Clinical Associations of Chronotypes in Adolescents and Young Adults with Mental Disorders

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Declaration of Originality

To the best of my knowledge, this thesis contains no copy or paraphrase of work published by another person, accept where duly acknowledged in the text. This thesis contains no material that has been presented for a degree at the University of Sydney or any other University.

Co-Author Declaration

We the undersigned acknowledge the following statement:

This thesis principally represents the work of Miss Sarah Fares. A/Prof Sharon Naismith provided considerable support in all the empirical studies and in the preparation of the Introduction, Methods and Discussion chapters of this thesis. A/Prof Rebecca Robillard support was most prominent in study design, data interpretation and in the editing of written work. A/Prof Sharon Naismith provided a great amount of support in all the empirical studies and provided critical review of the Methods and Discussion chapters of this thesis. Prof Ian Hickie and Dr Daniel Hermens provided assistance with study design and comments on manuscript drafts for the papers on which they are authors. Django White also provided assistance with data collection and interpretation as well as providing comments on manuscript drafts for the papers.

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Declaration of Scientific Work

This thesis comprises two studies conducted in collaboration with the aforementioned co-authors. While these co-authors have been instrumental in the study design, program implementation, data collection, data interpretation and providing critical review of the manuscripts, I played a key role in the analysis of the data provided in this thesis. In terms of data collection, I assisted with the clinical assessments and collection of data for the two studies, and I provided program support in other areas as needed. In addition I completed the processing and analysis of all magnetic resonance imaging data used in the studies. I was responsible for all the statistical analyses presented in the manuscripts comprising this thesis and as previously stated, with the assistance of co-authors, the preparation and publication of all the work presented. Finally under the supervision of Rebecca Robillard, I assisted in conducting overnight sleep assessments for studies not involved with this thesis.

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Abstract

Youth represents a sensitive period for the onset of both circadian disturbances and mental disorders. There are some suggestions that circadian disturbances may be an early feature or may directly contribute to the emergence, perpetuation, and recurrence of some mental disorders, particularly affective disorders. A person's 'chronotype' characterises their circadian preferences for early or late bed and wake times and their peak cognitive and physical activities across the 24-hour period. In this thesis, the chronotype of young persons with various mental disorders is examined.

Study 1 evaluated chronotypes, as assessed with the Horne-Östberg questionnaire, in young people with emerging anxiety, depression, bipolar, or psychotic disorders and healthy controls. Associations between Morningness-Eveningness preference and the severity of various psychiatric symptoms were assessed. Four hundred and ninety-six individuals aged 12-30 years (mean age + SD: 19.5 + 4.2) were divided according to primary diagnosis and were assessed with the Social and Occupational Functioning Scale (SOFAS), the Hamilton Depression Rating Scale (HDRS), the Brief Psychiatric Rating Scale (BPRS), the Kessler Psychological Distress Scale (K10) and the Horne-Östberg Morningness-Eveningness questionnaire (ME). A significant diagnostic group effect was found for the ME (ANOVA: $F_{(4, 491)} = 9.1$, $p < 0.001$) and remained significant after controlling for age and gender (ANCOVA: $F_{(4, 489)} = 8.2$, $p < 0.001$). Post hoc tests showed that the anxiety ($p < 0.001$), depression ($p < 0.001$), bipolar ($p < 0.001$) and psychosis ($p = 0.045$) groups had significantly lower ME scores (i.e. higher eveningness) compared to the control group. Significant negative correlations were found between clinical scales (i.e. HDRS, BPRS, SOFAS, K10) and ME for all diagnostic groups, suggesting that participants with more pronounced eveningness had worse symptom severity than those with more pronounced morningness.

Study 2 examined temporal variations in chronotypes and investigated longitudinal associations between changes in Morningness-Eveningness preference and changes in symptom profiles in 133 young people (12-35 years) with primary depression or bipolar disorder. From a categorical perspective, 33% of all participants shifted to a later chronotype from baseline to follow-up ($F_{(1, 105)} = 7.5$, $p = 0.007$). After controlling for age, gender and longitudinal period length, significant interactions showed that participants who shifted to earlier chronotypes showed more prominent longitudinal improvements in depressive ($F_{(1, 108)} = 4.6$, $p = 0.035$) and negative ($F_{(1, 115)} = 6.6$, $p = 0.011$) symptoms on the BPRS than participants who remained in the same chronotype category or shifted to later chronotypes.

The results obtained from these studies suggest that many young persons with emerging mental disorders present with a strong eveningness preference, which is in turn associated with worse clinical profiles. Longitudinally, those persons with depression or bipolar disorder who shift towards more morningness also showed the strongest clinical improvements. Overall, these findings suggest that evening chronotypes are associated with worse psychiatric symptom severity and highly likely to be reflective of state changes across the course of mental illnesses. These findings have implications for clinical practice in young persons with emerging mental disorders. Morningness-Eveningness preference is unlikely to be a static trait in the context of youth and mental disorders. Treatment strategies targeting the circadian system are highly likely to be relevant for patients presenting with affective disorders and late chronotypes.

List of Tables and Figures

Chapter 1

Thesis Overview

This thesis presents findings from two studies that examined morningness-eveningness preference for sleep, wake time and cognitive/physical activity (i.e. chronotype) in young people with primary anxiety, depression, bipolar, or psychotic disorders. The initial study is the first study to investigated associations between morningness-eveningness preference and the severity of various psychiatric symptoms across primary diagnosis subgroups. Studies in the past have looked at the association between chronotype and depression, anxiety, bipolar or psychosis separately; however this is the first study to compare the association across all primary diagnostic subgroups. The second study assessed the association between longitudinal changes in chronotype and psychiatric symptomatology.

The GENERAL INTRODUCTION section begins with the epidemiology of mental disorders, followed by an overview of chronotype and circadian systems. The characteristics of circadian rhythms during adolescence, and the intrinsic and extrinsic factors that influence psychiatric disorders are then discussed. The association between chronotype, circadian rhythms, and mood in mental disorders emerging during adolescence are then addressed. This is followed by sleep behaviour in youth. Lastly, the general introduction addresses risk factors for developing mental disorders during youth, as well as possible associations between circadian and chronotype changes and different types of mental disorders. This section ends with a description of the main aims of these studies and their respective hypotheses.

The METHODS section describes the details of the participants, procedures and measurements involved in the two studies. The statistical methods used to test the hypotheses are also reported.

The final GENERAL DICUSSION section brings together the overall findings related to each initial study aim. This section also highlights the relationship between the two studies and previous findings. Study limitations, clinical implications, and future directions are also discussed.

General Introduction

1.1 Mental Disorders: Prevalence and Chronicity

Mental disorders are currently one of the leading causes of disability worldwide, and one of the leading causes of burden of disease and injury in Australia (The Australian Bureau of Statistics 2009; Ohaeri 2003). On the basis of health economic measures and epidemiological data, the severity of mental disorders has been identified to be a major health issue, with major depression anticipated to be responsible for the largest burden of disease in the general population within the next 25 years (Kessler et al. 2009). Mood disorders are the second most common mental health disorders worldwide, with anxiety being the first (Kessler et al. 2005; Brucusa and Lacono 2007; Conradi et al. 2008). Unfortunately, persons with mental disorders often do not seek help and therefore do not receive the necessary treatments (Metraux et al. 2012), resulting in poorer quality of life and social functioning (WHO 2002).

The Composite International Diagnostic Interview (WHO 1997) has been used to identify the incident rates of various mental disorders in adults worldwide based on the major psychiatric classification systems: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Results in 10,641 participants (mostly adults aged between 18 and 35 years) highlighted frequent psychological distress due to the low consultation rates among those with disability and multiple concurrent disorders (Andrews et al. 2001). In 2007, the Australian Bureau of Statistics conducted a national survey which measured the mental health and wellbeing of individuals aged between 16 and 86 years. It was estimated that 7.2 million Australians (45% of all respondents) had experienced a mental disorder at some point in their lifetime, with mood disorders currently affecting 6% of that subgroup (Australian Bureau of Statistics 2007).

Sleep disturbances and circadian disruptions are among the most common symptoms in mental disorders (Kessler et al. 2005) and may likely play a role in the pathogenesis of mood disorders (Germain and Kupfer 2008). Such common disruptions include changes in core body temperature, as well as in cortisol and melatonin secretion (Srinivasan et al. 2009a; Brown et al. 2004; Koorengevel et al. 2000). These disruptions are associated with increased severity and chronicity of mood disturbances (McClung 2007; Kudielka et al. 2007).

1.1.1 Anxiety disorders

Many adolescents experience anxiety related to social and environmental factors as they are forming their sense of identity (Last et al. 1997). Severe levels of anxiety are correlated with negative outcomes such as difficulties with peer relationships, drug abuse, academic issues, and the onset of comorbid disorders (e.g. major depressive disorder) (Reavley et al. 2010). Anxiety is typically tied to pervasive feelings of nervousness, fear, apprehension, and worry (Ritzman 1988). Low levels of fear and anxiety are common and are considered normal; however, when their intensity increases, these emotions may affect daily functioning. For instance, anxiety can impact on performance levels, social life, cognition and emotional regulation. Adolescents with high levels of anxiety face difficult challenges. For example, anxiety is highly likely to have a negative influence on relationships, academic results, and future comorbidities (Collimore and Rector 2014; Fulford 2015; Pabst et al. 2009; Ritzman 1988; Tully et al. 2009).

Anxiety disorders are the most common type of mental illnesses found in adolescents in the United States, affecting 5.7% to 28.8% of young people (Kessler et al. 1994; Costello et al. 2003; Kashani and Orvaschel 1988). Similarly, in Australia, anxiety disorders are also the most common mental illness experienced during youth, affecting roughly one in every 10 young persons aged 18 to 24 years (Reavley et al. 2010). Social anxiety and post-traumatic stress disorder have been reported to be the most common types of anxiety disorders (Kessler

et al. 2007). Serious anxiety symptoms often emerge around the age of 11 years, which is significantly younger than the age of onset typically reported for the majority of other mental disorders (Kessler et al. 2005). Of note, the age of onset varies depending on the type of anxiety disorder. For example, separation anxiety and particular specific phobias often occur at a younger age than panic disorder, generalised anxiety disorder, and post-traumatic stress disorder (Kessler et al. 2007). It is important to identify the factors associated with anxiety in younger people, as they in turn inform targeted interventions.

There is an increase in the prevalence of anxiety symptoms in adolescence (Boyd et al. 2000). In many youth cases symptoms are present, but do not meet full criteria for anxiety disorders, therefore young persons are left untreated which can lead to insidious emotional, behavioural and functional difficulties. The prevalence of significant symptoms suggestive of any anxiety disorders during adolescence is 32% (Boyd et al. 2000). Another study showed that anxiety disorders are one of the most common mental disorders found in youth, with a prevalence of 19% over a period of 12 months in those aged 12–19 years (Essau et al. 2002). Importantly, some studies have identified a high prevalence of sub-clinical anxiety symptoms in adolescents which often cause considerable psychological distress. These findings highlight the importance of identifying and treating early signs of anxiety to minimise their impact on global mental health and well-being.

1.1.2 Depression

Young persons with depression typically present with low mood, lack of pleasure or interest in occupational and social activities, lack of motivation, increased/decreased appetite, sleep disruption, diminished concentration, negative thoughts, as well as suicidal thoughts and actions (Boyd et al. 2000). Insomnia was classified as a symptom of depression until 1996, when Breslau identified how insomnia was a condition of its self and no longer just a symptom (Breslau, 1996). In many cases, depression first appears in adolescence, with

prodromal symptoms recognised during early teens (Bridge and Brent 2004; Burke et al. 2005). There are a number of factors that influence the risk of depression, including genetic vulnerability (i.e. when the illness has affected other family members) (Serretti et al. 2003). The first episode of depression is also often influenced by stressful life events, such as family problems and social or work related issues (Burke et al. 2005). Low self-esteem and low self-efficacy, often resulting in a sense of hopelessness, as well as fluctuating mood also characterise the early stages of depression (McClung 2007). In Australia, the lifetime prevalence of depression is high. Epidemiological studies have shown that one in every five adolescents may be diagnosed with unipolar depression by the age of 18 years (Birmaher et al. 1996; Lewinsohn et al. 1993). It is also estimated that every year roughly 7% of individuals aged 16 to 24 years go through a depressive episode *(Australian Bureau of Statistics 2007)*. Depressive symptoms are higher in female (8.4%) than in male (4.3%) adolescents *(Australian Bureau of Statistics 2007)*. The World Health Organisation (WHO) estimates that depression will be the number one health concern across all nations by 2030 (WHO 2008). Diagnosis, treatment, and intervention strategies for depression are of high importance as they are likely to have a strong impact on global population health. Therefore, understanding some of the factors that may influence depression, such as developmental changes and circadian disruptions, is indeed crucial.

Longitudinal studies of clinical populations in various communities suggest that depressive episodes remit within one year for 60 to 90% of adolescents (Brucusa and Lacono 2007). Furthermore, a follow-up study identified that 50 to 70% of patients whose symptoms remit experience further depressive episodes within five years (Dunn and Goodyer 2006). When depression persists over a considerable length of time, there is often an increase in depressive symptom severity and in comorbidity with other mental illnesses, such as anxiety disorders

(Andrews et al. 2001). Therefore, understanding the factors influencing the development and chronicity of depressive symptoms is imperative.

1.1.3 Bipolar disorder

Bipolar disorder is a chronic and severe mood disorder characterised by the presence of mania or hypomania (Woznaik et al. 1995). Emotional changes (fluctuating mood) are the core feature of this neuropsychiatric disorder. Manic states are characterised by elevated mood, an increase in impulsive and spontaneous behaviour (e.g. talkativeness, participation in risky activities, excessive spending and increased sexual activity), grandiosity, concentration difficulties, and decreased sleep duration combined with high subjective energy levels (Fears and Reus 2015). Studies have shown dysfunction in behaviour, attention, working memory, and emotional processing during manic states (Hantouche and Akiskal 2005). In the depressive state of bipolar disorder, patients show signs of low-mood, poor motor skills, suicidal thoughts, fatigue, and memory impairments (Fears and Reus 2015). Euthymia is a 'normal' state during which patients are not in a manic or depressive episode. Unfortunately, the time between the first manic episode and a formal diagnosis of bipolar disorder may range from 5 to 10 years (Grunze 2015).

Individuals who suffer from bipolar I disorder, experience a cycle of extreme mood fluctuations between depression and mania. Individuals with bipolar II disorder experience hypomania (Grunze 2015). Despite the fact that both manic and depressive phases are intense, individuals with bipolar disorder spend more time in the depressive phase, which can make it challenging to accurately diagnose bipolar disorder (Hantouche and Akiskal 2005). The primary stages of bipolar disorder are often quite difficult to diagnose due to similar symptomology to depression. Therefore, management is also quite problematic. Initially, bipolar disorder can be perceived as unipolar depression until a clear manic/hypomanic

episode occurs. In addition, epidemiological studies show that the incidence of unipolar depression is three times higher than that of bipolar disorder (Weissman et al. 1996). A study highlighting the complexity associated with diagnosing and managing bipolar disorder showed that 47% of individuals with bipolar disorder were initially diagnosed with unipolar depression, noting it took approximately 7 years on average to properly diagnose these individuals with bipolar disorder (Ghaemi et al. 1999). This leads to a delay in the implementation of appropriate treatment and management strategies (Hantouche and Akiskal 2005).

In Australia, bipolar disorder is estimated to affect at least one in every 100 people at some point during their lifetime (AIHW 2007). Approximately 0.7% of males and 1.0% of females aged 18 to 24 years have an episode of mania in a given year (Faust et al. 2006; Mitchell et al. 2004). Bipolar disorder is the tenth leading disorder contributing to the burden of disease and injury in Australia for males aged between 15 and 24 years, and is the ninth for females in the same age range (AIHW 2007). Roughly 50% of people with bipolar disorder will develop this disorder by their early to mid-20's (Jablensky et al. 2000). The clinical profile of bipolar disorder varies between youth and older adults. A longitudinal study compared outpatient visits between youths and adults during a period of 4 years (Moreno et al. 2007). It was found that most visits by youths with bipolar disorder were made by males (66.5%), whereas most visits by older adults with bipolar disorders were made by females (67.6%). This study also found that youth with bipolar disorder were more likely to receive a comorbid diagnosis of attention-deficit/hyperactivity disorder than older adults. Also, youth patients received higher rate of prescribed psychotropic medications than older adults. Like depression, there are various risk factors that influence the development of bipolar disorder. These include genetic vulnerability, psychological factors such as emotional or physical

abuse, lifestyle stressors, and biological factors such as birth complications and circadian rhythms abnormalities (Fears and Reus 2015).

During the early stages of bipolar disorder, patients who are inaccurately diagnosed with unipolar depression often get treated with antidepressant drugs such as selective serotonin re-uptake inhibitors. These drugs can contribute to the emergence of manic episodes, thus leading to adverse consequences in the presence of underlying bipolar disorders (Berk et al. 2007). In such cases where there are delays in the formal diagnosis of bipolar disorder, patients may not receive appropriate medications, such as lithium or other mood stabilisers shown to be effective for bipolar disorder. There are some indications that lithium is a more effective intervention early in the course of the disorder and that its efficacy deteriorates after several mood episodes (Perlis et al. 2004). Early and accurate diagnoses, as well as implementation of appropriate therapeutic strategies, are thus crucial when managing bipolar disorder.

1.1.4 Psychotic disorders

Psychotic disorders are characterised by changes in how a person views and interprets reality, often affecting emotional, perceptual, behavioural and cognitive functioning. Emotional and perceptual changes related to psychotic disorders include mood swings, feeling fewer emotions than other individuals, feelings of detachment from one's thoughts, feeling that one's surroundings are not real, and hallucinations (Kapalka 2010). Behavioural changes include social isolation, issues interacting with work colleagues, peers or family members, and motivational problems. Lastly, cognitive changes include delusional thinking, fixed thoughts, atypical reasoning, and impaired concentration (Evans 1982). In addition, persons with psychotic disorders often have disorganised and disrupted sleeping patterns (Franzen and Buysse 2009). Psychosis has been shown to be heritable, but is also known to have environmental influences (Os et al. 2004). Recent studies have identified that schizophrenia

results from the interaction of environmental and genetic factors that leads to changes in the brain occurring simultaneously with the maturation of the central nervous system (Oertel-Knochel et al. 2011).

A psychotic episode affects around one in every 100 Australians (AIHW 2007). In Australia, approximately 0.2 to 0.3% of females and 0.3 to 0.5% of males aged 18-24 years are diagnosed and treated for psychosis (Jablensky 2000). Roughly, 50% of individuals who develop a psychotic disorder will develop it during their early 20's, but the age of onset is reportedly slightly older in females than males (Jablensky et al. 2000; Kessler et al. 2007). In Australians between 15 and 24 years of age, schizophrenia is the third for males and fifth for females leading mental disorder and contributor to the burden of disease and injury respectively (AIHW 2007).

Psychotic disorders are a diverse group of illnesses including schizophrenia, schizoaffective disorder, delusional disorder (Hodgman 2006; Pencer et al. 2005; Henderson 1985). A study by Johns and colleagues highlighted that persons of African-Caribbean background were 2.5 times more likely to admit to hallucinations than the white British population (Johns et al. 2002). Similarly, another study demonstrated that psychotic symptoms were more pronounced in persons of African-Caribbean ethnicity than by white British children (Laurens et al. 2008). Despite the fact that such studies did not find a significant association with migration status, a larger descriptive Australian study with more than 10,641 people identified that non-English speaking migrants were more likely to report psychotic symptoms on interview (Scott et al. 2006). There are various social risk factors for schizophrenia which influence the course of illness. These include lower socioeconomic background, unemployment, and disruption in family affairs.

1.2 Chronotype

Chronotypes reflect the individual preference for the time at which one is more inclined to sleep, wake-up, and undergo demanding physical and cognitive tasks (Peres et al. 2011; Korczak et al. 2008; Preckel et al. 2011; Short et al. 2013; Soehner et al. 2011; Horne and Ostberg 1976). These preferences vary considerably across the population, ranging from eveningness to morningness (Preckel et al. 2011). Due to its strong correlation with physiological circadian measures, which require substantial time and financial resources to collect, self-report measures of chronotypes are a non-invasive proxy used to characterise circadian profiles (Horne and Ostberg 1976). Morning type and evening type individuals fundamentally differ in terms of their sleep-wake patterns and the peak periods of key behavioural and biological rhythms (Yoon and Shapiro 2013). Evening types are likely to prefer being more active towards the end of the day, whereas morning types have a tendency to initiate their activities within the earlier hours of the day (Lehnkering and Siegmund 2007). Chronotypes are also characterised by different degrees of inter-individual variability in circadian phases and sleep schedules, with evening types displaying more variability in rising and bed times than morning types (Martin and Martin 2013; Randler 2008; Escribano et al. 2012).

