep parameters and urinary melatonin. This information provides some

promising external validity to the usefulness of questionnaires in the clinical setting for episode prediction, maintenance, and prevention.

Biological rhythms constitute a wide range of physiological and psychosocial functions that are assessed on the BRIAN, that were not addressed in this study. Further assessment of the activity, eating pattern and social domains with objective measures is imperative. As mentioned in chapter 3, the BRIAN social domain could be objectively assessed with the newly developed smartphone application, *MoodRhythm* (Matthews et al., 2016), which detects social rhythms from sensory activity monitored by the accelerometer in a cell phone, a factor that is based on the assumption that the phone is on the individual's person at all times. Although the BRIAN assesses overall biological rhythm disruption, an objective validation of each domain would provide clinicians with unequivocal data shedding light on which parameters of biological rhythms may be affected to a greater degree in patients, and how those domains contribute to inter-individual symptom severity. Furthermore, it may be of interest to test the BRIAN in populations with different psychiatric conditions if it is to be used as a clinical screening tool, so as to detect discriminant validity of the questionnaire (Moro et al., 2014). In our analyses conducted in chapter 2, the BRIAN did not detect differences between MDD and BD subjects, which could mean one of two things. Depression and bipolar disorder display similar pathophysiological mechanisms, and can be assessed for circadian disturbance using the same constructs, or, the BRIAN items require refining so to dissociate biological rhythm disruption in depression from mania.

It must be taken into consideration that the BRIAN questionnaire assesses biological rhythm disturbance over the last 15 days by means of self-report. The point of validating this questionnaire is to enable a quick, accurate, cost-efficient and feasible method of assessing disruption, however patients are likely subject to recall biases. While our actiwatches were monitoring subjects in one-minute epochs continuously for 15 days, the measurement the BRIAN

records is at one time point, asking subjects to recall events accurately for the two weeks prior, which could potentially be contributing to why we did not see greater group differences and correlations with circadian variables. In future it might be of interest to consider using the BRIAN weekly, or even have subjects complete the questionnaire once per day as part of a diagnostic assessment. This would also add insight into whether subjective biological rhythm disruption is a state or trait feature of affective disorders.

Circadian rhythms and cognition

In chapter 4 we looked at preclinical and clinical studies investigating the impact of circadian disturbance on cognition. Although the literature within and between species is inconsistent as to whether similar rhythmicity exists in cognitive domains, there are a few conclusions to address. The degree to which cognitive domains are affected by circadian disturbances varies. Alertness and attention tend to steadily increase and maintain a high level of performance throughout the waking day, displaying a decline around the 16h mark. In memory, both humans and animals have been reported to display rhythmicity that shows a 1-4h phase delay with respect to the CBT. Executive functions are more widely tested in humans than animals. Inhibition has been reported to act in a phase delay of about 100 minutes with respect to CBT and flexibility peaks early in the morning, as CBT is rising. To assess the robustness of these results, we are in the process of calculating effect sizes for both human and animal studies.

A major finding noted in the chapter 4 discussion is the lack of methodological harmony between human and animal studies. These are issues that must be addressed prior to assessing rhythmicity in cognitive variables. There are very few studies that begin with hypothesis-driven preclinical results that end with affirmative clinical results in neuropsychiatric disorders (Talpos & Steckler, 2013). Different tasks are used to assess the same parameter in humans (i.e. continuous performance test versus psychomotor vigilance task to assess aspects of sustained

attention and reaction time), and animals (i.e. Barnes Maze versus Morris Water Maze to evaluate spatial learning and memory), which are usually chosen at the investigator's discretion. It is difficult to make conclusions about deficits associated with circadian rhythm dysregulation in each species alone due to differences that may involve task sensitivity to rhythmicity. Moreover, a question is raised of task translation between species in order to provide feasible animal models that bear some approximation to higher complexities seen in humans (for example, episodic memory is thought to be unique to humans) (Keeler & Robbins, 2011). One approach researchers are taking involves "back-translation" from human models to animal models. Keeler & Robbins (2011) discuss the CANTAB Paired Associates Learning (PAL) task that evaluates features of visual memory and learning using a touch screen. Patients will recall several abstract visual objects with short delays between probe and recall, with increasing levels of difficulty. Several studies have modeled a PAL in rodents after the human CANTAB task (Bartko et al., 2011, Kim et al., 2015; Talpos et al., 2009), where similar effects of hippocampal deficits in humans have been observed in rodents. Translational models such as this will allow researchers to engage in a priori hypothesis testing in preclinical representations and provide meaningful clinical results, rather than making post hoc conclusions generalized between species (Talpos & Steckler, 2013).