The Horne-Östberg morningness-eveningness questionnaire (ME) consists of 19 items which cover preferences for bed time, habitual rising time, time of physical and cognitive activities, peak alertness times, and the time at which one feels most tired. The Horne-Östberg ME questionnaire generates a total score which can be considered as a continuous variable or used to categorise individuals into specific chronotype subgroups (i.e. evening types, morning types, and neither type). Total scores range from 16 to 86; higher scores are indicative of being more of a morning type and lower scores are indicative of being more of an evening type. Morningness-eveningness scores between 86 and 70 are considered to reflect

'definite/extreme morning' chronotype, 69-59 to reflect 'moderate morning' chronotype, 58-42 to reflect 'intermediate' chronotype, 41-31 to reflect 'moderate evening' chronotype, and 30-16 to reflect 'definite/extreme evening' chronotype. The Horne-Östberg ME questionnaire is one of the most commonly used tools to assess an individual's chronotype and has been validated by numerous studies (Drennan et al. 1991; Abe et al. 2011; Chelminski et al. 1999; Kim et al. 2010; Matthews 1988; Morales et al. 2008; Morales and Sorroche 2008; Muro et al. 2009).

Evening types tend to experience increased levels of daytime sleepiness, daydreaming, and maladaptive beliefs about sleep in comparison to morning types (Randler 2011a; Morales and Sorroche 2008). Moreover, eveningness is associated with poorer sleep quality (Selvi et al. 2010). As will be described below in more detail, the progressive delay in circadian rhythms and in the sleep-wake cycle which takes place during adolescence is often accompanied by a shift towards later chronotypes, and this often extends in young adulthood (Crowley et al. 2007; Hagenauera and Leea 2012; Garcia et al. 2001). Adolescents with later chronotypes or with stronger evening preference are at higher risk for mental disorders such as depression, anxiety, bipolar disorder, and psychotic disorder (Willis et al. 2005; Randler 2011a; Merikanto et al. 2013; Muro et al. 2009; Ohayona and Roth 2003; Roberts et al. 2002). Furthermore, eveningness preference is associated with poor academic/work performance, increased behavioural and emotional problems, higher levels of alcohol, and drug consumption and higher suicide rates (Reavley et al. 2010; Murray et al. 2003; Germain and Kupfer 2008). By contrast, morning types appear to have better mental and physical health (Cavallera and Giampietri 2007).

Previous studies have reported evening chronotype and circadian disruptions in individuals suffering from various mental disorders such as anxiety, depression, bipolar disorder and psychosis as compared to healthy controls (Short et al. 2013; Scott et al. 2014; Justice et al.

2009; Gregory et al. 2005; Daniel et al. 1989). For example, persons with generalised anxiety who present with evening chronotypes have worse anxiety than persons with anxiety disorders who have earlier chronotypes (Alvaro et al. 2014; Pabst et al. 2009). Findings showed that the association between evening chronotypes and depressive or anxiety symptoms is stronger in younger individuals (Drennan et al. 1991). Another study in adolescents with depression showed worse sleep and alertness disturbances in evening types than in morning types (Short et al. 2013). Nevertheless, few studies have focussed on adolescence, young adulthood and the early stages of mental disorders. The association between evening chronotype and mental disorders are discussed in depth in section 1.5 with a focus on youth in section 1.6.

1.3 Endogenous Circadian Rhythms

To understand circadian disturbances in adolescents with mental disorders, it is important to consider the underlying neurobiological drivers of circadian functions. Human circadian rhythms are regulated by the suprachiasmatic nucleus (SCN) which synchronizes the brain and body to the 24-hour day-night cycle. The SCN is the 'master clock' that produces rhythmic outputs governing a wide array of physiological and psychological functions. The SCN maintains optimal synchronisation of these functions across the 24-hour cycle (Moore 2013). The circadian system can be divided into three components: i) the SCN acts as a pacemaker by generating the core circadian rhythms, ii) the input pathways (e.g. retinohypothalamic tract) to the SCN reset the timing of these circadian rhythms, and iii) the output signals then regulate circadian gene expression promote circadian behaviour and physiology (Lowrey and Takahashi 2011). The 'master clock' is influenced by extrinsic synchronising factors (called zeitgebers), such as light, as well as intrinsic factors, such as melatonin (Cajochen et al. 2006; Esseveldt et al. 2000; Burke et al. 2005).

Melatonin is a soporific hormone that helps regulate the internal body clock's cycle of sleep and wakefulness (Cagnacci et al. 1997). A study by Laposky and Turek (2009) observed two probable pathways by which melatonin influences circadian rhythms. Firstly, melatonin has chronobiotic abilities, enabling it to phase shift circadian rhythms. Secondly, melatonin promotes sleep onset and stability via its hypnotic effect (Laposky and Turek 2009). Melatonin also has hypothermic effects at physiological levels, for example it is responsible for the drop in core body temperature throughout the night (Aizawa et al. 2002). Daylight is one of the main synchronizers of the biological clock. SCN neurons are sensitive to light stimulations reaching the retina. Light exposure drives molecular changes in photopigments in the retina which generate nerve impulses travelling along the retino-hypothalamic tract to reach the SCN (Moore 2013; Tischkau and Krager 2014). A reduction in light intensity to the retina then causes the SCN to send nerve impulses to the pineal gland. These impulses, then trigger the pineal gland to produce melatonin (Esseveldt et al. 2000; Cagnacci et al. 1997). The light transmitted from the eyes to the SCN and subsequently to the pineal gland becomes electrical; the pineal gland transforms the electrical impulse, which might be linked, for example to the darkness signal, to a chemical message. This is then transferred by blood from the pineal gland to other sectors of the human body (Moore 1983). Circadian rhythms can either be phase advanced or delayed depending on various factors, one being when the individual is exposed to light (Peres et al. 2011; Shanahan and Czeisler 1991; Morales and Sorroche 2008). Light exposure in the evening can cause a delay in the phase of circadian rhythms, whereas light exposure in the early morning does result in a phase advance (Shanahan and Czeisler 1991).

Cortisol secretion also follows a circadian rhythm. Cortisol levels begin to rise approximately two to three hours after sleep onset and continue to rise into the early waking hours. Cortisol levels peak in the morning and gradually decline over the day until reaching the nadir point at

about midnight (Kudielka et al. 2007). Cortisol secretion affects many physiological functions and, in addition to its involvement in stress responses, also promotes alertness (Wilson 2014). Cortisol also has anti-inflammatory effects that suppress the production of numerous pro-inflammatory mediators (cytokines) which can be harmful in excess (Tracey et al. 1986).

1.3.1 The association between chronotype and circadian rhythms

Chronotypes are strongly associated with endogenous circadian profiles. For example, nadir core body temperature occurs approximately two hours earlier in individuals with morning chronotypes than in evening type individuals (Baehr et al. 2000). In addition, the acrophase of serum cortisol is approximately 55 minutes later in evening types than in morning types (Heitkemper and Bailey 2001). From a behavioural perspective, morning types have earlier rise and bed times than evening types (Morales and Sorroche 2008). Morning types have peak performances in the earlier part of the day, whereas evening types tend to perform better in the evening (Horne and Ostberg 1976; Vitale et al. 2013).

Circadian disruptions, and the commonly related sleep curtailing, alter several brain functions, resulting in decreased attention, alertness, mood, and motivation (Matthews 1988). Vigilance, or alertness, is a state of elevated readiness for efficient performance, an aspect of cognition closely related to the ability to sustain attention to relevant stimuli (Lim and Dinges 2008). Vigilance follows a strong circadian pattern which is influenced by the SCN and chronotypes (Dongen and Dinges 2005). One way of differentiating chronotypic preference is through repeated measures of vigilance across different circadian phases. The Psychomotor Vigilance Task (PVT) is a commonly used tool to measure vigilance and is known to be highly sensitive to both circadian and homeostatic variations (Graw et al. 2004). During the PVT, participants complete a sustained attention reaction time task based on a visual cue. The individual presses the response button as soon as the stimulus appears, and aims to keep

response times as short as possible (Kaida et al. 2006). Morning types have lower levels of vigilance as measured by the PVT in the evening, as well as higher vigilance levels and earlier cortisol peak in the morning (Natale and Cicogna 1996; Dongen and Dinges 2005). Also, delaying bedtime induces a greater decrease in alertness in morning types than in evening types (Breithaupt et al. 1978), while evening types show the reverse pattern (Clodoré et al. 1986; Horne et al. 1980; Mongrain et al. 2008; Matchock and Mordkoff 2009). Evening types are more likely to have overall lower vigilance and slower psychomotor functions during the daytime. Slower daytime psychomotor functions have also been associated with depression. This association was notably found in timed drawing tasks, with results showing a significantly slower drawing speed in patients with depression than in controls (Van Hoof et al. 1993; Sabbe et al. 1996). Lower vigilance levels and deficits in effortful attention and cognitive speed have also been associated with a range of mood disorders, including young adults diagnosed with unipolar depression (Pardo et al. 2006) or bipolar disorder (Burdick et al. 2009). Importantly, a decrease in vigilance due to sleep deprivation is highly likely to lead to accidents as people become less aware of their external environment (Gold et al. 1992).

1.4 Circadian Disruptions, Physical Health, Cognition and Mood

While few experimental studies are available to establish causality, several associative findings suggest that circadian disturbances may have serious adverse consequences on physical health. For example, abnormal circadian profiles are linked to illnesses such as metabolic syndrome and sleep disorders (Huang et al. 2011; Okawa and Uchiyama 2007). Circadian disruptions are also linked to mood alterations, a phenomenon which may likely increase the risk for manic or depressive episodes (Benedetti et al. 2003). Accordingly, as will be described in more detail in section 1.8, individuals with mood disorders have more significant circadian disturbances than healthy controls (McClung 2007).

Abnormal regulation of core body temperature and melatonin can result in altered physical and mental health. For example, higher incidences of cancers are found among those with melatonin disruptions (Chu et al. 2008; Hoffman et al. 2008; Hoffman et al. 2009). Also, disruptions in thermoregulation and melatonin levels have been found in persons with mood disorders (Kudielka et al. 2007; Koorengevel et al. 2000; Lewy 2013). Studies have identified that low cortisol levels are associated with a high prevalence of fatigue (Kumari et al. 2009). Imbalances in cortisol are also associated with immune dysfunction (Kudielka et al. 2007).

In addition, persons for whom circadian disruptions lead to delayed sleep onset is highly likely to face some degree of sleep deprivation if they need to wake up early in the morning to attend school or work. Considering the known effects of sleep loss on mood, cognition, metabolic and autoimmune functions (Anderson et al. 2013; Schmid et al. 2015), this sleep curtailing is likely to further worsen the effects of circadian disruptions on mental and physical health. For example, a longitudinal study in young persons with affective disorders showed that lower sleep efficiency was associated with longitudinal worsening of manic symptoms (Robillard et al. 2015a). The study further showed that shorter total sleep time and lower circadian amplitude were associated with greater declines in verbal memory.

Overall these findings highlight that sleep and circadian disturbances are associated with worse outcomes in terms of mental health, physical health and cognition. Further work on the nature and longitudinal course of circadian disruptions in the context of mental disorders could provide valuable insights for adapted prevention and treatment.

1.5 Chronotypes in Mental Disorders

The previous sections established that chronotypes are closely related to endogenous circadian rhythms and that several circadian abnormalities are associated with mental disorders. It may thus be expected that chronotypes should also be associated with mental disorders. Accordingly, a high prevalence of evening chronotypes has been reported in different types of mental disorders, including anxiety (Willis et al. 2005), depression (Merikanto et al. 2013; Drennan et al. 1991; Barba et al. 2009; Takashi Abe 2011; Abe et al. 2011), bipolar disorder (Mansour et al. 2005; Wood et al. 2009) and psychotic disorders (Roberts et al. 2002; Breslaua et al. 1996; Ohayon et al. 1998; Daniel et al. 1989).

1.5.1 Chronotypes, symptomatology and clinical profiles

Using the morningness-eveningness questionnaire, a study found how evening types demonstrated higher rates of suicidal ideation, lower work functioning, and higher levels of anxiety, depression, and paranoid symptoms when compared to morning chronotypes (Merikanto et al. 2013). Studies have found a correlation between depressive symptoms and chronotype preference, suggesting how eveningness is highly likely to have a negative influence on mood disorder symptom profiles (Germain and Kupfer 2008; McClung 2013). Similarly, Hasler and colleagues (2010) found higher depression scores based on the Beck Depression Inventory in evening chronotypes when compared to morning types (Hasler et al. 2010). Eveningness is also associated with worse symptom chronicity and comorbidity in people with depression (Gregory et al. 2005; Barba et al. 2009; Merikanto et al. 2013; Takashi Abe 2011). While evening chronotype may likely increase the risk of depression, some results suggest how a shift towards morningness co-occurs with a reduction in depression following treatment (Corruble et al. 2014). However further research is required to confirm this finding. In terms of daytime functioning, individuals with bipolar disorder II have been found to report lower evening tiredness than those with bipolar disorder I, and

individuals with depression report being less alert in the morning than those with bipolar disorder I (Chung et al. 2012), suggesting that in addition to sleep-wake timing, there may be differences in the circadian modulation of alertness across diagnoses. Overall, these studies suggest that a strong preference towards eveningness is highly likely to increase the risk of developing a mental disorder, or influence the symptomology and trajectory of mental disorders.

1.5.2 Chronotypes and clock genes

All individuals have their own preferences for the times at which to wake up, do demanding cognitive and physical tasks, and go to sleep. As described above, inter-individual differences in chronotype preference are associated with differences in the timing of various cognitive and physiological functions (Onder et al. 2014; Roeser et al. 2013; Randler 2008). Similarly, daily feeding also varies across individuals; however this is regulated by the peripheral clock (Dibner et al. 2010). Several genes that interact through intracellular auto-regulatory transcriptional-translational feedback loops within the master clock play a central role in regulating these circadian rhythms (Lowrey and Takahashi 2011; Ueda et al. 2005). For example, the CLOCK gene switches from transcriptional activation to transcriptional repression, allowing the circadian regulation of gene expression (Kondratov et al. 2006; Kondratov 2007). This CLOCK gene has been linked with eveningness and delayed sleep phase (Katzenberg et al. 1998). A study by Benedetti and colleagues in patients with bipolar disorder showed how individuals with the C allele of CLOCK had more eveningness and a delayed sleep onset as well as shorter sleep duration when compared to patients who did not have the C allele (Benedetti et al. 2007). Also, the C allele has been associated with reduced sleep duration and higher reoccurrence of manic episodes (Benedetti et al. 2003; Serretti et al. 2003). In addition, certain allelic combinations of PER3, NPAS2 and BMAL1 are linked to reduced sleep efficiency and higher risk for affective disorders (Lamont et al. 2007). This

suggests that inter-individual characteristics of clock genes and their association with chronotypes may likely be linked to affective disorders.

1.6 Circadian Rhythms and Chronotypes in Youth

There is a progressive delay in circadian rhythms that takes place during youth (Crowley et al. 2007; Hagenauera and Leea 2012; Garcia et al. 2001; Roenneberg et al. 2004). Similarly, morningness-eveningness preferences are known to change during this life period. Most children and pre-adolescents (ages 4 to 11 years) typically present with high morningness (Werner et al. 2009). During adolescence, the prevalence of morning types decreases and there is an increase in eveningness which is often accompanied by delayed wake up times (Randler 2011a). Preference for eveningness usually peaks around the age of 20 and subsequently shifts back towards morningness during adulthood (Roenneberg et al. 2004). Adolescents have a higher preference towards eveningness when compared to middle-aged individuals (Morales and Sorroche 2008). Pubertal development during adolescence is one of many internal factors influencing circadian preference changes as reproductive hormones play a part in shifting chronotypes towards eveningness (Randler et al. 2009; Hagenauera and Leea 2012). Circadian disruptions and phase delays occur frequently during youth, which could highly contribute to the emergence of mental disorders (Short et al. 2013). As discussed in the sections below, changes in sleep and circadian preference during youth are influenced by numerous cognitive, social and biological factors.

1.7 Potential Factors Influencing Sleep and Circadian Rhythms in Youth

1.7.1 Cognitive and social factors

Adolescence is a maturation period with a potential for disorientation and conflict, as well as opportunities for biological and emotional development (Randler et al. 2009). Understanding the issues that arise for adolescents trying to overcome the obstacles related to this tumultuous period of life may help us to explain the emotional, behavioural and physical struggles that arise during this developmental period, such as chronotype changes. There are numerous hormonal, physical, mental and cognitive changes occurring in the gap between childhood and adulthood. For example, Piaget's theory highlights that a critical stage in adolescence is the development of abstract thinking (Piaget 1972). Also, Erikson suggested that adolescence is a period where one formulates his or her individual identity and finds a sense of belonging. This self-seeking period may also be associated with an increased risk of mental illness, poor sleep and attention problems across the transition period from childhood to adulthood (Erickson 1968).

Controlled laboratory studies showed that adolescents maintain a circadian phase delay (i.e. later sleep, wake, peak cognitive and physical performance times) when following a regulated schedule with limited social influence and sufficient sleep time (Carskadon et al. 2004; Crowley et al. 2007). Nevertheless, day to day activities influence circadian rhythms (Peres et al. 2011). School schedules usually have early start times, requiring early wake-up times which conflict with the normal circadian phase delay occurring in adolescence (Carskadon 2011). Early wake-up times due to school schedule combined with delayed sleep onset time and minor decrease in sleep efficiency during the night, often leads to accumulated sleep loss throughout weekdays (Appleman et al. 2015). Consequently, later sleep onset time, longer sleep duration, and later wake time are some of the most consistent findings when comparing sleep-wake patterns in adolescents during weekends to those during school days (Short et al.

2013; Escribano et al. 2012). Accordingly, the National Sleep Foundation reported that over 45% of adolescents in the United States have inadequate sleep (Israel and Roth 1991). Delaying school start time by roughly 30 minutes has been shown to result in a substantial increase of sleep duration (i.e. 45 minutes), accompanied by significant improvements in alertness and mood (Owens et al. 2010). In addition to school scheduling, night time use of technology and later social times are external factors that affects sleep patterns and psychological state due to later bed times and early wake times (Carskadon 2011; Carskadon et al. 2004). Gamble and team also highlight how electronic devices in bedrooms is associated with poor sleep (Gamble et al,. 2014). Gradisar and team put together a review that presents findings from 41 surveys of adolescents sleep patterns and problems worldwide across a period of 10 years. Common findings across the surveys included: sleep patterns tended to delay as age increased, thus restricting school night sleep. North America and Europe bedtimes were earlier than Asian adolescents which resulted in higher rates of daytime sleepiness. The study also found that weekend sleep data was generally consistent worldwide, with more total sleep times and bedtimes being roughly 2 hours later (Gradisar et al. 2011).

1.7.2 Biological factors

A person's unique genetic makeup influences their behaviour and development (Morales et al. 2014). The influence of genetic makeup on human development was the dominant notion in the early twentieth century (Hall 1904). Recent studies acknowledge the interaction with not only the biology but also the environmental factors in adolescent development (Lerner et al. 2010). Changes in circadian preference are influenced by numerous internal biological and external environmental factors also known as 'zeitgebers'. During a two year study using actigraphy and maturation scales, Sadeh and colleagues found that delayed sleep phase and disrupted sleep patterns are associated with hormonal and pubertal development (Sadeh et al.

2009). As noted earlier, changes in developmental patterns may likely influence chronotypic preference and this could, in turn, influence emerging mental disorders. However, there are no longitudinal studies directly addressing this question.

1.8 Sleep Behaviour in Youths with Mental Disorders

Since later chronotypes are associated with sleep disturbances (Yun et al. 2015; Selvi et al. 2010), it may be relevant to assess sleep patterns in young persons with marked eveningness and mental disorders. For instance, a study conducted in 318 South Australian high school students aged 12 to 18 years found that chronotype independently predicts both insomnia and depression (Alvaro et al. 2014). Indeed, amongst adolescents, those who experience poor sleep quality is highly likely to be more prone to mental disorders, notably anxiety and depression (Tully et al. 2009). Specifically, sleep disruptions in adolescence are associated with persistent psychiatric symptoms which, in turn, appear to be associated with an increased symptom severity of mental disorders (Alfano et al. 2010; Mullin et al. 2011; Randler 2011a; Randler 2011b). The following sections examine sleep disturbances linked to different mental disorders with a focus on adolescents and young adults.

1.8.1 Anxiety disorders

Similar to what is reported in adults, studies conducted in youths suggest that the occurrence of anxiety disorders is associated with sleep complaints and disruptions, including poor sleep quality, longer sleep onset latency, and higher sleep-related daytime disruptions, such as decreased diurnal vigilance and increased daydreaming (Alvaro et al. 2014; Pabst et al. 2009; Alfano et al. 2007). Furthermore, a longitudinal epidemiological study found that individuals suffering from depression and anxiety had a higher lifetime prevalence of sleep disturbances (Gregory et al. 2005). A study on adolescents and children with generalised anxiety disorder

reported that 49% of participants had sleep disturbances in adolescence and 56% in childhood (Masi et al. 2004). Pina and team found that 57% of adolescents with anxiety disorder experienced trouble sleeping as well as reduced sleep quality when compared to controls (Pina et al. 2002). A study using the Achenbach Child Behaviour Checklist found a significant correlation between anxiety symptoms and sleep disruptions in children (Johnson et al. 2000). The study reported that 28.6% of children who had sleep disturbances also demonstrated a clinical level of anxiety symptoms. Another study also found a significant association between sleep disturbances and anxiety levels, due to common factors such as being afraid of sleeping alone, nightmares, bedtime resistance, and sleep anxiety (Gregory et al. 2005). In addition, an objective polysomnography study in youths showed that participants with anxiety disorders had increased sleep onset latency and reduced latency to rapid eye movement (REM) during sleep when compared to controls (Alfano et al. 2013). These results are parallel to findings in adolescents with major depression (Armitage et al. 2000; Reynolds III et al. 1983).

Sleep disturbances have been constantly reported as a clinical feature correlated with various anxiety disorders, such as separation anxiety disorder, social phobia, panic disorder with or without agoraphobia, specific phobia, and obsessive-compulsive disorder (American Psychiatric Association. 1994). In fact, the relationship between sleep disturbances and anxiety seems to vary across different types of anxiety disorders. For example, a study found an association between sleep disturbances and separation anxiety as well as generalised anxiety disorder, but no significant association with social anxiety (Alfano et al. 2007). Another study found that youth with generalised anxiety disorder had higher rates of sleep disturbances than youths with social anxiety disorder, social phobia, and obsessive–compulsive disorder (Alfano et al. 2010).

1.8.2 Depression

Sleep abnormalities in depressed adolescents are similar to those typically observed in adults; however, results are less consistent among adolescents. A review indicated that adolescents suffering from major depression had a reduction in slow wave sleep and a shortening of REM latency, with a lengthening of the first REM episode (Riemann et al. 2001). A study comparing 97 adolescents with major depression reported less slow wave sleep and greater sleep disturbances in males than in females (Robert et al. 2006). A more recent study also identified gender differences in adolescents, noting that males with major depression had lower slow wave activity during the patient electroencephalographic (EEG) reading, suggesting abnormality in brain rhythm, in the early nights compared to controls. No difference was found between females with and without major depression (Lopez et al. 2012). The same study also reported that adolescent males with major depression had a higher percentage of REM sleep and shorter REM latency (when compared to controls), with no difference found in the female group (Lopez et al. 2012). In addition, shorter latency to REM sleep as well as increased REM sleep may be associated with higher risk for depression in adolescents (Rao et al. 2009).

1.8.3 Bipolar disorders

Similar to what has been reported in unipolar depression, persons suffering from bipolar disorder experience disturbances in sleep continuity, longer sleep onset latency and a shorter interval between sleep onset and the onset of (REM) sleep compared to healthy controls (Robillard et al. 2013b; Geoffroy et al. 2014; Winkler et al. 2005; Millar et al. 2004). Similarly, another study demonstrated that 70% of patients with bipolar disorder in the euthymic phase presented with impaired sleep efficiency and lower daytime activity when compared to normal controls (Harvey et al. 2005). Harvey and team found that people with bipolar disorder had lower daytime activity levels, longer subjective sleep onset latency and

longer sleep duration than normal controls (Harvey et al. 2005). Decreased need for sleep is one of the diagnostic criteria of manic episodes (DSM-5; American Psychiatric Association 2013). Studies have shown that the onset of a manic/hypomanic episode is characterized by a sudden reduction in sleep duration and a decrease in the amount of REM during sleep, along other symptoms (Bunney et al. 1972; Sitaram et al. 1978; Kupfer and Heninger 1972). These sleep changes that occur during a manic phase typically worsen across the episode (Post et al. 1977; Bunney et al. 1972). In addition, the switch from mania to the depressive phase has been associated with increased total sleep duration and REM sleep (Bunney et al. 1972). Sleep reduction is not necessary part of the diagnosis of a mania; however large-scale studies have demonstrated how reduced sleep represents a core element during the occurrence of a manic episode and a significant predictor of recurrence (Kessler et al. 1997)

1.8.4 Psychotic disorders

Studies have shown that adolescents with psychotic disorders have increased sleep onset latency and higher levels of sleep disruptions when compared to controls (Lunsford-Avery and Mittal 2013). For instance, a study found that adolescents with schizophrenia had higher sleep fragmentation when compared to adolescents with depression as well as healthy controls (Riemann et al. 1995). Similarly, a study done by Lunsford-Avery evaluated how sleep difficulties may be associated with increased vulnerability of symptoms in individuals at risk of psychosis. The researchers compared 33 adolescents at ultra-high risk for psychosis with 33 healthy controls and found greater sleep disturbances, including increased sleep onset latency and poorer sleep efficiency, in the UHR group (Lunsford-Avery et al. 2013). This finding demonstrates the importance of the continuum between sub-threshold and clinical psychosis phenotypes in the general population.

Overall, there is a bidirectional relationship between the presence of mental disorders such as anxiety, depression, bipolar and psychotic disorders and sleep disruption where one is highly

likely to influence the other in adolescents. These sleep abnormalities may also be associated with the chronotype abnormalities and circadian rhythm disruptions discussed in section 1.9. The following section covers circadian disruptions and the association of evening chronotype across mental disorders.

1.9 Circadian Rhythm Disruptions in Mental Disorders

A growing body of literature suggests that circadian disturbances and eveningness may play a role in the pathogenesis of mental disorders as they are associated with higher symptom severity and chronicity (McClung 2007; Kudielka et al. 2007; Justice et al. 2009; Selvi et al. 2010; Robillard et al. 2015b). Higher depressive symptoms, increased incidence of suicidal thoughts, higher levels of anxiety, and increased paranoia have been reported in evening types when compared to morning types in adolescents (Merikanto et al. 2013). Similarly, other studies have highlighted that evening chronotypes in adolescents are strongly correlated with depressive and anxiety symptoms (Gregory et al. 2005; Alvaro et al. 2014). The association between chronotype change and mental disorders is highly likely to inform the optimisation of treatment strategies using circadian-based therapies. Understanding chronotype preferences linked to various mental disorders during youth could therefore yield valuable clinical information to be implemented at the early stages of mental disorders.

Studies examining specific subgroups of psychiatric disorders have found circadian disruptions in individuals suffering from various mental illnesses, such as anxiety, depression, bipolar disorder, and psychotic disorders (Jagannath et al. 2013; Justice et al. 2009; Okawa and Uchiyama 2007; Gregory et al. 2005). There is limited research comparing evening chronotypes across multiple disorders; however, some studies compared physiological and behavioural characteristics related to chronotypes across diagnostic

subgroups. For example, persons with bipolar I disorder have higher evening tiredness than those with bipolar II disorder (Chung et al. 2012). In terms of the timing of the sleep-wake schedule, actigraphy studies have shown that young people with unipolar depression or bipolar disorder have a significantly later sleep offset (i.e. wake up time) when compared to controls (Robillard et al. 2013b; Robillard et al. 2015b).

1.9.1 Circadian rhythms and anxiety disorder

There have been very few studies investigating circadian variations in melatonin, cortisol and core body temperature in patients with anxiety disorders. A study did however, demonstrate that adults with anxiety disorders had a lower cortisol awakening response when compared to controls (Hek et al. 2013). This is consistent with the notion that chronic anxiety may result in a change in hypothalamic-pituitary-adrenal axis (HPA-axis) activity (Van Cauter et al. 1996). Another study used melatonin-based treatment in male laboratory animal centre a-strain mice that had anxiety-like behaviour and found a significant improvement, showing reductions in locomotor activity and anxiety-like behaviour (Kumar et al. 2014).

1.9.2 Circadian rhythms and depression

Individuals suffering from depression display reduced circadian amplitude in numerous internal biological rhythms when compared to healthy controls. Such intrinsic rhythms include core body temperature, melatonin, cortisol, and thyroid stimulating hormone (Kennedy et al. 1989; Carman et al. 1976; Elsenga and Hoofdakker 1988; Kirkegaard and Faber 1998). In addition, this diminished amplitude of core temperature, cortisol and melatonin significantly correlates with increased depression severity (Ehlers et al. 1993). This suggests that a reduction in circadian amplitude may influence depressive symptoms and/or that more severe depressive states may reduce circadian amplitude. It has been proposed that clock gene variations due to changes in amplitude and timing of the master clock may generate a chronobiological vulnerability in persons with mood disorders (Benedetti et al.

2003). Diminished amplitude is not the only circadian rhythm abnormality in mood disorders; studies have also found that delayed biological rhythms are strongly associated with mood disorders (Chung et al. 2012). For example, patients with seasonal depression tend to display a phase delay in internal rhythms, such as body temperature and melatonin release, when compared to healthy controls (Carman et al. 1976; Kennedy et al. 1989). Another study supports these findings, demonstrating that those who suffer from depression display deregulated melatonin levels when compared to controls (Selvi et al. 2010).

In addition, elevated cortisol levels due to hyperactivity of the HPA-axis are associated with an increased incidence of depression (Burke et al. 2005; Brown et al. 2004). A more recent study found that higher cortisol activity is associated with worse depressive symptoms (Morris et al. 2012). In fact, there are indications that depression is linked to higher evening cortisol and lower morning cortisol, which is further associated with difficulties falling asleep at night as well as fatigue in the morning (Van den Bergh and Van Calster 2009). Similarly, individuals who have evening chronotypes have increased cortisol levels in the evening compared to normal individuals (Randler and Schaal 2010). Therefore, higher evening cortisol levels may be a common feature of both depression and later chronotypes.

Circadian synchrony (defined by the time relationship between endogenous circadian rhythms and the sleep-wake cycle) plays a fundamental role in regulating and determining alertness, mood, sleep duration, cognition, and physiological functions (Cajochen et al. 2006; Esseveldt et al. 2000). We recently identified marked circadian desynchrony in a subgroup of young people with mood disorders (Robillard et al. In preparation). The study found major misalignment in 25% of participants with affective disorders suggesting that delayed melatonin may play a central role in circadian desynchrony (Robillard et al. In preparation).

The most repeated finding of biological rhythm abnormalities that have been reported in depressive patients include variations in mood, core body temperature, motor activity, brain activity, hormone secretion, such as cortisol and melatonin, evening preferences, disrupted sleep–wake cycle, and seasonal mood variation (Lewy 2013; Kennedy et al. 1989; Elsenga and Hoofdakker 1988; Kirkegaard and Faber 1998; Abe et al. 2011). Many patients who have depression demonstrate a consistent daily cycle of mood changes, which typically includes worse mood in the morning (Benedetti et al. 2003). However, changes in mood also vary with symptom severity as suggested by Murray and team who found that individuals with more severe depression showed more pronounced diurnal variation in mood as well as disturbed circadian functions when compared to the low depression group (Murray 2007).

1.9.3 Circadian rhythms and bipolar disorder

During all phases of bipolar disorder, it has been typically noted that patients have significant disruptions to the circadian and sleep-wake systems (Ng et al. 2015). However, an actigraphy study found no significant difference in sleep onset/offset times between adolescents with bipolar disorder and controls, although this was based on just four nights of recording (Mullin et al. 2011). Other studies have found worse sleep phase delay in youths with bipolar disorder than in those with unipolar disorders and healthy controls from the same age group (Robillard et al. 2013b).

Previous studies have found that bipolar disorder is associated with circadian disruptions including a high prevalence of delayed sleep onset (Mansour et al. 2005; Geoffroy et al. 2014; Das et al. 2011). Studies have reported that mood stabilizers assist in restoring circadian rhythms in persons with bipolar disorder (McClung 2007; Wirz-Justice 2006). Mondin and team were the first to suggest the social 'zeitgebers' theory, where patients with bipolar disorder are more susceptible to sleep-wake and circadian disruptions based on variations in their day to day routines such as sleep/wake times and peak cognitive and

physical activity (Mondin et al. 2014). Over time, there has been an accumulation of evidence that identifies that stress resulting from lifestyles choices can increase the disruption of social rhythms and sleep patterns in individuals with bipolar disorder, which thus increases the risk for a depressive or manic episode (Shen et al. 2008; Fears and Reus 2015). A healthier lifestyle and social stability are correlated with improved sleep quality and decreased risk of a mood episode (Selvi et al. 2010).

1.9.4 Circadian rhythms and psychotic disorder

Sleep and circadian disturbances are commonly found in schizophrenia. A study by Bromundt and team found delayed melatonin onset and higher levels of daytime sleepiness in patients with schizophrenia (Bromundt et al. 2011). Another study in people with schizophrenia showed severe circadian misalignment, including phase-advance/delay in melatonin cycles and highly irregular and fragmented sleep periods (Wulff et al. 2012). Another study in men with schizophrenia found that circadian time-keeping and pituitary-adrenal functions were normal but prolactin secretion was hyper-responsive to the physiologic stimulus of sleep onset (Cauter et al. 1991). Rao and team reported that individuals with schizophrenia were phase advanced when compared to controls (Rao et al. 1994). Overall, these findings have not been entirely consistent, although it can be suggested that individual's with psychotic disorders have disruptions in endogenous circadian rhythms. In line with the numerous neurobiological abnormalities found in schizophrenia, circadian and sleep disturbances are prevalent in individuals with this mental disorder (Franzen and Buysse 2009; Kapalka 2010).

1.9.5 Association between eveningness and mental disorders in young people

Associations between eveningness preference and psychiatric symptoms, such as feeling depressed and altered mood, is commonly reported by adolescents (Kim et al. 2010; Pabst et al. 2009). The shift from morningness to eveningness during adolescence is associated with

significantly higher emotional and behavioural difficulties and an increase in suicide thoughts (Gau et al. 2007). Another study found an association between eveningness preferences and depressive symptoms that was particularly pronounced in younger individuals in comparison to those that were middle aged (Kim et al. 2010). Reports have shown that evening chronotypes are associated with different types of mental disorders in youth, such as depression and anxiety (Pabst et al. 2009). Also, delayed sleep phase in youth has been reported in individuals with mood disorder (Robillard et al. 2013b). Considering the frequent overlaps in symptomatology across diverse mental disorders during youth, there is a need to investigate the associations across chronotypes and psychopathological symptoms beyond primary diagnostic classification. Most studies have so far focussed on single diagnostic subgroups and have not yet compared circadian or sleep-wake profiles in large samples across multiple disorders.

In addition, studies have often been limited to later periods of life. Therefore, little is known about how circadian profiles during the critical youth period relate to the symptomatology of different types of mental disorders. The effect of evening preference on mental health during youth may be modulated by developmental changes in circadian rhythms. Considering the effects of circadian alterations on mood and wellbeing and the strong associations between morningness-eveningness preference and various psychiatric symptoms, the rapid changes in circadian rhythms and chronotypes taking place during adolescence may contribute to the emergence, severity and chronicity of mental disorders. Further research is required to evaluate the specificity of chronotype preferences across multiple mental disorders and possible variations across illness trajectory.

1.9.6 Longitudinal changes in chronotype and mental disorders

Few studies have focussed on longitudinal changes in chronotypes. Data shows that adolescents with evening chronotypes that persist into adulthood may be particularly

vulnerable to developing mental disorders at later ages (Merikanto et al. 2013; Hidalgo et al. 2009). Thus, individuals maintaining high eveningness beyond adolescence may have worsening clinical profiles with advancing age. Das and colleagues observed that morningness generally increases with age in patients with bipolar disorder (Das et al. 2011). This study, however, was cross-sectional and thus did not examine whether this phase shift in chronotype was associated with changes in clinical profiles longitudinally. Kraemer and team highlighted the need for longitudinal data on pubertal development, predominantly when trying to understand distinct developmental trajectories or disease processes (Kraemer et al. 2001).

Increasing evidence suggests that the active realignment of circadian rhythms may be linked to clinical improvements in persons with mood disorders (Hickie et al. 2013a; Winkler et al. 2005). However, little is known about the possible association between longitudinal changes in morningness-eveningness preference and symptom severity. While there are no comparative findings assessing morningness-eveningness preference change over a period of time in the same individuals. However, a large study demonstrated that reduced sleep in youth predicted subsequent depressive symptoms after a follow-up period of 4 weeks (Roberts et al. 2009). In addition, Wong and team observed that long term sleep problems are associated with suicidal thoughts and suicide attempts in adolescents and young adults across three waves of data collected between 1994 and 2002 (Wong and Brower 2012). Later chronotypes are associated with reduced sleep, and therefore changes in chronotypes may also relate to symptom worsening over time (Garcia et al. 2001). If longitudinal changes in morningness-eveningness preferences do occur across phases of mental disorders, monitoring these changes may have useful clinical implications, particularly in terms of prevention strategies.

1.10 Mental Disorders, Circadian Profiles and Stages of Illness

This thesis is based on a sample of young persons across various stages of illness, including individuals at the early stages of mental disorders as well as individuals with severe and persistent disorders. The onset of some mental disorders often occurs early in childhood or adolescence when intrinsic features of sub-threshold symptoms are sometimes unclear. It often takes several years to form final accurate diagnostic impressions. For example, studies have found that the mean delay for the accurate diagnosis of anxiety disorders generally ranges between 6 to 23 years, depending on the specific disorder (Wang et al. 2005). There are delays in formal diagnosis notably due to symptoms overlapping in the early stages of different mental disorders. In these cases treatment can be delayed or, at times, inappropriate. Clinical researchers from the Brain and Mind Centre have developed a clinical staging model to better assist in the early management of emerging mental disorders. This model consists of four stages which aid in using early non-specific intervention strategies as they are not limited to classical diagnostic categories. In fact, this model is focussed on symptom severity and related functional impairments rather than simple diagnostic groups.

This clinical staging model proposes a common starting point of mental disorders where there are shared biological risk factors related to adolescent onset which subsequently progress to a more definite syndrome (McGorry et al. 2006). In this model, Stage 0 refers to periods when individuals may be at risk of psychotic or severe mood disorder but show no symptoms currently. Stage 1a, also referred to as help-seeking, reflects when the individual portrays some mild symptoms. To be classified as Stage 1b (also known to be the attenuated syndrome stage), an individual's symptoms have progressed from mild to moderate, however, the symptoms remain sub-clinical, and thus the individual does not fully meet criteria for a specific disorder. Stage 2 is also called the discrete disorder phase as it is analogous to a full threshold disorder as per DSM-IV criteria. If symptoms persist over a period of 12 months

the individual will then be in Stage 3 or the recurrent/persistent period. Lastly Stage 4, which is known as the severe, persistent, and unremitting stage, is where most of the symptoms of a disorder are present and have persisted over several years (Hickie et al. 2013b).

Table 1: Clinical staging model for mental disorders, reproduced from (Hickie et al. 2013b)

Stages	0	1a	1b	2	3	4
Description	Recognisable risk factors to psychiatric illness.	Help-seeking subjects with symptoms: non-specific mild to moderate anxiety or depression symptoms.	Attenuated Syndromes: Specific symptoms of severe anxiety, moderate depression, brief hypomania or brief psychotic phenomena. Symptoms have progressed but have not met complete threshold of a formal diagnosis.	Discrete Disorder: Clear episodes of manic, psychotic or severe depressive disorders. Full threshold disorder with moderate-severe symptoms and persistence over time.	Recurrent Or Persistent Disorder: Incomplete remission from discrete disorder at 12 months after reasonable course of treatment (of at least 3 months duration).	Severe, persistent and unremitting illness assessed after at least 24 months of engagement with relevant specialized clinical services and interventions.

Researchers have used the clinical staging model to assess the stages of mental disorders in relation to various psychiatric biomarkers. For example, a study of 154 help-seeking individuals found that delayed sleep phase in young people with a mental disorder is associated with more persistent illness (Scott et al. 2014). In addition, Scott and team found that the subgroup of patients with later stages of illness had a later acrophase of the activity-rest cycle. Furthermore, regardless of diagnostic categories, the proportion of individuals with delayed sleep-wake patterns progressively increased across later stages of illness (Scott et al. 2014). Similarly, using actigraphy in young outpatients with a primary diagnosis of anxiety, depression, bipolar, or psychotic disorder, a previous study found that all diagnostic subgroups had significantly delayed sleep-wake schedules compared to healthy controls (Robillard et al. 2014).