Conclusion

The ultimate goal of this thesis was to investigate the relationship between objective and subjective circadian rhythm disturbances and mood disorders. This was done by comparing several measurements both self-reported and objectively that are known to be sensitive to dysregulation in mood. It is of importance to highlight the finding that BRIAN scores detect group differences similar to that of urinary melatonin measurements between controls and BD, suggesting lower levels of melatonin secretion are associated with greater subjective biological rhythm disturbance, a finding that was further corroborated by a significant correlation. Our results provide meaningful evidence of the use of subjective ratings in the clinical setting,

however further systematic objective validations are warranted. These findings further corroborate theories that circadian disturbance may be at core of mood disorders, which are an important target of intervention and prevention. We also investigated the impact of circadian rhythm dysregulation on cognitive performance. The results of this review provide promising evidence of using translational models to identify patterns of rhythmicity in cognitive domains of attention, memory and executive function, however much work still has to be done. This was of interest due to the known interaction between reduced cognitive capacity associated with circadian disturbance, and its involvement in mood (Boland & Alloy, 2013; McKenna & Tyler, 2012).

Additional References

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C: American Psychiatric Association.
- Bakish D. New standard of depression treatment: remission and full recovery. J Clin Psychiatry. 2001;62 Suppl 26: 5-9.
- Bartko, S. J., Romberg, C., White, B., Wess, J., Bussey, T. J., & Saksida, L. M. (2011). Intact attentional processing but abnormal responding in M 1 muscarinic receptor-deficient mice using an automated touchscreen method. *Neuropharmacology*, 61(8), 1366-1378.
- Betchel, W. (2015). Circadian rhythms and mood disorders: are the phenomena and mechanisms causally related? *Frontiers in psychiatry*, 6.
- Becker, C., Zeau, B., Rivat, C., Blugeot, A., Hamon, M., & Benoliel, J. J. (2008). Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. *Molecular psychiatry*, 13(12), 1079-1092.
- Benson, K. L., & Zarcone, V. P. (1993). Rapid eye movement sleep eye movements in schizophrenia and depression. *Archives of General Psychiatry*, 50(6), 474-482.
- Boivin, D. B., Czeisler, C. A., Dijk, D. J., Duffy, J. F., Folkard, S., Minors, D. S., ... & Waterhouse, J. M. (1997). Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Archives of General Psychiatry*, 54(2), 145-152.
- Boland, E. M., & Alloy, L. B. (2013). Sleep disturbance and cognitive deficits in bipolar disorder: toward an integrated examination of disorder maintenance and functional impairment. *Clinical psychology review*, 33(1), 33-44.
- Boudebesse, C., Geoffroy, P. A., Bellivier, F., Henry, C., Folkard, S., Leboyer, M., & Etain, B. (2014). Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiology international*, 31(5), 698-704
- Burgess, H. J., Trinder, J., Kim, Y., & Luke, D. (1997). Sleep and circadian influences on cardiac autonomic nervous system activity. *American Journal of Physiology-Heart and Circulatory Physiology*, 273(4), H1761-H1768.
- Cagampang, F. R., & Bruce, K. D. (2012). The role of the circadian clock system in nutrition and metabolism. *British Journal of Nutrition*, 108(03), 381-392.
- Cajochen, C., Khalsa, S. B. S., Wyatt, J. K., Czeisler, C. A., & Dijk, D. J. (1999). EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 277(3), R640-R649.
- Coque L, Mukherjee S, Cao JL, Spencer S, Marvin M, Falcon E, et al. (2011): Specific role of VTA dopamine neuronal firing rates and morphology in the reversal of anxiety-related, but not depression- related behavior in the ClockDelta19 mouse model of mania. Neuropsychopharmacology 36:1478–1488.
- Charmandari, E., Chrousos, G. P., Lambrou, G. I., Pavlaki, A., Koide, H., Ng, S. S. M., & Kino, T. (2011). Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man. *PLoS One*, 6(9), e25612.
- Chaudhury, D., & Colwell, C. S. (2002). Circadian modulation of learning and memory in fearconditioned mice. *Behavioural brain research*, 133(1), 95-108.