It may be expected that more individuals who are evening chronotypes and have circadian disturbances would be in Stages 1b and later stages according the clinical staging model. Yet, it is also possible that changes in chronotype may be an early feature in the emergence of various mental disorders and may thus appear at earlier stages. Elevated rates of moderate and extreme evening chronotypes have been observed in individuals presenting with various mental disorders, including anxiety (Willis et al. 2005), depression (Merikanto et al. 2013; Drennan et al. 1991; Barba et al. 2009; Takashi Abe 2011; Abe et al. 2011), bipolar disorder (Mansour et al. 2005; Wood et al. 2009) and psychotic disorders (Roberts et al. 2002; Breslaua et al. 1996; Ohayon et al. 1998; Daniel et al. 1989). In line with the staging model, the later finding supports the notion that some features of mental illnesses, such as later chronotypes, may not be specific to diagnostic subgroups. However, very few studies have compared circadian and sleep-wake disturbances across multiple disorders.

1.11 Aims and Hypotheses

Study One

This study aimed to assess morningness-eveningness preferences in young people with primary anxiety, depression, bipolar, or psychotic disorders, and to investigate the associations between morningness-eveningness preference and the severity of various psychiatric symptoms.

It was hypothesised that:

1. Participants with mental disorders would have elevated eveningness (i.e. lower morningness-eveningness scores) in comparison to healthy controls, but the most pronounced eveningness would be found in the depression and anxiety groups;

2. From a categorical perspective, evening chronotypes would be more prominent across persons with mental disorders than in healthy controls; and,

3. Later chronotypes would be associated with greater symptom severity.

Study Two

Study 2 aimed to assess: i) temporal variations in morningness-eveningness preference over the course of affective disorders during youth and ii) interactions between longitudinal changes in chronotypes and longitudinal changes in psychiatric symptoms.

It was hypothesised that:

1. Morningness-eveningness preference would vary across the course of affective disorders.

2. Those who shift towards earlier chronotypes over time would have decreased symptom severity in comparison to those who remained stable in their chronotypes or shifted towards later chronotypes.

1.12 Methodology

1.12.1 Participants

In Study 1, 496 individuals were recruited, including 67 healthy controls from the community and 429 help-seeking individuals with emerging mental disorders.

One hundred and twenty-three of these participants also took part in the second longitudinal study. In addition, a further 10 individuals (i.e. independent of Study 1) also participated, giving a total of 133 individuals for study 2. These 10 individuals participated in study 2, but not in study 1 due to the different age cut off: Study 1 included individuals aged between 12 and 30 years, whereas study 2 included individuals between 12-35 years. In addition, only 123 individuals from study 1 had follow-up data.

For both studies, primary diagnoses were determined by mental health professionals based on criteria from the DSM-IV (American Psychiatric Association 2000). For study 1, participants were divided into five groups according to their primary diagnosis: healthy controls, anxiety disorders [e.g. social anxiety disorder (n = 14), generalised anxiety disorder (n = 33) and obsessive-compulsive disorder (n = 5); total n = 52], unipolar depression (n = 194), bipolar disorder (n = 101), and psychotic disorder [e.g. schizophrenia (n = 22), first episode psychosis (n = 44), schizoaffective disorder (n = 7) and drug induced psychosis (n = 9) , total n = 82]. For study 2, participants were divided into two groups on the basis of their primary diagnosis: unipolar depression (n = 63) and bipolar disorder (n = 70). Then, study 2 participants were further divided into two additional categories: the 'earlier chronotype shifters group', which included individuals who shifted to earlier chronotypes categories across the longitudinal period, and the 'stable/eveningness shifters' which included individuals whose chronotype shifted later or remained stable. Exclusion criteria for both studies included intellectual disability, current primary substance dependence, poor English

skills, head injury with a loss of consciousness exceeding 30 minutes, and major medical or neurological condition. In study 1, none of the participants from the control group reported having any mental disorder or endorsed a clinically significant level of depression symptoms on the 17-item Hamilton Rating Scale for Depression (HDRS, score above 7) *(Hamilton 1960)*. All participants in both studies gave written informed consent prior to entering the studies. Written consent was obtained from the parents or legal guardians of all participants who were younger than 16 years of age. The study protocols were approved by Human Research Ethics Committee of the University of Sydney.

1.12.2 Setting

Participants from both studies were recruited from early intervention private services for mental health problems in young people in the Inner Sydney area (the Brain and Mind Clinic at the Brain and Mind Centre, and the *headspace* centre, Camperdown, Sydney, Australia) (Scott et al. 2009; Scott et al. 2012). All patients from the aforementioned clinics who were deemed able to provide informed consent were systematically offered the opportunity to enter the study. The Brain and Mind Centre is an independent organisation that helps young people aged 12 to35 years with mental disorders. The organisation's main purpose is to offer appropriate assessment during the early stages of illness and provide early and accurate treatment for various mental disorders. Various intervention strategies targeting the social aspects of youth mental health can be employed, including using cognitive behaviour therapy in patients with early psychosis (Addington et al. 2006; Thomson et al. 2012), addressing the relationship between binge drinking and depression with its associated range of neurocognitive difficulties (Hermens et al. 2013; Naismith et al. 2012b; Hickie et al. 2005; Hermens et al. 2011), dealing with the stress and anxiety that is formed by lack of confidence and external factors (Hickie 2008), using discernible biomarkers to help patients anticipate

the emergence of mood episodes (Robillard et al. 2013b), including those based on changes in circadian rhythms (Hickie et al. 2013c; Robillard et al. 2013b; Robillard et al. 2015a).

1.12.3 Clinical assessments and self-report

As part of a standard structured assessment, research psychologists conducted a comprehensive range of clinical and neuropsychological assessments. They also asked participants to complete questionnaires within four weeks of these assessments. A complete list of these measures is included in Appendix 1. For this thesis, only a subset of these broader measures was examined, as detailed below. For study 2, the longitudinal interval between the baseline and follow-up self-report was 576.3 ± 211.5 days. During this interval, participants were receiving standard clinical care.

Clinical Assessments

The Social and Occupational Functioning Scale (SOFAS; Goldman et al. 1992)

The SOFAS is a clinician-rated scale which concentrates predominantly on the individual's level of social and occupational functioning. Level of functioning is assessed in relation to school, work and interpersonal relationships for the person's current circumstances (i.e. the level of functioning at the time of the evaluation). SOFAS scores of 70 or less are considered to indicate considerable difficulties in socio-occupational functioning.

The SOFAS was used in study 1 to provide information on the group's overall social and occupational behaviour, and determine whether there was worse functioning depending on their chronotype. A previous study used the SOFAS with patients in three different settings (inpatient, outpatient and rehabilitation) to determine if this instrument could differentiate the groups based on social functioning (Saraswat et al. 2006). It was found that the SOFAS was able to differentiate patients on their level of socio-occupational functioning, after controlling for the age of onset of symptoms and clinical status. This indicates that the SOFAS has good

discriminant validity and can be used to examine changes in levels of social and occupational functioning.

The Hamilton Depression Rating Scale - 17 item version (HDRS; (Hamilton 1960)

The HDRS is the most commonly used clinician-administered depression assessment scale (Bech et al. 2002). A semi-structured interview is used to rate depressive symptoms over the prior week, with items rated from 0 to 4 (symptom is absent, mild, moderate, or severe) or 0 to 2 (absent, slight or trivial, clearly present). The total score is the sum of each item. For the 17-item version, scores can range from 0 to 54. Scores in the range of 0-7 are within the normal range, scores above 7, 13 and 19 are considered to reflect mild, moderate and severe depressive symptoms respectively. Since the HDRS is a multi-dimensional scale, identical total scores from different individuals may have different clinical meanings (Bech et al. 2002). Therefore, in addition to the total HDRS score, there are subscales that can be calculated to differentiate clusters of symptoms, including anxiety (agitation, subjective and somatic anxiety, hypochondriasis and insight about depressive state), depression (covering depressed mood, guilt, suicidality, disengagement in occupational and recreational activities, psychomotor slowing), somatic (covering loss of appetite, weight loss, loss of interest in sex and somatic symptoms) and insomnia (covering lack of sleep and sleep disturbance).

Studies have demonstrated internal consistency of different versions of the HDRS. A study reported internal consistency coefficients of 0.83 for HDRS-17 and 0.88 for HDRS-24 (Rush et al. 2003). Inter-rater reliability has been reported to be very high for HDRS total scores where all items showed satisfactory reliability when the scale was administered in accordance with interview guidelines (Moberg et al. 2001). Similarly, another study reported inter-rater reliability in 21 psychiatry students who had little experience with the HDRS (Muller and Dragicevic 2003). Another study showed that scores on the HDRS improved in accuracy

greatly following the use of appropriate training and planned interviews (Kobak et al. 2003). Bech and team demonstrated that the validity of the HDRS ranged from 0.65 to 0.90 when measuring depression severity symptoms such as depression, guilt, suicidal thoughts, anxiety, agitation, somatic and paranoid symptoms (Bech et al. 2002). They also found that HDRS scores were significantly associated with clinician-rated measures such as the Montgomery–Åsberg Depression Rating Scale and the Inventory of Depressive Symptomatology–Clinician-Rated scale. The HDRS was suited for the current studies as its subscales assess different types of symptoms related to depression. Also, this scale is the most widely used worldwide.

The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962)

The BPRS was used to determine the severity of 24 psychiatric symptoms rated from not present (i.e. score of 1) to extremely severe (i.e. score of 7). Notably, the BPRS assesses:

- A patient's degree of concern over bodily health (e.g. whether physical health complaints have realistic bases or not)
- Anxiety symptoms (e.g. apprehension, tension, fear, panic or worry)
- Depressive symptoms (e.g. sadness, unhappiness, anhedonia and preoccupation with depressing topics, suicidal thoughts)
- Disproportionate concerns or remorse for past behaviour
- Hostility (e.g. animosity, contempt, belligerence, threats, arguments, tantrums, property destruction, fights, and any other expression of hostile attitudes or actions)
- Elevated mood (i.e. euphoria)
- Grandiosity (e.g. exaggerated self-opinion)
- Suspiciousness

- Hallucination (e.g. reports of perceptual experiences in the absence of relevant external stimuli)

- Unusual thoughts

- Bizarre behaviour

- Self-neglect

- Other psychiatric observations

In addition to a total score, specific subscales were computed for the two studies in this thesis (Overall and Gorham 1962):

- The positive symptoms factor reflects the severity of hostility, grandiosity, suspiciousness, hallucinations, unusual thoughts and behaviour and conceptual disorganisation.

- The negative symptoms factor is derived based on self-neglect, blunted affect, emotional withdrawal, motor slowing and uncooperativeness.

- The depression factor integrates somatisations, anxiety, depression, suicidality, guilt and self-neglect.

- The mania factor encompasses elation, conceptual disorganisation, tension, uncooperativeness, excitement, distractibility and hyperactivity.

Studies have demonstrated that the BPRS is a sensitive and valid measure of symptom reduction occurring after effective interventions (Gigantesco et al. 2006; Ballerini et al. 2007; Inch et al. 1997). Less clinically experienced professionals have been shown to administer the BPRS with high levels of inter-rater reliability in psychiatric patients (Ventura et al. 1993; Roncone et al. 1999). A study found that the BPRS could be a useful instrument to measure symptom severity and change in symptom status also in outpatients presenting with unipolar depression (Zanello et al. 2013).The BPRS scale is quick and efficient and is one of the only

instruments that covers such a broad range of symptoms related to different mental disorders within the same scale. The four BPRS subscales are relevant in the current studies as they were used to determine whether different subtypes of symptoms were related to various mental disorders depending on and individual's chronotype.

Questionnaires

Horne-Östberg Morningness-Eveningness Questionnaire (HO; Horne and Ostberg 1976).

The ME is a 19-item questionnaire evaluating the time at which one feels most alert, and prefers to go to sleep, wake-up and conduct different types of activities. A total score is generated ranging between 16 and 86. Lower scores on the ME indicate preference for eveningness, while higher scores indicate preference for morningness. From a categorical perspective, ME scores can also be used to classify morningness-eveningness subgroups, or chronotypes:

- Definite/extreme morning (scores 86-70)

- Moderate morning (scores 69-59)

- Intermediate (scores 58-42)

- Moderate evening (scores 41-31)

- Definite/extreme evening (scores 30-16)

The original article related to this questionnaire demonstrated that the peak time for subjective alertness correlated with the time of peak body temperature *(HO; Horne and Ostberg 1976)*. Furthermore, evening types had a later peak of oral temperature than morning types, and the intermediate types had their peak in temperature between the two groups. This questionnaire has been demonstrated to be a reliable measurement of chronotype. For example, a study presented a detailed description of chronotypes in children aged 4 to 11 years by using the children's chronotype questionnaire (CCTQ), the ME and the Mid-sleep

Point on Free Day's questionnaire. The validity of these questionnaires was established via comparisons with actigraphy. Test-retest reliability was also assessed for all three chronotype measures and sleep/wake parameters. Overall, the findings indicate moderate to strong agreement between the three measures and adequate associations between chronotype measures and sleep/wake parameters assessed by actigraphy. Temporal stability (i.e. reliability) was deemed to be excellent (Werner et al. 2009). Another study in middle-aged individuals showed that eveningness was associated with later bedtime and wake time (Tillard et al. 2004). They also found a positive correlation between age and morningness. This study concluded that the Horne-Östberg morningness-eveningness questionnaire could be useful when investigating age-related changes in circadian preference. Anderson and team found an internal consistency of 0.83 for the morningness-eveningness questionnaire. Twenty percent of the participants in this study completed the questionnaire eight weeks later and the scores had a classical test–retest reliability coefficient of 0.77 (Anderson et al. 1991).

Overall, the ME questionnaire is a valid and reliable instrument to measure chronotype. This questionnaire is the focal measurement in the current studies as it characterises the individual's morningness-eveningness preference. Other morningness-eveningness questionnaires could have been used in the current studies such as the Munich Chronotype Questionnaire (MCTQ). However, the Horne-Östberg questionnaire was chosen as is has been validated in persons with mental disorders and addresses time preferences for activities conducted in the wake life, whereas MCTQ is limited to sleep time parameters (Zavada et al. 2005). In addition, the ME questionnaire is the most widely used self-report scale to measure circadian profile and, in order for the current studies to be properly compared to previous findings, we have decided to use the same questionnaire.

Kessler Psychological Distress Scale (K10; Kessler and Mroczek 1992, 1994)*.*

The K10 is a 10-item questionnaire assessing an individual's level of psychological distress, with scores above 9, 15 and 21 considered to reflect low, moderate and high psychological distress, respectively. It is a questionnaire designed to measure non-specific psychological distress regarding negative emotional states experienced in the past 30 days, such as psychological fatigue, nervousness, depression and agitation (Slade et al. 2011). Research has indicated that the K10 can be used as a screening tool to identify cases of psychological distress and possible mental disorders (Andrews and Slade 2001). A study examining the reliability and validity of the K10 found that this questionnaire has high internal consistency and concurrent validity and recommended the K10 as a brief screening and diagnostic tool for current affective disorders (Hides et al. 2007). This scale is an important tool in the current thesis as it helps to show if there are any differences in psychological distress depending on chronotype.

Chapter 2

<u>Clinical correlates of chronotypes in young persons with mental disorders</u>

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ABSTRACT

While important changes in circadian rhythms take place during adolescence and young adulthood, it is unclear how circadian profiles during this period relate to emerging mental disorders. This study aimed to: i) characterise morningness-eveningness preference in young people with primary anxiety, depression, bipolar or psychotic disorders as compared to healthy controls, and ii) to investigate associations between morningness-eveningness preference and the severity of psychiatric symptoms. Four hundred and ninety-six males and females aged between 12 and 30 years were divided into five groups according to primary diagnosis. The Hamilton Depression Rating Scale, and the Brief Psychiatric Rating Scale were administered by a research psychologist and participants completed the Kessler Psychological Distress Scale and the Horne-Östberg Morningness-Eveningness Questionnaire (ME). ME scores were significantly lower (i.e. higher levels of eveningness) in all patient diagnosis subgroups compared to the control group. The psychosis group had higher ME scores than the depression and anxiety group. Compared to the control group, the anxiety, depression and bipolar subgroups had a significantly higher proportion of 'moderate evening' types, with a similar trend for the psychosis group. The proportion of 'extreme evening' types was significantly higher in the anxiety and depression subgroups than in the control group. Lower - ME scores correlated with worse psychological distress in males from the bipolar group. Lower ME scores correlated with higher depression severity in females with depression and in males with bipolar disorder. These results suggest that young persons with various mental disorders, especially those with affective disorders, present with a stronger eveningness preference and higher rates of evening chronotypes than healthy controls from the same age group. Later chronotypes were generally associated with worse psychological distress and symptoms severity. These associations were modulated by sex and primary diagnosis.

Keywords: Chronotypes, morningness-eveningness preference, anxiety, depression, bipolar disorder, psychotic disorders, psychiatric symptoms

<u>INTRODUCTION</u>

Youth represents a sensitive period for the onset of both circadian disturbances and mental disorders. A progressive delay in circadian rhythms and in the sleep-wake cycle takes place during adolescence and often extends into young adulthood (Crowley et al. 2007; Hagenauera and Leea 2012; Garcia et al. 2001). This is commonly accompanied by a shift towards later chronotypes (i.e. 'evening' types as opposed to 'morning' types), with a stronger preference to go to sleep, wake-up and undertake cognitive and physical activities at later times of the day, compared to children and older adults (Fronczyk and Dragan 2006). A growing body of literature suggests that circadian disturbances, notably delayed rhythms, may play a role in the pathogenesis of mental disorders (Boivin 2000; McClung 2007; Germain and Kupfer 2008; Lamont et al. 2007; Wulff et al. 2010). Later chronotypes resulting from developmental circadian changes during youth may thus exacerbate emerging mental disorders.

Substance use, anxiety and mood disorders have been highlighted as the most frequent axis-1 disorders occurring in persons with either delayed sleep phase syndrome or evening chronotypes (Reid et al. 2012). Elevated eveningness preference has been observed in individuals presenting with various mental disorders, including anxiety (Willis et al. 2005), depression (Gaspar-Barba et al. 2009; Merikanto et al. 2013; Drennan et al. 1991), bipolar disorder (Mansour et al. 2005; Wood et al. 2009), and psychotic disorders (Mansour et al. 2005). Very few studies have compared circadian or sleep-wake profiles in large samples and across multiple disorders. In one such study comparing ME scores across persons with bipolar disorder, psychotic disorders and healthy controls observed that both clinical groups had lower scores (i.e. more eveningness) than controls (Mansour et al. 2005). Using

actigraphy in young outpatients with a primary diagnosis of anxiety, depression, bipolar or psychotic disorders, we recently observed that all diagnostic subgroups presented delayed sleep-wake schedules compared to healthy controls, with pronounced sleep onset delays in the anxiety and depression subgroups and marked delays in wake up times in the bipolar and psychosis subgroups (Robillard et al. 2014). We also found that the anxiety, bipolar and, to a lesser extent, depression subgroups had a later acrophase (i.e. peak) of the rest-activity cycle. Importantly, regardless of diagnostic categories, the proportion of young persons with various mental disorders who also present with delayed sleep-wake patterns has been reported to increase progressively across later stages of illness (Scott et al. 2014). In terms of daytime functioning, individuals with bipolar disorder II have been found to report lower evening tiredness than those with bipolar disorder I, and individuals with depression report being less alert in the morning that those with bipolar disorder I (Chung et al. 2012). This suggests that, in addition to abnormalities in sleep-wake timing, there may be alterations in the circadian modulation of alertness across mental disorders.