- Chung, S., Lee, E. J., Yun, S., Choe, H. K., Park, S. B., Son, H. J., ... & Son, G. H. (2014). Impact of circadian nuclear receptor REV-ERBα on midbrain dopamine production and mood regulation. *Cell*, *157*(4), 858-868.
- Depp CA, Strassnig M, Mausbach BT, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. Bipolar Disord. 2014;16(4):422-431.
- Devan, B. D., Goad, E. H., Petri, H. L., Antoniadis, E. A., Hong, N. S., Ko, C. H., ... & McDonald, R. J. (2001). Circadian phase-shifted rats show normal acquisition but impaired long-term retention of place information in the water task. *Neurobiology of learning and memory*, 75(1), 51-62.
- Dijk, D. J., Duffy, J. F., & Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *Journal of sleep research*, 1(2), 112-117.
- Dockray, G. J. (2012). Cholecystokinin. Current Opinion in Endocrinology, Diabetes and Obesity, 19(1), 8-12.
- Duffy, A., Grof, P., & Alda, M. (2000). The implications of genetic studies of major mood disorders for clinical practice. *The Journal of clinical psychiatry*, 61(9), 630-637.
- Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. J Clin Psychiatry. 2009;70 (suppl 3):22-29.
- Faria, A. D., de Azevedo Cardoso, T., Mondin, T. C., de Mattos Souza, L. D., da Silva Magalhaes, P. V., Zeni, C. P., ... & Jansen, K. (2015). Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. *Journal of affective disorders*, 186, 145-148.
- Geoffroy PA, Boudebesse C, Bellivier F et al. Sleep in remitted bipolar disorder: a naturalistic case-control study using actigraphy. J Affect Disord 2014;158:1–7.
- Giglio, L. M., Magalhães, P. V., Kapczinski, N. S., Walz, J. C., & Kapczinski, F. (2010). Functional impact of biological rhythm disturbance in bipolar disorder. *Journal of psychiatric research*, 44(4), 220-223.
- Gnam W., S.-H.A., Mustard C., Rush B., Lin E., 2006. The economic costs of mental disorders and alcohol, tobacco, and illicit drug abuse in Ontario, 2000: a cost-of-illness study. Centre for Addiction and Mental Health Toronto.
- Gooley, J. J., Lu, J., Chou, T. C., Scammell, T. E., & Saper, C. B. (2001). Melanopsin in cells of origin of the retinohypothalamic tract. *Nature neuroscience*, 4(12), 1165-1165.
- Gritton, H. J., Kantorowski, A., Sarter, M., & Lee, T. M. (2012). Bidirectional interactions between circadian entrainment and cognitive performance. *Learning & Memory*, 19(3), 126-141.
- Gulevich, G. D., Dement, W. C., & Zarcone, V. P. (1967). All-night sleep recordings of chronic schizophrenics in remission. *Comprehensive psychiatry*, 8(3), 141-149.
- Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W. A., & Beekman, A. T. F. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica*, 122(3), 184-191.
- Harrington, M. E., & Rusak, B. (1988). Ablation of the geniculo-hypothalamic tract alters circadian activity rhythms of hamsters housed under constant light. *Physiology & behavior*, 42(2), 183-189.