Beyond diagnostic group comparisons, the severity of some psychiatric symptoms has been linked to later chronotypes (Chelminski et al. 1999; Fronczyk and Dragan 2006; Pabst et al. 2009; Abe et al. 2011). For instance, amongst individuals with anxiety disorders, those with evening chronotypes have higher levels of anxiety than those with morning chronotypes (Willis et al. 2005). Similar findings have been found for depressive, manic and paranoid symptoms (Ong et al. 2007; Gaspar-Barba et al. 2009; Abe et al. 2011). Notably, evening chronotypes are associated with more chronic and severe depressive symptoms in adolescents (Pabst et al. 2009; Kim et al. 2010; Abe et al. 2011; Merikanto et al. 2013). A recent study which examined multiple subtypes of symptoms simultaneously in a large group of undergraduate students (mean age of 19 years) reported that, compared to intermediate and/or morning types, young persons with evening chronotypes endorsed worse symptoms on most

subscales of the Brief Symptom Rating Scale, including depression, anxiety, paranoid ideations and psychoticism (Hsu et al. 2012). In addition, evening chronotypes have been associated with worse sleep disturbances and daytime tiredness, increased behavioural and emotional problems, poor academic/work performance, higher levels of alcohol and drug consumption and higher suicidality (Gaspar-Barba et al. 2009; Adan 1994; Prat and Adan 2011; Giannotti et al. 2002). Considering the frequent overlaps in symptomatology across diverse mental disorders during youth, there is a need to investigate the associations between chronotypes and psychopathological symptoms beyond primary diagnostic classification. Most studies have so far focussed on single diagnostic subgroups and have often been limited to later periods of adulthood. However, little is known about how circadian profiles during the critical youth period relate to the symptomatology of different types of mental disorders.

Chronotypes have been observed to vary across sexes, but findings are not entirely consistent: a meta-analysis concluded that males have later chronotypes than females (Randler 2007), but other large scale studies reported the opposite pattern (Merikanto et al. 2012; Paine et al. 2006). Importantly, cross-sectional studies have suggested that age differences in chronotypes between adolescents and young adults are modulated by sex, suggesting that males generally reach a peak in the shift towards eveningness at later ages than females (Tonetti et al. 2008; Randler 2007; Roenneberg et al. 2007). Sex differences in chronotype may therefore influence the link between circadian preference and mental disorders emerging during youth. Although findings are not entirely consistent, there are some indications from the adult literature that sex modulates the relationship between chronotypes and traits related to mental disorders. For instance, one study in middle age adults demonstrated a negative correlation between morningness and anxiety in females, but not in males (Díaz-Morales and Sánchez-Lopez 2008). In a younger sample of university students, higher neuroticism-anxiety was found in morning types compared to neither types for males, and in neither types compared to

morning types for females, suggesting that this trait is linked to more morningness in males and to lower morningness in females (Muro et al. 2009). Conversely, another study conducted in university students reported that higher eveningness correlated with higher anxiety in males, but not in females, and that higher eveningness correlated with higher psychoticism in females, but not in males (Matthews 1988). Subsequently, a large scale study conducted in 10 to 16 year olds observed a stronger association between later chronotypes and moodiness in males compared to females (Gau and Merikangas 2004). While these studies were conducted in the general community, there is a need to clarify how sex may modulate the relation between chronotypes and psychiatric symptomatology in clinical populations.

The current study aimed to: i) characterise morningness-eveningness preference in young people with primary anxiety, depression, bipolar or psychotic disorders as compared to healthy controls, and ii) to investigate how morningness-eveningness preference relates to the severity of psychiatric symptoms across sex and primary diagnosis subgroups. It was hypothesised that: i) all diagnosis subgroups would have stronger eveningness preference than controls, and ii) that more pronounced eveningness preference would be associated with worse symptom severity. While the nature and direction of these associations were expected to vary between males and females, sex analyses remained exploratory.

MATERIALS AND METHODS

Participants

Four hundred and ninety-six individuals aged between 12-30 years participated in this study (see Table 2 for sample characteristics). These included 67 healthy controls recruited from the community via advertisements in newspapers and word of mouth and 429 help-seeking patients with emerging mental disorders recruited from early intervention public services for mental health problems in young people [the Brain and Mind Clinic at the Brain & Mind Research Institute (affiliated to the University of Sydney), and the *headspace* centre (a government funded service (National Youth Mental Health Foundation)), Camperdown, Sydney, Australia; both deserving the Inner Sydney area; (Scott et al. 2009; Hickie et al. 2012)].All patients from the aforementioned clinics who were deemed able to provide informed consent were systematically offered to enter the study. Participants were divided into five groups according to their primary diagnosis: healthy controls, anxiety disorders (e.g. social anxiety disorder (n = 14), generalised anxiety disorder (n = 33) and obsessive-compulsive disorder (n = 5); total n = 52), unipolar depression (n = 194), bipolar disorder (n = 101), and psychotic disorder (e.g. schizophrenia (n = 22), first episode psychosis (n = 44) and schizoaffective disorder (n = 7), drug induced psychosis (n = 9) , total n = 82). Primary diagnoses were determined by independent mental health professionals based on criteria from the Diagnostic and Statistical Manual for Mental Disorders IV. Exclusion criteria for all participants were: intellectual disability, current primary substance dependence, poor English skills, head injury with a loss of consciousness exceeding 30 minutes, and major medical or neurological condition. Furthermore, none of the participants from the control group reported having any mental disorder or endorsed a clinically significant level of depression symptoms on the Hamilton Rating Scale for Depression (HRSD, score above 7; (Hamilton 1960)). Two patients were excluded because they sustained a loss of consciousness for more than 30 minutes and one was excluded because he had epilepsy. All participants gave written

informed consent prior to entering the study. Written consent was obtained from the parents or legal guardians of all participants who were younger than 16 years old. The study protocol was approved by Human Research Ethics Committee of the University of Sydney and conforms to international ethical standards (Portaluppi et al. 2010).

Clinical assessments and self-report

All participants filled out the Horne-Östberg Morningness-Eveningness Questionnaire (ME; (Horne and Ostberg 1976) and the Kessler Psychological Distress Scale (K10; (Kessler and Mroczek 1992, 1994)). The ME is a 19-item questionnaire evaluating the time at which one feels most alert, and prefers to go to sleep, wake-up and conduct different types of activities, generating a total score ranging between 16 and 86, with higher scores reflecting stronger morningness. ME scores between 86 and 70 are considered to reflect 'definite/extreme morning' chronotype, 69-59 to reflect 'moderate morning' chronotype, 58-42 to reflect 'intermediate' chronotype, 41-31 to reflect 'moderate evening' chronotype, and 30-16 to reflect 'definite/extreme evening' chronotype. The K10 is a 10-item questionnaire assessing the level of psychological distress, with scores above 9, 15 and 21 considered to reflect low, moderate and high psychological distress, respectively.

As part of a standard structured assessment conducted within four weeks of questionnaire administration, research psychologists rated current functioning and symptoms on a battery of clinical scales. The level of functioning with regards to school, work and interpersonal relations was assessed with the Social and Occupational Functioning Scale (SOFAS; (Goldman et al. 1992). SOFAS scores of 70 or less are considered to indicate considerable difficulties in socio-occupational functioning. The 17-item version of the HRSD was also administered (HRSD; (Hamilton 1960)). HRSD total scores above 7, 13 and 19 are

considered to reflect mild, moderate and severe depressive symptoms respectively. The Brief Psychiatric Rating Scale (BPRS; (Overall and Gorham 1962)) was used to determine the severity of 24 psychiatric symptoms rated from 'not present' (i.e. score of 1) to 'extremely severe' (i.e. score of 7). Scores for the following BPRS subscales were analyzed: positive symptoms, negative symptoms, depression and mania.

Statistical analysis

Chi-square tests were used to compare the proportion of females across the primary diagnostic subgroups. A Kruskal-Wallis H test was used to assess age differences across all groups. The proportion of individuals with moderate and extreme evening and morning chronotypes were compared across each primary diagnostic subgroup using Chi-square tests. ME scores were submitted to a two-way ANCOVA (5 primary diagnostic groups * 2 sex) controlling for age, with least significant difference (LSD) post hoc tests.

Correlations were performed to evaluate associations between ME scores and K10, SOFAS, HRSD and BPRS scores for males and females with primary anxiety, depression, bipolar or psychotic disorders. Spearman's rank-order correlations were used for SOFAS and BPRS scores. Pearson correlations were used for K10 and HRSD scores. Partial correlations were conducted to determine whether each significant correlation remained significant after controlling for age. The false discovery rate approach (Benjamini and Hochberg 1995) was used to account for multiple correlations (q = 0.05).

One individual from the anxiety group was excluded from all analyses because of outlying data on the ME and three individuals (one from the bipolar group and two from the psychosis group) were excluded from the BPRS analyses because of outlying BPRS data (>3 interquartile range). One individual from the depression and 1 from bipolar group was

excluded due brain injury, 1 individual in the psychosis group was excluded due to history of epilepsy. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for windows 20.0: SPSS, Inc., Chicago, IL, USA).

RESULTS

Sample characteristics

Table 2 reports sample characteristics and clinical ratings across the five primary diagnostic subgroups. A significant effect of age was found (χ^2 (4) = 64.4, p < 0.001). The control group was significantly older than the depression (p < 0.001), anxiety (p < 0.001) and bipolar (p = 0.002) groups, but no significant age difference was found between the control and the psychosis group. The proportion of females significantly differed across the primary diagnostic subgroups (χ^2(4) = 42.4, p <0.001). Compared to the proportion of females in the control group (55%), the proportion of females was significantly higher in the bipolar group (72%, p = 0.024) and significantly lower in the psychosis group (26%, p < 0.001).

Morningness-eveningness preference across primary diagnostic subgroups

Figure 1 shows mean ME scores across the five primary diagnostic subgroups. A significant main effect of group was found in ME scores (F (4, 485) = 7.7, p < 0.001). Compared to the control group, the anxiety (p < 0.001), depression (p < 0.001), bipolar (p < 0.001) and psychosis (p = 0.028) groups had significantly lower ME scores (i.e. reflecting higher eveningness). The psychosis group had a significantly higher ME score (i.e. reflecting lower eveningness) than the depression (p = 0.001) and anxiety (p = 0.046) groups. No other group comparison reached the significance threshold. No significant main effect of sex or interaction between sex and group were found.

Figure 2 presents the percentages of individuals whose ME score fell into the 'extreme evening' or 'moderate evening' chronotype range across each primary diagnosis subgroup. There were significant group differences in the proportions of 'moderate morning' (χ (4) = 14.9, p = 0.005), 'moderate evening' (χ (4) = 12.6, p = 0.014) and 'extreme evening' (χ (4) = 12.0, p = 0.018) types. The anxiety (χ (1) = 7.2, p = 0.007), depression (χ (1) = 8.5, p = 0.004), and bipolar (χ (1) = 9.8, p = 0.002) subgroups comprised a significantly lower proportion of 'moderate morning' types compared to the control group. The proportion of 'moderate evening' types was significantly higher in the anxiety (χ (1) = 7.6, p = 0.006), depression (χ (1) = 11.0, p = 0.001) and bipolar (χ (1) = 6.6, p = 0.010) subgroups than in the control group. Similarly, the psychosis group tended to have a higher proportion of 'moderate evening' types than the control group (χ (1) = 3.1, p = 0.077). The proportion of 'extreme evening' types was significantly higher in the anxiety (χ (1) = 6.72, p = 0.010) and depression (χ (1) = 7.1, p = 0.008) subgroups than in the control group.

Associations between morningness-eveningness and clinical ratings

Statistics for correlations between ME scores and clinical ratings are reported in table 3. After correcting for multiple comparisons, lower ME scores (i.e. higher eveningness) correlated with higher psychological distress on the K10 in males from the bipolar subgroup (r = -0.73, p < 0.001). Lower ME scores correlated with higher HRSD scores in females from the primary depression subgroup (r = -0.39, p < 0.001). Lower ME scores also correlated with higher depression symptoms on the BPRS within females from the depression group (r_s = -0.31, p = 0.003) and within males from the bipolar group (r_s = -0.58, p = 0.002). These correlations remained significant after controlling for age. No other correlation remained significant after applying the correction for multiple tests.

DISCUSSION

To our knowledge, this study is the first to investigate the nature and clinical correlates of morningness-eveningness preference across multiple mental disorders. Our sample of young persons with mental disorders presented a stronger eveningness preference and higher rates of 'moderate and extreme evening' types than healthy controls from the same age group, especially those with affective disorders. Furthermore, higher eveningness was associated with worse clinical profiles and this was influenced by sex and primary diagnosis.

The present findings suggest that higher eveningness and increased prevalence of late chronotypes in young persons with various mental illness extend beyond normal age related changes. This was most pronounced in individuals with anxiety, depression and, to a lesser extent, bipolar disorder. The overall stronger preference towards eveningness in all clinical subgroups compared to healthy controls after controlling for age is in accordance with our previous observations of delayed actigraphic sleep-wake patterns in young persons with anxiety, depression, bipolar and psychotic disorders (Robillard et al. 2015b). Parallel to previous findings (Reid et al. 2012), our results suggests that this increased tendency towards eveningness is more pronounced in individuals with affective disorders than in those with psychotic disorders.

In line with previous studies (Abe et al. 2011; Merikanto et al. 2013), our results indicate that stronger eveningness preference is associated with elevated psychological distress and more severe psychiatric symptom severity. The most robust associations pertained to depressive symptom in the subgroups with mood disorders and were influenced by sex. Higher eveningness correlated significantly with depressive symptoms rated on both the HRSD and the BPRS in participants with primary depression, but this was significant only in females. In

males from the bipolar subgroup, stronger eveningness was associated with general psychological distress and depressive symptoms. Males from the bipolar subgroup with stronger eveningness also presented with worse positive symptoms which could be reflective of manic-like states involving symptoms such as hostility, grandiosity, suspiciousness, unusual thoughts and disorganisation, but this was no longer significant after correcting for multiple correlations. Overall, these findings build on previous evidence from non-clinical populations where chronotype variation amongst symptomatic/asymptomatic subgroups also appears to be influenced by sex (Díaz-Morales and Sánchez-Lopez 2008).

Despite their later chronotypes, young individuals often have to attend school or work in the morning, which often curtails sleep, leading to transient sleep loss. Furthermore, later chronotypes have been associated with poorer sleep consolidation (Soehner et al. 2011; Onder et al. 2014). From this perspective, later chronotypes are likely to amplify sleep disturbances commonly occurring in young people with mental disorders. Furthermore, considering the negative impacts of reduced sleep duration and quality on psychiatric symptoms, the association between later chronotypes and clinical outcomes in young persons with mental illnesses may be modulated by sleep disturbances. In support of this hypothesis, later chronotypes in young persons have been found to modulate the bidirectional interaction between insomnia and depression (Alvaro et al. 2014).

Our findings reinforce previous evidence (Drennan et al. 1991; Mansour et al. 2005; Wood et al. 2009) highlighting progressive associations between later chronotypes and the severity of symptoms beyond mere diagnostic group differences. Considering that symptom severity typically varies over time, this raises the question as to whether morningness-eveningness preference could be influenced not only by individual traits, but also by clinical state. This is especially relevant in the context of developmental changes in the sleep-wake cycle, the

circadian system and the concomitant variations in chronotypes during youth (Garcia et al. 2001; Hagenauer and Lee 2012), a life period during which circadian preference does not appear to be static. For instance, the association between depression and eveningness appears to be moderated by age, being strongest in those younger than 21 years old, in those in their 50's and in those older than 59 years of age (Kim et al. 2010). It is also possible that later chronotypes in healthy individuals may be related to a higher risk to subsequently develop more severe mental illnesses. Further longitudinal studies are required to clarify possible state and trait influences on morningness-eveningness preference in mental disorders, notably by determining whether changes in symptom severity along the course of illness are accompanied by changes in morningness-eveningness preference within the same individual.

Some limitations inherent to the current study design need to be considered. Firstly, the control group was significantly older (23.5 years old on average) than the clinical subgroups (averages ranging from 19.4 to 22.0 years old). However, we attempted to limit the influence of age by controlling for this factor statistically. Missing data across the different scales, diagnostic subgroups and gender unfortunately limited the sample sizes precluding the use of regression modelling. While most psychotropic medications and the social and occupational impacts of mental disorders may influence sleep and possibly circadian rhythms, they may also mediate how morningness-eveningness preference relates to mental disorders, and could possibly have influenced the present findings. Also, the clinical subgroups were defined according to primary diagnoses and did not take comorbidities into account.

The stronger eveningness preference in young people with mental disorders and its association with worse clinical outcomes supports the notion that later chronotypes, beyond

normal developmental changes, may be a predisposing factor for more severe mental illness, a concurrent exacerbating factor, or a covariate of current clinical state. Importantly, treatments targeting the circadian system, such as sleep rescheduling, light or melatonergic agents, have been shown to induce mood improvements and a shift towards more morningness (Corruble et al. 2014; Rybak et al. 2006). Furthermore, there are some indications that chronotype may predict antidepressant response to these treatments. There is thus a need to further investigate changes in morningness-eveningness preference across the course of mental disorders and their relation to treatment outcomes.

Declaration of Interest

D.F. Hermens has received honoraria for educational seminars from Janssen-Cilag and Eli Lilly. E.M. Scott is the (unpaid) Clinical Director of Headspace Services at the Brain and Mind Research Institute (BMRI), the (unpaid) Coordinator of the Youth Mental Health Research Program at the BMRI, and Deputy Director of St Vincent's Private Hospital Young Adult Mental Health Unit. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. I.B. Hickie was a director of Headspace: The

National Youth Mental Health Foundation until January 2012. He is the executive director of the BMRI, which operates 2 early-intervention youth services under contract to Headspace. He is a member of the new Australian National Mental Health commission and was previously the CEO of Beyondblue: The National Depression Initiative. He has led a range of community-based and pharmaceutical industry–supported depression awareness and education and training programs. He has led depression and other mental health research projects that have been supported by a variety of pharmaceutical partners. Current investigator-initiated studies are supported by Servier and Pfizer. He has received honoraria for his contributions to professional educational seminars supported by the pharmaceutical in-dustry (including Servier, Pfizer, AstraZeneca, and Eli Lilly). No other competing interests declared.

Figure 1: Horne-Östberg Morningness-Eveningness scores across primary diagnosis subgroups
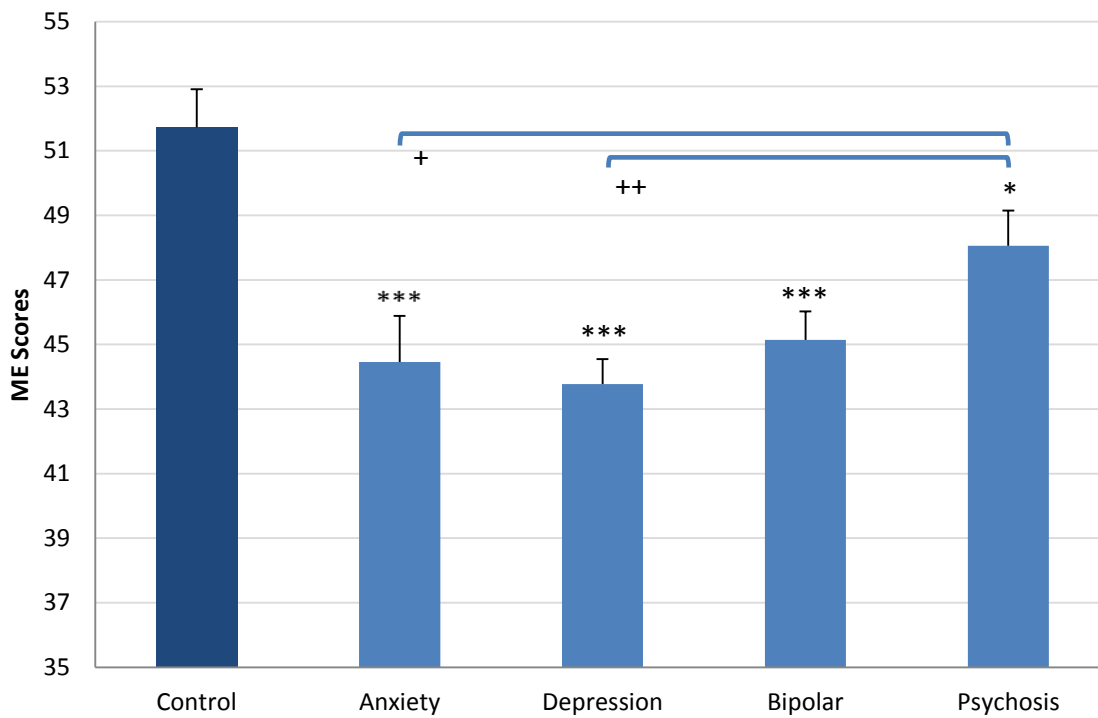
Means and SEM of Horne-Östberg Morningness-Eveningness (ME) scores for each primary diagnosis group. Asterisks indicate differences relative to the control group and plus signs indicate differences amongst patient diagnostic subgroups. $^{*/+}$ $p < 0.050$, $^{++}$ $p < 0.010$, *** $p < 0.001$.

Figure 2: Proportions of individuals with moderate and extreme evening chronotypes across primary diagnostic subgroups
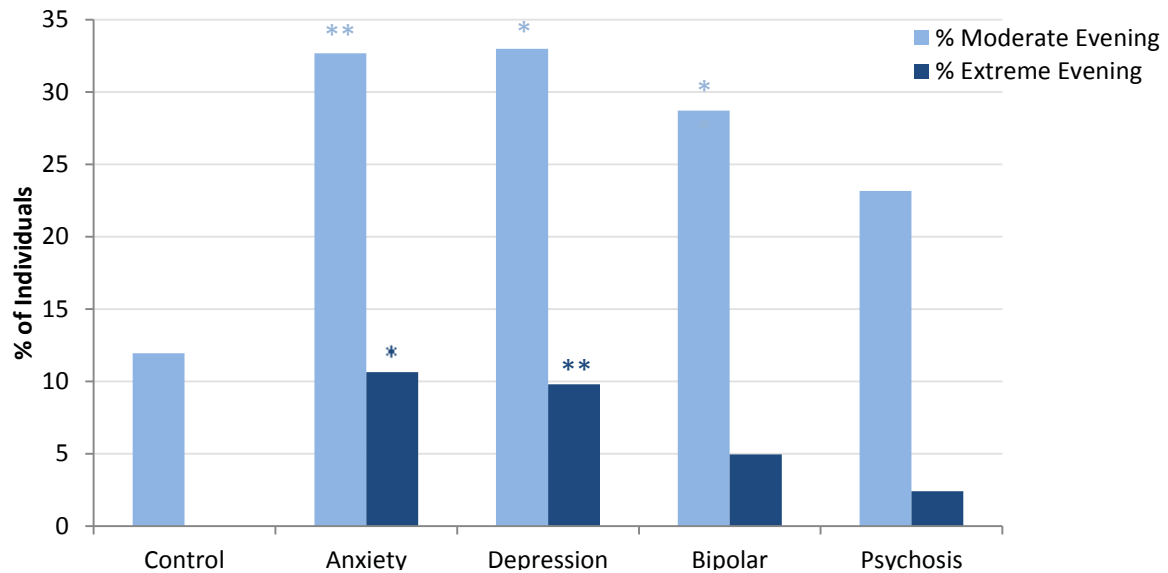
Asterisks indicate differences relative to the control group. * $p < 0.050$, **$p < 0.010$. No individual from the control group endorsed an extreme evening chronotype.

Table 2: Demographic characteristics, Horne-Östberg Morningness–Eveningness scores and clinical profiles across primary diagnostic subgroups

		Controls (n = 67)	Anxiety (n = 52)	Depression (n = 194)	Bipolar (n = 101)	Psychosis (n = 82)
	% Females	55.2%	51.9%	40.7%	72.3%	25.6%
	Age (years)	23.53 (3.60)	19.70 (4.35)	19.36 (4.01)	21.08 (3.80)	22.04 (4.16)
	% Smoking	22.4%	17.6%	27.0%	31.7%	34.6%
Medication	% Antidepressant	0.0%	13.7%	49.0%	37.6%	22.2%
	% Sedatives & Hypnotics	0.0%	2.0%	1.5%	0.0%	0.0%
	% Mood Stabilisers	0.0%	3.9%	5.6%	38.6%	6.2%
	% Antipsychotics	0.0%	5.9%	15.3%	42.6%	63.0%
	% Benzodiazepines	0.0%	2.0%	2.6%	3.0%	3.7%
	% Stimulants	0.0%	3.9%	2.0%	5.0%	0.0.%
	Years of Education	14.40 (2.08)	11.52 (2.49)	11.43 (2.55)	12.64 (2.12)	11.93 (2.15)
	Occupational status Employed/Student	88.1%	64.7%	67.3%	77.2%	49.4%
Living status	% independent/alone	16.4%	20.9%	5.6%	9.9%	11.1%
	% independent/ roommate	47.7%	57.1%	28.6%	39.6%	37.0%
	% living with parents	13.4%	16.1%	48.5%	35.6%	40.7%
Clinical Scales	SOFAS	90.84 (4.02)	64.17 (12.27)	60.93 (11.03)	62.84 (10.68)	53.18 (11.76)
	K10	14.54 (3.21)	26.41 (7.93)	29.57 (7.43)	27.42 (8.06)	24.24 (8.57)
	HRDS$_{total}$	1.92 (1.92)	12.26 (7.85)	13.88 6.70)	11.75 (6.80)	10.02 (6.21)
	BPRS$_{positive}$	7.56 (0.92)	9.50 (2.22)	9.96 (2.65)	10.95 (4.10)	12.31 (5.14)
	BPRS$_{negative}$	5.13 (0.49)	6.95 (2.50)	7.12 (2.72)	6.35 (2.08)	8.79 (3.37)
	BPRS$_{depression}$	7.35 (1.84)	13.09 (5.15)	14.63 (4.74)	13.67 (4.89)	11.86 (4.77)
	BPRS$_{mania}$	7.15 (0.51)	8.81 (2.65)	9.18 (2.78)	10.60 (4.08)	9.01 (2.56)
	ME	51.82 (9.98)	45.03 (11.01)	43.77 (10.82)	45.13 (8.93)	48.05 (9.91)

Proportions of females and means (standard deviations) for age, Horne–Östberg Morningness–Eveningness (ME) scores, SocioOccupational Functioning Scale (SOFAS), Kessler Psychological Distress Scale (K10), Hamilton Depression Rating Scale (HRSD) and subscales from the Brief Psychiatric Rating Scale (BPRS).

Table 3: Correlations between Horne-Östberg Morningness-Eveningness scores and clinical variables

	Anxiety			Depression			Bipolar			Psychosis		
	r	p	BH$_{critical}$	R	p	BH$_{critical}$	r	p	BH$_{critical}$	r	p	BH$_{critical}$
Males												
SOFAS	.52	.023	.010	.13	.304	.026	.24	.258	.023	.03	.844	.046
K10	-.40	.084	.014	-.24	.037	.013	-.73	<.001*	.001	-.30	.023	.009
HRSD $_{total}$	-.18	.424	.031	-.16	.180	.018	-.47	.022	.008	-.23	.123	.016
BPRS$_{positive}$	.05	.845	.046	.05	.678	.039	-.47	.018	.006	-.27	.071	.013
BPRS$_{negative}$	-.07	.793	.044	-.12	.318	.028	.07	.747	.042	-.06	.678	.038
BPRS$_{depression}$	-.15	.523	.034	-.14	.236	.021	-.58	.002*	.003	-.15	.315	.027
BPRS$_{mania}$	.11	.643	.038	.12	.344	.029	-.03	.899	.049	-.19	.206	.020
Females												
SOFAS	.31	.172	.017	.14	.197	.019	-.30	.029	.012	-.22	.371	.030
K10	-.11	.625	.037	-.24	.015	.004	.04	.768	.043	-.54	.016	.005
HRSD $_{total}$	-.22	.302	.025	-.39	<.001*	.002	-.04	.745	.041	-.28	.254	.022
BPRS$_{positive}$	-.20	.341	.029	-.17	.085	.015	-.14	.247	.021	-.16	.513	.033
BPRS$_{negative}$	-.15	.475	.032	-.23	.026	.011	-.29	.021	.007	.06	.804	.045
BPRS$_{depression}$	-.07	.738	.040	-.31	.003*	.004	-.07	.595	.035	.04	.860	.048
BPRS$_{mania}$	.04	.848	.047	-.05	.607	.036	.00	.995	.050	-.27	.266	.024

Socio-Occupational Functioning Scale (SOFAS), Kessler Psychological Distress Scale (K10), Hamilton Depression Rating Scale (HRSD), Subscales from the Brief Psychiatric Rating Scale (BPRS), BH$_{critical}$ (Benjamini-Hochberg critical value), *Correlations which remained significant after correcting for multiple tests (i.e. p-value below BH$_{critical}$.

Chapter 3

Longitudinal changes in chronotype in young persons with depression or bipolar disorder

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ABSTRACT

Youth is a fragile period due to the frequent onset of both circadian disturbances and mental disorders. 'Chronotype' ('morningness-eveningness' preference) refers to an individual's circadian preference for early or late sleep and wake times, as well as preferred time to conduct physical and cognitive activities. Adolescents with affective disorders and evening chronotypes have previously been shown to have worse symptom severity than those with morning chronotypes. However, little is known about how chronotypes may change with the course of illness and altered symptom severity. In a youth sample with affective disorders the current study aimed to assess: i) the temporal variations in morningness-eveningness preference according to illness course, and ii) the longitudinal associations between changes in morningness-eveningness preference and changes in psychiatric symptoms.

This sample included 133 individuals with depression or bipolar disorders between 12 and 35 years of age. At two time points [baseline and follow-up; mean longitudinal interval = 1.6 (0.6) years], the Hamilton Depression Rating Scale, and the Brief Psychiatric Rating Scale (BPRS) were administered by a research psychologist and participants completed the Horne-Östberg Morningness-Eveningness Questionnaire (ME). Between baseline and follow-up, participants received standard clinical care. For some analyses, participants were divided into two groups based on changes in chronotype from baseline to follow-up (i.e. "earlier chronotype shifters" and "stable/eveningness shifters").

Results showed that there was an overall shift towards morningness from baseline to follow-up (p < 0.010). Specifically, from baseline to follow-up, 33% of the participants shifted towards an earlier chronotype category. After controlling for age, gender and duration of follow-up period, these "earlier chronotype shifters" showed a more pronounced decrease from baseline to follow-up on the BPRS subscales for depression (F (1, 108) = 4.6, p = 0.035) and negative symptoms (F (1, 115) = 6.6, p = 0.011) than the "stable/eveningness shifters".

Overall, these findings suggest that, in young persons with affective disorders, chronotypes are not stable across the course of illness and shift towards earlier circadian preference when psychiatric symptoms improve.

INTRODUCTION

During brain maturation, subcortical regions develop earlier than the prefrontal cortex, leaving a gap during which adolescents have heightened emotionality, a factor which may be associated with an increased risk of developing affective disorders (Casey et al. 2010). Indeed, affective disorders have increased in prevalence amongst youth (Andrews et al. 2001), and epidemiological data suggests that 6.3% of Australians aged 16-24 are diagnosed with affective disorders (Reavley et al. 2010). This is of concern given that affective disorders are associated with psychosocial and vocational dysfunction, as well as heightened disability (Hamilton et al. 2011). Efforts to better understand factors associated with symptom onset, perpetuation and recurrence is therefore warranted.

Research attempting to delineate the links between affective disorders and the circadian system has received an increasing amount of attention in recent years (Kessler et al. 2005; Justice et al. 2009; Robillard et al. 2013b; Naismith et al. 2012a). Specifically, studies have shown that it is important to consider a person's chronotype. Chronotypes, or morningness-eveningness preference, reflect the individual preference for the time at which to sleep, wake-up, and undergo peak physical and cognitive activities (Horne et al. 1980). Morningness-eveningness preference is known to vary across age (Randler et al. 2009). Studies show that early morning preference often occurs in children and shifts towards stronger eveningness preference during adolescence (Kim et al. 2002; Werner et al. 2009). Pubertal development is likely to be a key influence of chronotype (Lerner et al. 2010; Roenneberg et al. 2004) as reproductive hormones are likely to play a part in driving chronotype preference towards eveningness (Randler et al. 2009; Hagenauera and Leea 2012). Indeed, longitudinal studies over a two-year period have shown that hormonal and pubertal changes are linked with delays (shifts towards eveningness) in sleep and sleep disruption (Sadeh et al. 2009). Additionally, chronotype changes across different age groups may also be modulated by sex,

with females generally reaching a peak in the shift towards eveningness at earlier ages than males (Tonetti et al. 2008; Randler 2008; Roenneberg et al. 2004). Chronotype preference starts to shift back towards morningness during adulthood (Thorleifsdottir et al. 2002; Garcia et al. 2001; Roenneberg et al. 2004). Emerging research suggests that certain chronotypes may have a greater propensity for negative emotionality and affective features Specifically, an eveningness preference (i.e. 'owls' or evening types) appears to be an independent risk factor for worse negative emotionality (Simor et al. 2015). Thus it is possible that individuals who continue to have later chronotypes during young adulthood may be more prone to affective disorders. Conversely, a shift towards earlier chronotype may be associated with improved well-being.

In support of this notion, a growing body of literature highlights that elevated rates of moderate and extreme evening chronotypes are observed in adolescents and adults with affective disorders (Mansour et al. 2005; Wood et al. 2009; Merikanto et al. 2013; Selvi et al. 2010; Gau and Merikangas 2004). Evening types have higher levels of depressive, paranoid, and manic symptoms than morning types (Ong et al. 2007; Gau and Merikangas 2004; Barba et al. 2009). Similarly, evening chronotypes are associated with severe depressive symptoms in youth (Barba et al. 2009; Merikanto et al. 2013; Takashi Abe 2011). This is consistent with our previous study, which showed that young persons with anxiety, depression, bipolar, and psychotic disorders have stronger eveningness preference than healthy controls (Fares et al. 2015). We also observed that later chronotypes were generally associated with worse psychological distress and symptoms severity (Fares et al. 2015). The association between depressive symptoms and eveningness preference has been found to be stronger in youth in comparison to adults between 20 and 50 years of age (Kim et al. 2010; Barba et al. 2009; Kitamura et al. 2010). This has been proposed to be related to the progressive delay in circadian rhythms which takes place during adolescence (Fares et al. 2015). Kraemer and

colleagues highlighted the need for longitudinal data in relation to mental health and pubertal

development, predominantly when trying to understand distinct developmental trajectories or

disease processes (Kraemer et al. 2001). The correlations between affective symptoms and

eveningness preference suggest that chronotype preference may influence an individual's

clinical state and/or that a change in clinical state may influence chronotype. Increasing

evidence suggest that the active realignment of circadian rhythms may be linked to clinical

improvements in persons with mood disorders (Hickie et al. 2013a; Winkler et al. 2005).

However, little is known about the possible association between longitudinal changes in

morningness-eveningness preference and symptom severity.

Despite their considerable changes across age and their correlation with symptom severity,

chronotypes have classically been considered as a fixed predefined trait. Accordingly, there

appears to be a genetic predisposition to chronotypes, with stronger eveningness being linked

to certain polymorphisms of 'clock' genes involved in circadian regulation, such as CLOCK

3111C (Katzenberg et al. 1998). Similarly, associations between higher eveningness and the

C/C allele of CLOCK have been reported in persons with bipolar disorder (Benedetti et al.

2003; Serretti et al. 2003; Benedetti et al. 2007). However, this fixed trait view is less

consistent with other findings which suggest that sleep profiles and chronotypes may change

along the course of mental illnesses. For instance, we recently observed in young persons

with affective disorders that lower sleep efficiency is associated with longitudinal worsening

of manic symptoms (Robillard et al. 2015a). Similarly, a large cohort study showed that

reduced sleep in youth predicts depressive symptoms (Roberts et al. 2009). In addition, long-

term sleep problems are associated with suicidal thoughts and suicidal attempts in adolescents

and young adults across a longitudinal period of eight years (Wong and Brower 2012). Since

later chronotypes are often associated with reduced sleep duration and poorer sleep quality

(Garcia et al. 2001), these findings may indirectly support the hypothesis that later

chronotypes may be linked to longitudinal worsening in symptom severity along the course of affective disorders. Accordingly, in a large open study, depressed participants who received agomelatine (a melatonin agonist with antidepressant properties) shifted towards higher morningness preference along the course of treatment and this change was greater in individuals who had greater reductions in depressive symptoms following treatment (Corruble et al. 2014).

The current study aimed to assess: i) the temporal variations in morningness-eveningness preference along the course of affective disorders during youth and ii) interactions between longitudinal changes in morningness-eveningness preference and longitudinal changes in psychiatric symptoms. It was hypothesised that morningness-eveningness preference would vary across the course of affective disorders. It was also hypothesised that those who shift towards increased morningness over time would have decreased symptom severity in comparison to those who remained stable in their morningness-eveningness preference or shifted towards increased eveningness.

METHOD

Participants

One hundred and thirty three individuals with affective disorders aged between 12 and 35

years took part in this study. Participants were recruited from early intervention services at

the Brain & Mind Centre, and the *headspace* centre (Camperdown, Sydney, Australia) both

serving the Inner Sydney area (Scott et al. 2012). As described previously (Fares et al. 2015),

all diagnoses were determined by a mental health professional based on the Diagnostic and

Statistical Manual for Mental Disorders-IV-TR (American Psychiatric Association, 2000).

Participants were divided into two groups on the basis of their diagnosis (see Table 4 for

sample characteristics): unipolar depression (n = 63) and bipolar disorder (n = 70). Exclusion

criteria for all participants were: intellectual disability, head injury with a loss of

consciousness exceeding 30 minutes, current substance dependence, insufficient English, and

major neurological or medical conditions. This study was approved by the University of

Sydney's Human Research Ethics Committee, and all participants gave written informed

consent prior to participation in the study. Written consent for participants who were younger

than 16 years of age was obtained from the participant's parent or legal guardian.

Clinical Assessments and Self-Report

Clinical assessments and self-report were conducted at baseline and follow-up. The

longitudinal interval between baseline to follow-up was 1.6 (SD = 0.6) years long. During

this period, participants received standard clinical care at the Brain & Mind Centre or the

headspace centre (Scott et al. 2012).

A research psychologist administered the 17-item version of the Hamilton Depression Rating

Scale (HDRS) (Hamilton 1960). Total HDRS scores above 7, 13 and 19 are considered to

reflect mild, moderate and severe depressive symptoms respectively (Hamilton 1960). Total HDRS (HDRS-total) score was calculated, as well as a score excluding the three insomnia items (HDRS-insExcl). The Brief Psychiatric Rating Scale (BPRS), which is based on 24 items rated from 'not present' (i.e. score of 1) to 'extremely severe' (i.e. score of 7), was also administered (Overall and Gorham 1962). The following BPRS subscales were analysed: positive symptoms (BPRS-positive), negative symptoms (BPRS-negative), depression (BPRS-depression) and mania (BPRS-mania) (Overall and Gorham 1962).

Participant's morningness-eveningness preference was measured with the Horne-Östberg Morningness- Eveningness Questionnaire (ME) (Horne and Ostberg 1976). Total ME scores were used to categorise participants according to their chronotypes: 'definite / extreme morning' (ME scores between 70 and 86),'moderate morning' (between 59 and 69), 'neither' (between 42 and 58), 41-31 to 'moderate evening' (between 31 and 41) and 'definite / extreme evening' (between 16 and 31). Participants were also categorised into two longitudinal chronotype change groups: the "earlier chronotype shifters", which included individuals who shifted to an earlier chronotype category between baseline and follow-up, and the "stable/eveningness shifters", which included individuals whose chronotype remained stable or shifted later.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for windows 20.0: SPSS, Inc., Chicago, IL, USA) and Statistica 10 (Version 20.0. 2010). The significance level for all tests was set at $p < 0.05$.

For descriptive purposes, Mann-Whitney U and chi-square tests were used to compare respectively age and female to male ratios across these two groups. T-tests were used to assess the differences in baseline values for HDRS-total, HDRS-insExc, BPRS-positive, BPRS-negative, BPRS-depression and BPRS-mania amongst the two diagnostic groups.

ME scores were submitted to a two-way ANCOVA with one independent factor (i.e. 2 diagnostic groups: unipolar and bipolar) and one repeated measure (i.e. two time points: baseline and follow-up) controlling for age, gender and follow up period length. Chi-square tests were used to compare the distribution of ME change groups across the two diagnostic groups.

HDRS and BPRS scores were submitted to three-way ANCOVAs with two independent factors (i.e. two diagnostic groups: unipolar and bipolar; and two chronotype change groups: "earlier chronotype shifters" and "stable/eveningness shifters") and one repeated measure (i.e. two time points: baseline and follow-up) controlling for age, gender and follow up period length. Prior to analyses, HDRS-total, BPRS-total, BPRS-positive and BPRS-negative scores were log-transformed to improve normality.

RESULTS

Sample characteristics

Table 4 reports demographic characteristics across the two diagnostic subgroups at baseline. There was a significant age difference between the bipolar and depression group (U = 1639.5, p = 0.011). The proportion of females in both groups did not differ significantly ($\chi^2(1) = 0.97$ p = 0.334). There were significant differences in clinical scales between the diagnostic groups: compared to the bipolar group, the depression group had higher depression severity as assessed by HDRS-total (F (1, 458) = 10.1, p = 0.002) and BPRS-depression (F (1, 117) = 4.1, p = 0.046).