- Henry C, van den Bulke D, Bellivier F et al. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. Psychiatry Res 2008;159:1–6.
- Hinton, J. M. (1963). Patterns of insomnia in depressive states. Journal of Neurology, Neurosurgery & Psychiatry, 26(2), 184-189.
- Hidalgo, M. P. L., Zanette, C. B., Pedrotti, M., Souza, C. M., Nunes, P. V., & Chaves, M. L. F. (2004). Performance of chronotypes on memory tests during the morning and the evening shifts. *Psychological reports*, 95(1), 75-85.
- Hirschfeld RM, Dunner DL, Keitner G, Klein DN, Koran LM, Kornstein SG, et al. Does psychosocial functioning improve independent of depressive symptoms? A compari- son of nefazodone, psychotherapy, and their combination. Biol Psychiatry 2002;51:123-133.
- Hong, C. J., Huo, S. J., Yen, F. C., Tung, C. L., Pan, G. M., & Tsai, S. J. (2003). Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology*, 48(4), 186-189.
- Horowitz, T., & Wolfe, J. (2003). Memory for rejected distractors in visual search?. Visual Cognition, 10(3), 257-298.
- Huang N, Chelliah Y, Shan Y, Taylor CA, Yoo SH, Partch C, Green CB, Zhang H, Takahashi JS. Crystal structure of the heterodimeric CLOCK:BMAL1 transcriptional activator complex. Science. 2012;337:189–194.
- Judd, L. L., Schettler, P. J., Akiskal, H. S., Coryell, W., Leon, A. C., Maser, J. D., & Solomon, D. A. (2008). Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Archives of general psychiatry*, 65(4), 386-394.
- Keeler, J. F., & Robbins, T. W. (2011). Translating cognition from animals to humans. *Biochemical pharmacology*, *81*(12), 1356-1366.
- Kim, C. H., Heath, C. J., Kent, B. A., Bussey, T. J., & Saksida, L. M. (2015). The role of the dorsal hippocampus in two versions of the touchscreen automated paired associates learning (PAL) task for mice. *Psychopharmacology*, 232(21-22), 3899-3910.
- Krawczak, E. M., Minuzzi, L., Hidalgo, M. P., & Frey, B. N. (2016). Do changes in subjective sleep and biological rhythms predict worsening in postpartum depressive symptoms? A prospective study across the perinatal period. *Archives of women's mental health*, 1-8.
- Kripke, D. F., Mullaney, D. J., Atkinson, M., & Wolf, S. (1978). Circadian rhythm disorders in manic-depressives. *Biological psychiatry*.
- Lewy, A. J., Sack, R. L., Singer, C. M., & White, D. M. (1987). The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. *Psychopharmacology Bulletin*, 23(3), 349.
- Lopez AD, Murray CC (1998) The global burden of disease, 1990–2020. Nat Med 4: 1241–1243. pmid:9809543. doi: 10.1038/3218
- Magalhaes PV, Kapczinski F, Nierenberg AA, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012;125(4):303-308.
- Manning, J. S. (2015). Bipolar disorder, bipolar depression, and comorbid illness. Journal of Family Practice, 64(6), S10-S10.
- Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., ... & Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and

euthymic states in bipolar disorder. American Journal of Psychiatry, 161(2), 262-270.

- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, Kessler RC (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 64:543–552.
- Miller, T. H. (2016). Bipolar Disorder. Primary Care: Clinics in Office Practice, 43(2), 269-284.
- Miller, I. W., Keitner, G. I., Schatzberg, A. F., Klein, D. N., Thase, M. E., Rush, A. J., ... & Davis, S. M. (1998). The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *The Journal of clinical psychiatry*, 59(11), 608-619.
- Mondin, T. C., de Azevedo Cardoso, T., Jansen, K., da Silva, G. D. G., de Mattos Souza, L. D., & da Silva, R. A. (2015). Long-term effects of cognitive therapy on biological rhythms and depressive symptoms: A randomized clinical trial. *Journal of affective disorders*, 187, 1-9.
- Morin, L. P. (2013). Neuroanatomy of the extended circadian rhythm system. *Experimental neurology*, 243, 4-20.
- Morin, L. P., & Allen, C. N. (2006). The circadian visual system, 2005. *Brain research reviews*, 51(1), 1-60.
- Moro, M. F., Carta, M. G., Pintus, M., Pintus, E., Melis, R., Kapczinski, F., ... & Colom, F. (2014). Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): Some Considerations on its Screening Usefulness. *Clinical practice and epidemiology in mental health: CP & EMH*, 10, 48.
- Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remis- sion of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol Med 2010;40(1):41–50.
- Patten, S. B., Williams, J. V., Lavorato, D. H., Wang, J. L., McDonald, K., & Bulloch, A. G. (2015). Descriptive epidemiology of major depressive disorder in Canada in 2012. *The Canadian Journal of Psychiatry*, 60(1), 23-30.
- Patton, D. F., & Mistlberger, R. E. (2013). Circadian adaptations to meal timing: neuroendocrine mechanisms. *Frontiers in neuroscience*, 7, 185.
- Phan, T. H., Chan, G. C. K., Sindreu, C. B., Eckel-Mahan, K. L., & Storm, D. R. (2011). The diurnal oscillation of MAP (mitogen-activated protein) kinase and adenylyl cyclase activities in the hippocampus depends on the suprachiasmatic nucleus. *The Journal of Neuroscience*, 31(29), 10640-10647.
- Price, A. L., & Marzani-Nissen, G. R. (2012). Bipolar disorders: a review. *Am Fam Physician*, 85(5), 483-493.
- Ramírez, C., Talamantes, J., García, A., Morales, M., Valdez, P., & Menna-Barreto, L. (2006). Circadian rhythms in phonological and visuospatial storage components of working memory. *Biological Rhythm Research*, 37(5), 433-441.
- Refinetti, R. (2010). Entrainment of circadian rhythm by ambient temperature cycles in mice. *Journal of biological rhythms*, 25(4), 247-256.
- Rosenthal, N. E., Joseph-Vanderpool, J. R., Levendosky, A. A., Johnston, S. H., Allen, R., Kelly, K. A., ... & Starz, K. E. (1990). Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep*, 13(4), 354-361.

- Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatr Serv. 2009;60(2): 147-156.
- Rumble, M. E., White, K. H., & Benca, R. M. (2015). Sleep disturbances in mood disorders. *Psychiatric Clinics of North America*, 38(4), 743-759.
- Schaffer, A., Cairney, J., Cheung, A., Veldhuizen, S., & Levitt, A. (2006). Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics. *The Canadian Journal of Psychiatry*, 51(1), 9-16.
- Schmidt, C., Collette, F., Cajochen, C., & Peigneux, P. (2007). A time to think: circadian rhythms in human cognition. *Cognitive neuropsychology*, 24(7), 755-789.
- Silver, R., & Kriegsfeld, L. J. (2014). Circadian rhythms have broad implications for understanding brain and behavior. *European Journal of Neuroscience*, 39(11), 1866-1880.
- Snider, K. H., Dziema, H., Aten, S., Loeser, J., Norona, F. E., Hoyt, K., & Obrietan, K. (2016). Modulation of learning and memory by the targeted deletion of the circadian clock gene Bmal1 in forebrain circuits. *Behavioural brain research*, 308, 222-235.
- Sollars, P. J., Pickard, G. E., & Sprouse, J. S. (2010). Serotonin and the regulation of mammalian circadian rhythms. In *Elsevier Ltd*.
- Souêtre, E., Salvati, E., Belugou, J. L., Pringuey, D., Candito, M., Krebs, B., ... & Darcourt, G. (1989). Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry research*, 28(3), 263-278.
- St-Amand, J., Provencher, M. D., Bélanger, L., & Morin, C. M. (2013). Sleep disturbances in bipolar disorder during remission. *Journal of affective disorders*, 146(1), 112-119.
- Pearson, Caryn, Teresa Janz and Jennifer Ali. (2013). "Mental and substance use disorders in Canada" *Health at a Glance*. September. Statistics Canada Catalogue no. 82-624-X.
- Ratnasingham, S., Cairney, J., Manson, H., Rehm, J., Lin, E., & Kurdyak, P. (2013). The burden of mental illness and addiction in Ontario. *The Canadian Journal of Psychiatry*, 58(8), 529-537.
- Robillard, R., Naismith, S. L., Rogers, N. L., Scott, E. M., Ip, T. K. C., Hermens, D. F., & Hickie, I. B. (2013). Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *European Psychiatry*, 28(7), 412-416.
- Suarez, E. C., Krishnan, R. R., & Lewis, J. G. (2003). The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosomatic medicine*, 65(3), 362-368.
- Sylvia LG, Dupuy JM, Ostacher MJ et al. Sleep disturbance in euthymic bipolar patients. J Psychopharmacol 2012;26:1108–1112.
- Talpos, J., & Steckler, T. (2013). Touching on translation. *Cell and tissue research*, 354(1), 297-308.
- Talpos, J. C., Winters, B. D., Dias, R., Saksida, L. M., & Bussey, T. J. (2009). A novel touchscreen-automated paired-associate learning (PAL) task sensitive to pharmacological manipulation of the hippocampus: a translational rodent model of cognitive impairments in neurodegenerative disease. *Psychopharmacology*, 205(1), 157-168.