Longitudinal changes in Morningness-Eveningness

Figure 3 presents mean ME scores at baseline and follow-up in the depression and bipolar groups. After controlling for age, gender and longitudinal period length, a significant interaction between diagnostic groups and time was found (F (1, 128) = 11.6, p < 0.001). In both diagnostic groups, there was a significant shift towards increased morningness from baseline to follow-up, but this was slightly more pronounced in the depression group (p < 0.001) than in the bipolar group (p = 0.009). From a categorical perspective, 33% of the overall participant sample shifted to an earlier chronotype category (i.e. 'earlier chronotype shifters'). There was no significant difference in the proportions of 'earlier chronotype shifters' in the depression group and the bipolar group ($\chi(1) = 3.0$, p = 0.086).

Longitudinal clinical improvements in relation to changes in morningness-eveningness preference

Table 5 reports means clinical ratings at baseline and follow-up for the depression and bipolar disorder subgroups and the chronotype change groups. After controlling for age, gender and duration of follow-up period, significant interactions were found between chronotype change groups and time for BPRS-depression ($F (1, 108) = 4.6$, $p = 0.035$) and BPRS-negative ($F (1, 115) = 6.6$, $p = 0.011$). In the 'earlier chronotype shifters' group, BPRS-depression ($p < 0.001$) and BPRS-negative ($p = 0.002$) were significantly reduced from baseline to follow-up. In the 'stable/eveningness shifters' group, there was a more moderate reduction in BPRS-depression ($p = 0.040$) from baseline to follow-up, and there was no significant change in BPRS-negative ($p = 0.984$).

Main effects of time showed that HDRS-total ($F (1, 105) = 17.5$, $p < 0.001$), HDRS-insExc ($F (1, 102) = 16.5$, $p < 0.001$), BPRS-positive ($F (1, 113) = 19.4$, $p < 0.001$) and BPRS-mania ($F (1, 113) = 6.9$, $p = 0.010$) significantly decreased from baseline to follow-up. A main effect of chronotype change groups showed that BPRS-mania was higher in the 'earlier chronotype shifters' than in the 'stable/eveningness shifters' group ($F (1, 113) = 9.1$, $p = 0.003$). There was no significant interaction involving diagnostic groups for any clinical scale, nor any significant interaction between chronotype change groups and time for HDRS-total, HDRS-insExc, BPRS-positive and BPRS-mania.

DISCUSSION

This unique longitudinal study investigated variations in morningness-eveningness preference in young persons with affective disorders and explored the relationship between changes in morningness-eveningness preference longitudinally and in relation to changes in psychiatric symptoms. The findings suggest that during a follow-up period of approximately 1.6 years, there was a general shift towards morningness. Importantly, this longitudinal shift towards morningness was linked to clinical improvements. This suggests that chronotypes are not only trait markers, but that they are intertwined with a person's mental health state.

Previous studies have established that evening preference and/or delayed sleep phase are common in individuals with affective disorders (Abe et al. 2011; Chelminski et al. 1999; Merikanto et al. 2013; Chung et al. 2012; Wood et al. 2009; Mansour et al. 2005). Building on these previous observations, our results indicate that chronotypes can change over time in people with depression and bipolar disorder, and that individuals who shift towards more morningness also show improvements in mood and symptom profiles. The depression and bipolar groups showed a significant decrease in ME over time, however this was slightly more pronounced in those with depression. This may be due to the fact that, in this sample, those with depression had a higher level of eveningness at baseline than people with bipolar disorder. This is parallel to our previous study where the depression group had a somewhat higher percentage of extreme evening types compared to bipolar participants (Fares et al. 2015). Altogether, these findings provide further support for the link between mood and circadian rhythms, and suggest that chronotype may be a 'state' marker of symptoms in affective disorders.

The current study showed that young persons with affective disorders who eventually shifted towards earlier chronotypes significantly improved in depressive and negative symptoms. Conversely, those participants who maintained the same chronotypes or shifted towards more eveningness showed milder improvements in depressive symptoms and did not show any significant improvement in negative symptoms. In addition, regardless of 'time', the 'earlier chronotype shifters' group were found to have higher BPRS-mania scores, when compared to the 'stable/eveningness shifters'. It could be speculated that individuals with more severe mania symptoms, such as those with current or emerging bipolar illnesses, may have less stable chronotypes. Importantly, these results remained significant after controlling statistically for the effects of age. Also, the duration of follow-up period was briefer than the time span which would be expected to yield age-related changes across chronotype categories. Hence, the longitudinal changes in chronotypes observed herein are unlikely to be solely explained by developmental changes.

Psychiatric symptom severity typically varies over time and it may be possible that morningness-eveningness preference could be influenced not only by predefined individual traits, but also by clinical state. It is also possible that changes in circadian profiles and morningness-eveningness preference may drive changes in mood. This is especially relevant in the context of developmental changes in the sleep-wake cycle and the associated variations in chronotypes during youth (Garcia et al. 2001; Hagenauera and Leea 2012). Youth is a life period during which circadian rhythms and circadian preference do not appear to be static and these changes in chronotype may potentially increase one's susceptibility to mood disorders. For instance, Miller and colleagues suggested that eveningness may create vulnerability to depression due to delayed positive emotion (Miller et al. 2015). In addition, studies have shown how circadian variation have high association with affective disorders (Chung et al. 2012). This clock gene variations due to changes in amplitude and timing of the master clock

may generate a chronobiological vulnerability in persons with affective disorders (Benedetti et al. 2003).

While causality cannot be determined from the current findings, it could be speculated that changes in clinical states may influence chronotype and that changes in chronotype could influence clinical state. In any case, from a clinical and practical perspective, shifting to earlier circadian preference may possibly contribute to improve general well-being since morningness is associated with better mood (Randler 2008). Previous findings suggested that interventions' actively leading to circadian phase advances such a light therapy, melatonergic treatment, and sleep rescheduling can improve clinical state. For instance, a study on 70 inpatients with depression showed significant clinical improvements after three weeks of light therapy (Dallaspezia et al. 2012).Via their chronobiotic effects, these circadian-based interventions can lead to shifts in the sleep-wake cycle and daytime activity patterns, and may thus also lead to shifts in chronotypes. This is in accordance with a recent report showing that depressive participants shifted towards more morningness after agomelatine treatment (Corruble et al. 2014). Increases in morningness following chronotherapies could potentially be indicative of clinical improvement. There is a need to assess whether psychiatric symptoms in individuals with later chronotypes respond better to circadian based interventions than those with earlier chronotypes. Further longitudinal studies are required to evaluate chronotype and clinical changes across multiple mental disorders to determine whether the present findings are specific to affective disorders.

This study had some limitations which should be mentioned. While most psychotropic medications influence sleep and possibly circadian rhythms, they may also have an impact on morningness-eveningness preference, and could possibly have influenced the present findings. Measuring melatonin, cortisol and core body temperature may have provided

valuable insights about how chronotype changes relate to objective endogenous circadian profiles. In addition, actigraphy measures would have been helpful to determine if changes in chronotype were accompanied by differences in sleep and physical activity patterns from baseline to follow-up.

Conclusion

The current study assessed longitudinal shifts in chronotype in young persons with depression and bipolar disorder over a period of 1.6 years. Individuals who shifted towards earlier chronotypes showed greater improvements in depressive and negative symptoms, suggesting that chronotype may vary with clinical state. There is possibly a bi-directional relation between chronotypes and mood disorders, but future research should aim to evaluate whether interventions actively inducing shifts towards more morningness may have mood stabilising effects. Moreover, it will be relevant to assess whether psychiatric symptoms in persons with later chronotypes are more responsive to circadian-based interventions than psychiatric symptoms in individuals with earlier chronotypes.

Table 4: Sample characteristics across diagnostic subgroups

|	Depression	Bipolar
Age (mean (SD))	20.2 (4.0)	22.2 (4.8)
Gender (%Females)	61.9 %	70.0 %
Medications		
Antidepressants	41.3%	46.6%
Antipsychotics	15.9%	49.3%
Sedative & Hypnotics	0%	1.4%
Mood Stabilisers	7.9%	7.9%
Benzodiazepines	1.6%	4.1%
Stimulants	3.2%	5.5%
Anticonvulsants	0%	2.7%

Mean age and standard deviation (SD), proportions of females, and proportions of individuals taking various subtypes of psychotropic medications across the depression and bipolar disorder groups at baseline.

Table 5: Longitudinal changes in symptoms across diagnostic subgroups and chronotype change groups

| | Baseline (mean (SD)) | | | | Follow-up (mean (SD)) | | | | Statistics | | | | | | | | | |
| | Depression | | Bipolar | | Depression | | Bipolar | | Diagnostic Gr | | Time | | Chronotype Change Gr | | Chronotype Change Gr x Time | | Time x Diagnostic Gr | |
	MS	S/ES	MS	S/ES	MS	S/ES	MS	S/ES	F	p	F	P	F	P	F	p	F	p
HDRS-total	17.13 (6.8)	13.34 (5.3)	12.89 (7.2)	10.37 (7.1)	12.39 (7.3)	10.58 (6.1)	8.41 (6.0)	9.13 (7.0)	7.5	0.007	17.5	<0.001	2.6	0.109	3.1	0.082	<0.1	1.000
HDRS-insExc	14.67 (5.7)	11.65 (5.1)	10.63 (6.8)	9.27 (6.5)	10.35 (6.4)	9.00 (5.5)	7.23 (5.5)	7.77 (5.8)	6.7	0.011	16.5	<0.001	2	0.161	2.6	0.108	<0.1	0.950
BPRS-positive	11.04 (3.7)	10.94 (4.2)	10.61 (3.3)	10.41 (4.1)	9.25 (3.4)	9.91 (3.6)	9.59 (3.4)	8.87 (2.5)	0.4	0.508	19.4	<0.001	0.2	0.694	0.3	0.582	0.1	0.720
BPRS-depression	17.55 (5.4)	14.43 (5.2)	14.84 (5.6)	13.27 (5.2)	13.83 (5.8)	12.50 (4.6)	11.06 (4.5)	11.79 (4.4)	2.7	0.105	20.1	<0.001	2	0.165	4.6	0.035	0.3	0.583
BPRS-negative	8.21 (3.1)	7.22 (2.9)	7.37 (2.9)	7.00 (3.2)	7.21 (2.8)	6.88 (2.7)	6.18 (1.9)	6.81 (2.5)	1.3	0.256	6.5	0.012	1	0.311	6.6	0.011	0.1	0.809
BPRS-mania	10.21 (3.4)	9.81 (4.9)	11.72 (5.6)	9.37 (3.0)	9.62 (3.7)	8.34 (1.7)	9.65 (3.9)	8.77 (2.5)	0.4	0.519	6.9	0.010	9.1	0.003	1.5	0.222	0.2	0.665

Clinical ratings at baseline and follow-up for the depression and bipolar disorder subgroups and the chronotype change groups (Chronotype Change Gr: "earlier chronotype shifters" (MS) and "stable/eveningness shifters" (S/ES)), for or Hamilton Depression Rating Scale (HDRS), HRSD-total, HDRS-insExc (total excluding insomnia), Brief Psychiatric Rating Scale (BPRS).

Figure 3: Horne-Östberg Morningness-Eveningness questionnaire scores at baseline and follow-up
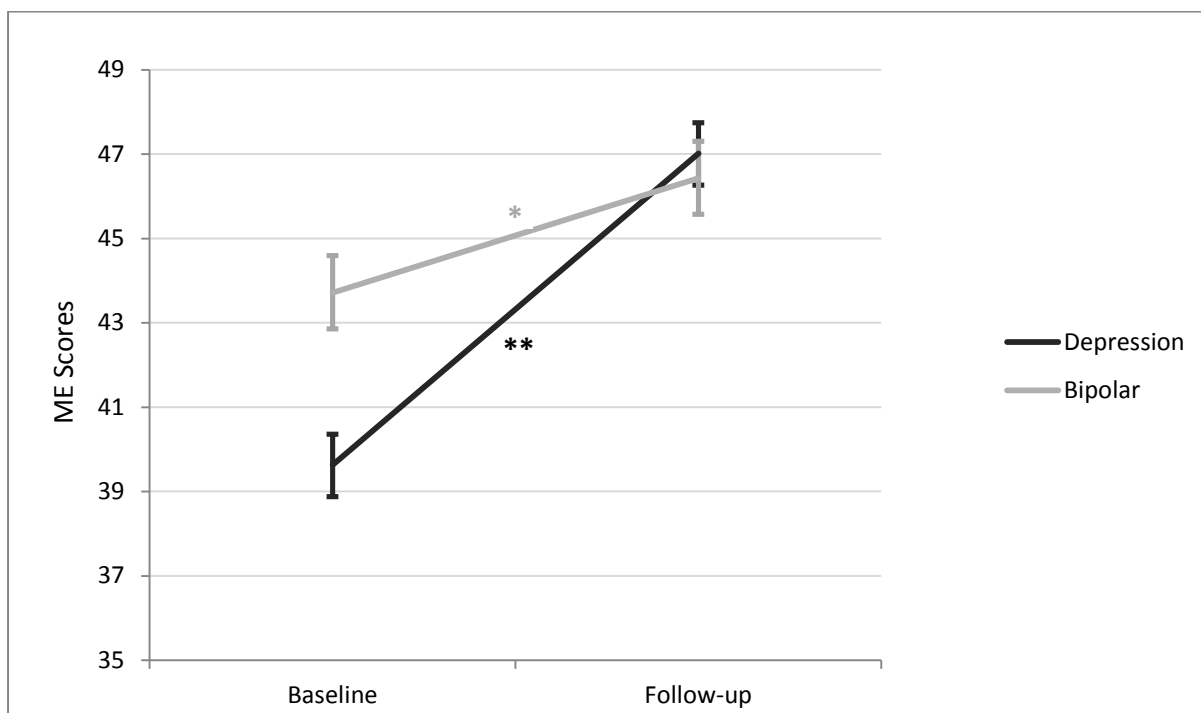
Means and SEM from Horne-Östberg (ME) scores at baseline and follow-up in each diagnostic group. *p < 0.010, **p < 0.001.

Figure 4: Brief Psychiatric Rating Scale subscales at baseline and follow-up
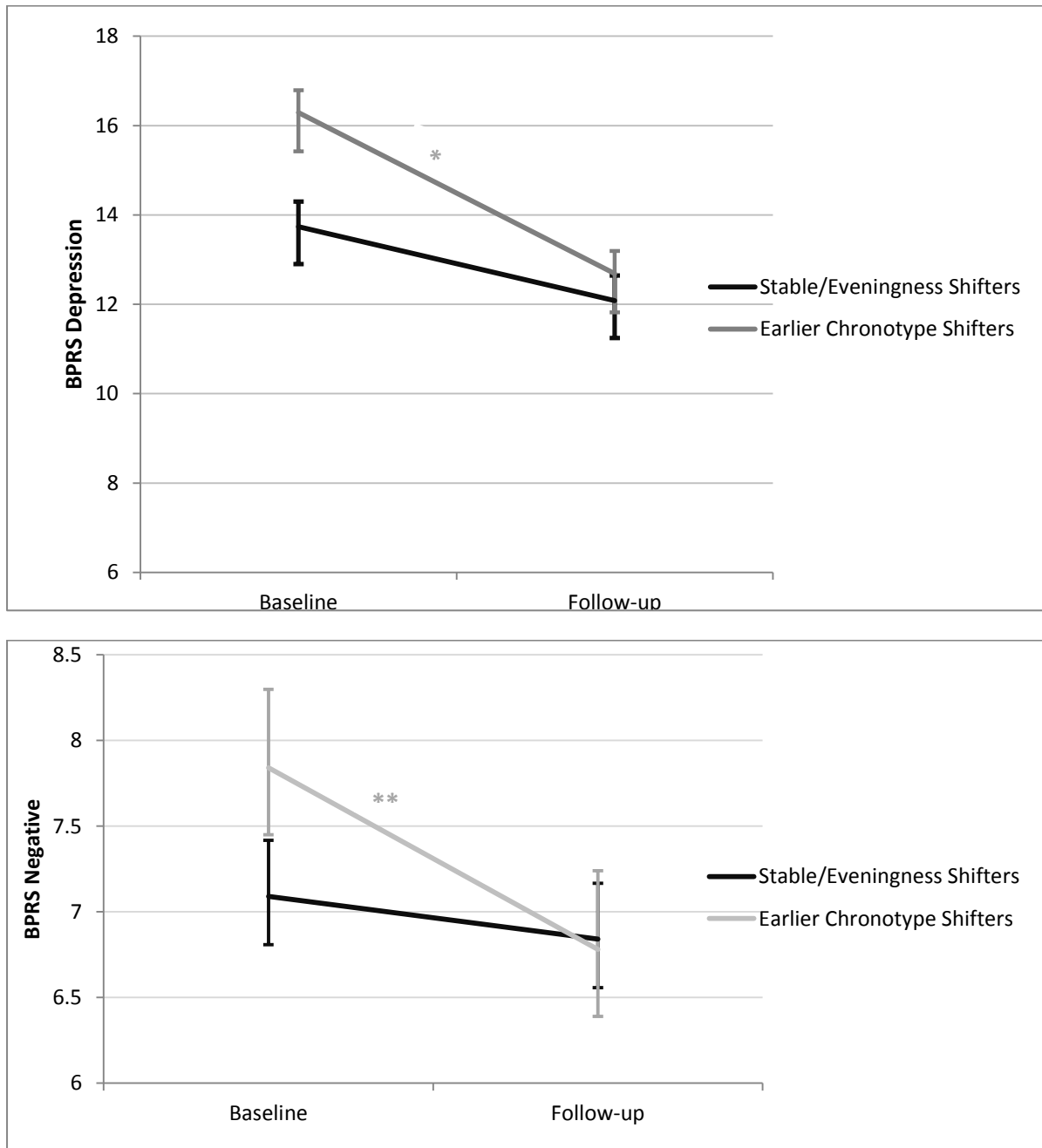
Means and SEM for the depression and negative symptoms subscales of the Brief Psychiatric Rating Scale (BPRS) at baseline and follow-up in the 'Earlier chronotype shifters' and 'Stable/Eveningness Shifters' group * $p < 0.001$, ** $p < 0.010$.

Chapter 4

4.1 General Discussion

The studies contained in this thesis are the first known to explore chronotypes across multiple mental disorders in young people. This work is also novel in its exploration of the associations between longitudinal changes in chronotype and clinical profile. Both studies employed a self-report chronotype measure to gauge morningness and eveningness preference. Study 1 examined chronotypic preference with respect to mental disorder subgroups and clinical state. Study 2 evaluated the relationship between chronotype and changes in clinical profile in young persons with affective disorders longitudinally.

The first research study (refer to Chapter 2) assessed morningness-eveningness preferences in young people with primary anxiety, depression, bipolar or psychotic disorders, and addressed the associations between morningness-eveningness preference and the severity of various psychiatric symptoms. This study showed that individuals with mental disorders presented a stronger eveningness preference than healthy controls. Compared to healthy controls from the same age group, all primary diagnostic groups had higher rates of 'moderate evening' types and some clinical groups had higher rates of 'extreme evening' types, especially those with affective disorders. Overall, higher eveningness was associated with worse clinical profiles and, in most instances, this was modulated by sex and primary diagnosis (this is discussed in depth in section 4.2). Our findings are aligned with previous literature highlighting elevated rates of moderate and extreme evening chronotypes in individuals with affective disorders (Barba et al. 2009; Merikanto et al. 2013; Takashi Abe 2011). However, our findings suggest that later morningness-eveningness preference is not specific to depression or bipolar disorder, but also extend to anxiety and, to some extent, psychotic disorders.

The second study (in Chapter 3) assessed changes in morningness-eveningness preferences over the course of affective disorders during youth. The study also investigated the associations between chronotypes and symptom profiles in young people with primary depression and bipolar disorder over an average follow-up period of 1.5 years. Before addressing this question, it would have been ideal to evaluate the temporal stability of morningness-eveningness preference of individuals with mental disorders including depression, anxiety, bipolar and psychosis, and compare their chronotype preference and clinical profile to healthy controls; however, there was not enough data for the anxiety, psychosis, and controls subgroups to perform these analyses. The second study demonstrated that chronotypes are not stable across the course of illness in people with affective disorders, and that individuals who shifted towards earlier chronotypes also experienced more pronounced clinical improvement from baseline to follow-up. Conversely, participants who had maintained the same chronotypes or shifted towards later chronotypes showed fewer improvements in their symptom profiles. Our overall findings suggested that chronotype preference could highly influence improvements in clinical states or vice versa. Speculations can be made in both directions and these possibilities are not mutually exclusive.