- Thase, M. E. (1998). Depression, sleep, and antidepressants. *The Journal of clinical psychiatry*, *59*(suppl 4), 55-65.
- Turek, F. W., Joshu, C., Kohsaka, A., Lin, E., Ivanova, G., McDearmon, E., ... & Eckel, R. H. (2005). Obesity and metabolic syndrome in circadian Clock mutant mice. *Science*, 308(5724), 1043-1045.
- Tye, K. M., Mirzabekov, J. J., Warden, M. R., Ferenczi, E. A., Tsai, H. C., Finkelstein, J., ... & Gunaydin, L. A. (2013). Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*, 493(7433), 537-541.
- Ulbricht, C. M., Rothschild, A. J., & Lapane, K. L. (2015). The association between latent depression subtypes and remission after treatment with citalopram: a latent class analysis with distal outcome. *Journal of affective disorders*, *188*, 270-277.
- Valdez, P., Ramírez, C., García, A., Talamantes, J., Armijo, P., & Borrani, J. (2005). Circadian rhythms in components of attention. *Biological rhythm research*, *36*(1-2), 57-65.
- Van Dongen, H. P., & Dinges, D. F. (2000). Circadian rhythms in fatigue, alertness, and performance. *Principles and practice of sleep medicine*, *20*, 391-9.
- Van Cauter, E. (1990). Diurnal and ultradian rhythms in human endocrine function: a minireview. *Hormone Research in Paediatrics*, 34(2), 45-53.
- Vujovic, N., Gooley, J. J., Jhou, T. C., & Saper, C. B. (2015). Projections from the subparaventricular zone define four channels of output from the circadian timing system. *Journal of Comparative Neurology*, 523(18), 2714-2737.
- Wardlaw, S. M., Phan, T. X., Saraf, A., Chen, X., & Storm, D. R. (2014). Genetic disruption of the core circadian clock impairs hippocampus-dependent memory. *Learning & Memory*, 21(8), 417-423.
- Welsh DK, Takahashi JS, Kay SA. Suprachiasmatic nucleus: cell autonomy and network properties. Annu Rev Physiol. 2010;72:551–577.
- Winokur, A., Gary, K. A., Rodner, S., Rae-Red, C., Fernando, A. T., & Szuba, M. P. (2001). Depression, sleep physiology, and antidepressant drugs. *Depression and anxiety*, 14(1), 19-28.
- Woo, Y. S., Rosenblat, J. D., Kakar, R., Bahk, W. M., & McIntyre, R. S. (2016). Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clinical Psychopharmacology and Neuroscience*, 14(1), 1.
- Wright, K. P., Hull, J. T., & Czeisler, C. A. (2002). Relationship between alertness, performance, and body temperature in humans. *American Journal of Physiology-Regulatory*, *Integrative and Comparative Physiology*, 283(6), R1370-R1377.
- Wyatt, J. K., Ritz-De Cecco, A., Czeisler, C. A., & Dijk, D. J. (1999). Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 277(4), R1152-R1163.
- Zelinski, E. L., Deibel, S. H., & McDonald, R. J. (2014). The trouble with circadian clock dysfunction: multiple deleterious effects on the brain and body. *Neuroscience & Biobehavioral Reviews*, 40, 80-101.
- Zhu, C. B., Blakely, R. D., & Hewlett, W. A. (2006). The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology*, 31(10), 2121-2131.

Zwanzger, P., Domschke, K., & Bradwejn, J. (2012). Neuronal network of panic disorder: the role of the neuropeptide cholecystokinin. *Depression and anxiety*, *29*(9), 762-774.