4.1.1 Association between eveningness and mental disorders

The present research provides further support to the notion of a strong relationship between circadian disruptions and eveningness preference in individuals with mental disorders such as depression (Nutt et al. 2008; Riemann et al. 2001; Selvi et al. 2010), anxiety disorders (Alfano et al. 2007; Alfano et al. 2010; Marcks et al. 2010), bipolar disorder (Chung et al. 2012a; Das et al. 2011; Harvey et al. 2005; Mansour et al. 2005) and psychotic disorders (American Psychiatric Association, 1994; Breslaua et al. 1996; Daniel et al. 1989). The overall stronger preference towards eveningness in participants with mental disorders as

compared to healthy controls is consistent with the results of previous studies (Das et al. 2011; Natale et al. 2005; Selvi et al. 2007) that have shown elevated rates of moderate and extreme evening chronotypes in samples with various mental disorders (Barba et al. 2009; Drennan et al. 1991).

4.1.2 Internal and external changes affecting the circadian system

In terms of the underlying chronobiological changes that occur during adolescence and in association with mental disorders, it is important to consider that the master clock is influenced by extrinsic factors, such as light exposure, and intrinsic factors, such as melatonin secretion and cortisol functions, as well as thermoregulation (Yoon and Shapiro 2013; Esseveldt et al. 2000). In studies 1 and 2, the impact of intrinsic/extrinsic factors on the association between chronotype and mental disorders was not evaluated. The possible involvement of such factors is discussed in the sections below.

As explained previously, light exposure, melatonin, thermoregulation and cortisol are focal synchronisers of the biological clock to the 24-hour period (Cagnacci et al. 1997; Wilson 2014). Therefore these factors may highly have been associated with chronotype preference and clinical severity in the current studies; however, this was not directly assessed. Previous studies have shown that light exposure in the evening can cause a delay in the circadian rhythm of the SCN (Shanahan and Czeisler 1991). Other studies have shown that disruptions in thermoregulation and melatonin levels are found in mood disorders (Kudielka et al. 2007; Koorengevel et al. 2000; Lewy 2013). Furthermore, depression is linked to higher evening cortisol and lower morning cortisol (Van den Bergh and Van Calster 2009). Similarly, lower circadian amplitude of core temperature, cortisol and melatonin have been significantly associated with depression severity (Ehlers et al. 1993). It could be hypothesised that individuals with mental disorders and evening chronotype may have disrupted

thermoregulation, melatonin and cortisol levels, and that a shift in chronotype towards morningness could be linked to a realignment of the intrinsic factors and exposure to extrinsic factors, possibly leading to (or resulting from) improved mental wellbeing. However, future research is required to evaluate the association between intrinsic/extrinsic chronobiological changes and chronotype preference occurring in adolescents with mental disorders.

4.1.3 Chronotype and pubertal development

Changes in the master clock are also influenced by pubertal development. Pubertal development during adolescence (described in Chapter 3) is one of many internal stimuli influencing the circadian preference shift towards eveningness, notably via changes in reproductive hormones (Randler et al. 2009; Hagenauera and Leea 2012).

As age increases from childhood to adolescence, eveningness becomes more pronounced and, similarly, mental disorders become more prevalent (Kim et al. 2002; Werner et al. 2009). Previous studies have described the association between age, pubertal development, and chronotype (Lerner et al. 2010; Roenneberg et al. 2004). It can be hypothesized that individuals who maintain high eveningness beyond adolescence instead of shifting back towards morningness may be more susceptible to mental disorders. Accordingly, the current studies showed that adolescents and young adults' chronotype preference may influence clinical state or, alternatively, that clinical state may influence chronotype. Specifically, eveningness was associated with worse symptom profile and higher rates of evening chronotypes were found in participants with mental disorders (main findings of study 1 and baseline data of study 2). The shift from eveningness to morningness and the association with clinical profile from baseline to follow-up in study 2 suggest that chronotypes are not just

fixed traits and may be linked to changes in clinical state (this is discussed further in section 4.3.2).

The findings of this study also suggest that the association between eveningness preference and clinical profile is beyond developmental changes in chronotypes. In study 1, age and gender were controlled for. Furthermore, youth with mental disorders were found to have later chronotypes than healthy young people from roughly the same age group. Therefore, the late chronotypes of participants with mental disorders cannot be explained entirely by their young age. It appears that both youth and mental disorders are factors related to later chronotypes, which may highly place young persons with mental disorders at elevated risk for marked eveningness and for the associated high psychiatric symptom severity. The association between earlier chronotype shifters and clinical symptoms is discussed in more detail in section 4.3. Importantly, considering the known association between chronotypes and mental disorders, there is a need to investigate whether youth may be a critical period for preventative intervention strategies and treatment options aiming to induce a shift towards morningness. This could be done by influencing the intrinsic/extrinsic factors affecting the circadian system such as melatonin, cortisol, light exposure and thermoregulation.

4.1.4 Sleep behaviour and chronotype in adolescence

Despite their later chronotypes and sleep-wake schedules, young individuals often have to wake up early in order to attend school or work, which often curtails sleep, leading to transient sleep loss. From this perspective, later chronotypes and their association with early school/work schedules are likely to amplify sleep disturbances commonly occurring in young people with mental disorders (Escribano et al. 2012). A study suggested that chronotype was indirectly related to academic performance in adolescence due to daytime sleepiness and

reduced sleep quality (Roeser et al. 2013). Considering the negative impacts of reduced sleep

duration and quality on psychiatric symptoms (Breslaua et al. 1996), the association between

later chronotypes and clinical outcomes that was observed in the young participants with

mental disorders may have been modulated by sleep disturbances. In support of this

hypothesis, later chronotypes in young persons have been found to modulate the bidirectional

interaction between insomnia and depression (Alvaro et al. 2014). Siversten and team also

support the suggestion of the bidirectional relationship between depression and insomnia by

demonstrating how both insomnia and depression significantly predict the onset of the other

disorder (Siversten et al. 2012). Finally, evening chronotype independently predicts and is

seen to be a risk factor for insomnia (Alvaro et al,.2014). The current studies focused on

chronotype only, but it would be relevant for future studies to evaluate the association

between eveningness, sleep behaviour, insomnia and mental illness in youth. Furthermore,

there is a need to determine whether improving sleep behaviour affects chronotype preference

and symptom profiles.

4.2 In Depth Discussion - Study 1

4.2.1 Morningness-eveningness preferences across mental disorders in youth

Study 1 assessed morningness-eveningness preferences in young people with primary

anxiety, depression, bipolar or psychotic disorders and aimed to investigate the associations

between morningness-eveningness preference and the severity of various psychiatric

symptoms. It was hypothesised that: i) participants with mental disorders would have the

latest chronotypes in comparison to controls, ii) evening chronotypes would be prominent

across mental disorders, but the most pronounced eveningness would be found in the

depression and anxiety groups, and iii) later chronotypes would be associated with greater

symptom severity. The first and third hypotheses were confirmed by the results. However, the second hypothesis was only partially supported as higher eveningness was found not only in individuals with depression and anxiety, but also in those with bipolar disorder. However this varied with sex.

4.2.2 Evening chronotypes in mental disorders

Results from study 1 show that pronounced eveningness and elevated rates of late chronotypes in young persons with various mental illnesses extend beyond normal age-related changes. This was most notable in individuals with anxiety, depression and bipolar disorder. The overall stronger preference towards eveningness in all clinical subgroups compared to healthy controls is consistent with previous findings of delayed actigraphic sleep-wake patterns in young persons with anxiety, depression, bipolar, and psychotic disorders (Robillard et al. 2014; Robillard et al. 2015b). More specifically, a previous study showed that the delay in actigraphy and melatonin profiles is more pronounced in young persons with bipolar disorder compared to unipolar depression (Robillard et al. 2013a). Conversely, within both current studies, our results suggest that eveningness preference may be slightly more pronounced in young persons with unipolar depression than in those with bipolar disorder. In the context of mental disorders during youth, there may thus be some degree of dissociation between circadian preference and the actual timing of the sleep-wake cycle or melatonin rhythm. Our findings suggest that evening chronotypes are common across multiple mental disorders during youth; however, the depression group had the highest percentage of evening types followed by those with anxiety. Previous studies have also found a higher association of evening chronotypes with depression than with anxiety (Ford and Kamerow 1989). For example, Siversten and team also could not establish a clear relationship between sleep and anxiety, which is interesting as sleep anxiety is generally high

in insomnia individuals and in those with delayed sleep phase disorder (Siversten et al. 2012). Several bipolar participants also had a late chronotype. The psychotic disorder group had a less prominent elevated rate of evening chronotypes. None of the controls fell into the evening type range, whilst some individuals from the anxiety, depression, bipolar, and psychosis groups did exhibit evening chronotypes. From the current study, it can be confidently concluded that elevated eveningness is found across multiple mental disorders in youth (i.e. later chronotype may highly be more linked to 'mental disorders' broadly rather than solely to depression or anxiety disorders).

Study 1 further showed that eveningness is associated with worse clinical profiles. More specifically, stronger eveningness preference was globally associated with poorer socio-occupational functioning, elevated psychological distress, and more severe psychiatric symptom severity. These associations were generally most pronounced for clinical factors related to each diagnostic subgroup, but were also strongly influenced by sex. In the following sections, these associations are discussed in more detail.

4.2.3 Chronotype and clinical profiles – Hamilton Depression Rating Scale

A correlation was found between higher depression severity, as rated by HDRS total score, and eveningness in females from the primary depression subgroup. This result is partially aligned with those of Vaccarino and colleagues who found that males and females with evening chronotypes had higher depressive scores on the HDRS in a sample of 2191 individuals diagnosed with depression (Vaccarino et al. 2008). Vaccarino's study had a much larger sample size than study 1, possibly explaining why there were significant associations only within females from the unipolar depression group.

Our study extends prior work by also including a concurrent comparison of individuals with psychotic, unipolar depression, bipolar disorder and anxiety disorders. There is frequent comorbidity between depression and other mental disorders such as anxiety and psychosis (Collimore and Rector 2014). In addition, during youth, when disorders are still emerging, the ultimate clinical trajectory is often unknown. In an analysis done by Sun and team, sub-threshold depressive symptoms were also common in those with anxiety or psychotic disorders (Sun et al, 2015). Thus, in the present studies, it is possible that depressive symptoms could mediate or contribute to the chronotypic profile of the anxiety, bipolar and psychosis groups. Our findings based on the HDRS, however, do not support this hypothesis since later chronotypes were not correlated with depressive symptoms in people with anxiety or psychotic disorders. Future research investigating whether depressive symptoms could mediate the chronotypic profile of anxiety or psychosis may aid in further understanding the association between mental disorders and chronotype preference. A larger sample of individuals with psychosis would also help to clarify the relationship between chronotype and symptom profile in this subgroup.

4.2.4 Chronotype and clinical profiles - Brief Psychiatric Rating Scale

The current study also used the BPRS to determine the severity of depressive, manic and psychotic (positive and negative) symptoms. Correlations were performed to evaluate associations between morningness-eveningness scores and BPRS subscales for these symptoms. Several correlations remained significant after controlling for age. In line with the HDRS results, higher eveningness was significantly associated with depressive symptoms rated on the BPRS scale in females with depression. In addition, a correlation between higher eveningness and depressive symptoms on the BPRS was also found in males with bipolar disorder. Furthermore, males from the bipolar subgroup with stronger eveningness also

presented with worse positive symptoms, but this correlation was no longer significant after correcting for multiple correlations. This may be due to the reason that males tend to generally be more evening type than females (Tsai et al,. 2004), therefore there is less room to show variability and thus less association would be found. Positive symptoms could partially reflect manic-like states involving grandiosity, suspiciousness, hostility, unusual thoughts and disorganisation. Previous studies have identified higher levels of manic symptoms in males than females, but these studies did not assess the association with chronotype (Kawa et al. 2005; Frye et al. 2003). Furthermore, females with bipolar disorder and higher eveningness tended to have more severe negative symptoms.

Altogether, this may suggest that, within young persons with bipolar disorder, later circadian preference may highly relate to worse depression symptom severity in both males and females (especially the blunted affect, emotional withdrawal, and general slowing components of depressive symptomatology for females (i.e. reflected here by negative symptoms)), but that males with later chronotypes may also have more florid symptoms relating to manic-like states such as suspiciousness, unusual thoughts, disorganisation, hostility and grandiosity (i.e. reflected here by positive symptoms). It is important, however, to take into account that the morningness-eveningness profiles of these participants could also have been affected by psychotropic medications and comorbid symptoms and conditions.

4.2.5 Chronotype and clinical profiles – Kessler Psychological Distress Scale

Study 1 is the first study to assess the association between general psychological distress and evening chronotypes across multiple mental disorders. After correcting for multiple comparisons, a significant correlation was identified between the psychological distress scale (i.e. K10) and chronotype within males from the bipolar subgroup, suggesting that

eveningness correlated with higher psychological distress. While young males with anxiety who endorsed later chronotypes tended to have worse socio-occupational functioning, they did not present with worse psychological distress. Of note, the sample size of the anxiety group may have been too small to yield a significant correlation.

4.2.6 Chronotype and clinical profiles – Social and Occupational Functioning Assessment Scale

The SOFAS is a clinical scale providing information on overall social and occupational functioning and allowed us to investigate if socio-occupational status is associated with chronotype. Our findings support previous research demonstrating that stronger eveningness preference is globally associated with poorer socio-occupational functioning in patients with depression (Glozier et al. 2014); however, there were no other correlations found between SOFAS and eveningness in the clinical sub-groups.

Study 1 demonstrates that eveningness is associated with multiple mental disorders. Overall, these findings are consistent with previous studies in non-clinical samples where chronotype variations amongst symptomatic/asymptomatic subgroups as well as in relation to sex (Díaz-Morales and Sánchez-Lopez 2008). Our findings build on previous evidence (e.g. Merikanto et al. 2013; Drennan et al. 1991; Mansour et al. 2005; Wood et al. 2009) highlighting progressive associations between later chronotypes and the severity of symptoms beyond mere diagnostic group differences. Considering that symptom severity typically varies over time, the question as to whether morningness-eveningness preference could be influenced not only by individual traits, but also by clinical state was raised. This is especially relevant in the context of developmental changes in the sleep-wake cycle and the concomitant variations in chronotypes during youth (Garcia et al. 2001; Hagenauera and Leea 2012), a life period

during which circadian rhythms and circadian preference are not static. Many studies describing chronotypes and clinical profiles are cross-sectional and thus have not yet looked at whether chronotypes influence clinical profiles in the long-term. Kraemer and team highlighted the need for longitudinal data in order to better understand distinct developmental trajectories and disease processes (Kraemer et al. 2001). In this regard, study 2 was conducted to delineate possible state and trait influences on morningness-eveningness preference in mental disorders, notably by determining whether longitudinal changes in symptom severity along the course of illness are accompanied by changes in morningness-eveningness preference within the same individual (discussed in depth below). The possibility that later chronotypes in persons with affective disorders may be related to a higher risk of subsequently developing a more severe mental illness was addressed in study 2.

4.3 In Depth Discussion - Study 2

Study 2 aimed to assess longitudinal changes in chronotypes and morningness-eveningness preference in relation to changes in symptom profile in young people with primary depression or bipolar disorder. The results confirmed the hypothesis that shifts towards morningness from baseline to follow-up was associated with decreased symptom severity.

As discussed in the previous sections, individuals with late chronotypes have higher levels of depressive, paranoid, and manic symptoms than those with morning chronotypes (Ong et al. 2007; Gau and Merikangas 2004; Barba et al. 2009). Similarly, evening chronotypes are associated with severe depressive symptoms in youth (Barba et al. 2009; Merikanto et al. 2013; Takashi Abe 2011). The present longitudinal results highlighted that the mean chronotypic preference in our sample of participants changed towards morningness along a mean longitudinal interval of 1.6 (SD = 0.6) years and that this shift was associated with improved mood and symptom profiles. These very interesting findings provide further

support for the aetiological link between mood and circadian rhythms, and suggest that a chronotype may be a 'state' marker of depression severity. The findings of study 2 are also aligned with findings from Gaspar-Barba and team suggesting that chronotypes have an influential effect on depressive episodes, with higher symptom severity being associated with evening type individuals (Barba et al. 2009).

Another study demonstrated that chronotype was related to changes in depressive symptoms among depressive and insomniac patients receiving cognitive behavioural therapy (Bei et al. 2015). This study showed that those with greater eveningness experienced less depressive symptom reduction. Similarly, Miller and colleagues showed that there is an association between morning chronotypes and healthy lifestyle behaviours in healthy adults. This study also suggests that eveningness may increase the vulnerability to depression due to delayed positive emotion (Miller et al. 2015). Randler observed that morning types had a more positive attitude towards life than evening types and that eveningness was associated with depression. He also found a positive correlation between morningness and physical and mental health as well as school functioning, suggesting that eveningness could be an unspecific risk factor for mental disorders and functional difficulties (Randler 2011b). The consistency across all these results shows that chronotype preference may improve clinical state or that improvements in clinical symptoms may influence chronotype preference.

4.3.1 Chronotype and changes in clinical profiles

Inter-individual variability in chronotype preference is linked to variations in mood and behaviour (Onder et al. 2014; Roeser et al. 2013; Randler 2008). In the present study, main effects of time indicated that the HDRS total, HDRS total excluding the insomnia item, BPRS positive symptoms and BPRS mania significantly decreased from baseline to follow-up.

These score reductions suggest that standard clinical care (and/or the passage of time) improved depressive, manic and positive symptoms in most participants. Importantly, in our young patients with affective disorders, there was also a significant shift towards increased morningness from baseline to follow-up. This longitudinal change in morningness-eveningness preference was slightly more pronounced in individuals with depression rather than those with bipolar disorder. After controlling for age, gender and follow-up duration, both the unipolar and bipolar groups showed a highly significant decrease in morningness-eveningness scores over time, but the depression group had a steeper decrease than the bipolar group. This slight diagnosis-specific difference may be attributable to higher rates of eveningness at baseline in the depression group compared to the bipolar group. This is consistent with study 1 where participants with depression had a higher percentage of eveningness compared to participants with bipolar disorders; however, one cannot rule out the influence of the timing at which the questionnaires and scales were completed. More specifically, it is possible that the bipolar participants were in varied clinical states (e.g. euthymic, depressive, manic, or shifting across episodes), whereas the depression group may have been in a more homogeneous clinical state.

From a categorical perspective, 33% of participants (19% from the depression group and 14% from the bipolar group) had a significant shift towards an earlier chronotype category from baseline to follow-up (i.e. earlier chronotype shifters were participants who shifted to earlier chronotypes during the longitudinal period; for example, from evening type to 'neither' type, from moderate morning type to definite/extreme morning type, etc.). The 'earlier chronotype shifters' group exhibited significant improvement in negative and depressive symptoms, as measured by the BPRS. The 'stable/eveningness shifters' group (i.e. participants who remained evening types or shifted to later chronotypes) had a more modest reduction in depressive symptoms from baseline to follow-up, but this finding was not significant. This

pattern of results suggests that shifting towards morning chronotypes may be associated positively with improvements in symptom profile. In addition to the gradual associations between later chronotypes and the severity of psychiatric symptoms observed in study 1, this further supports the possibility of state-dependent variations in chronotypes. In fact, the longitudinal nature of this association critically challenges the classical view that chronotypes are trait markers, suggesting rather that chronotypes may reflect a dynamic mixture of state and traits.

4.3.2 Pubertal development

Current findings suggest that age and pubertal development may influence morningness-eveningness preference during adolescence (Lerner et al. 2010). At first glance, one could wonder whether the longitudinal changes in chronotypes occurring in study 2 simply resulted from normal age-related changes. However, the interaction between chronotype change groups and longitudinal changes in symptom severity remained significant after controlling for the effects of age. Furthermore, the duration of the longitudinal period in study 2 was somewhat shorter than the time that would typically be required for developmental changes to occur. Therefore, while puberty may be a sensitive period for later chronotypes and the emergence of mental disorders, it seems that the association between shifts towards earlier chronotypes and improvements in depressive and negative symptoms is not primarily driven by age or pubertal changes. Also, there was no significant interaction involving diagnostic groups for any variable, suggesting that the relationship between changes in chronotypes and changes in clinical profiles was not significantly affected by subtypes of mood disorders.

A progressive delay in circadian rhythms takes place during adolescence and, over time, typically shifts back towards morningness; however, in some cases, individuals remain

evening types (Crowley et al. 2007; Hagenauera and Leea 2012; Garcia et al. 2001; Roenneberg et al. 2004). In study 2, the longitudinal shift towards earlier chronotypes seemed to extend beyond normal age-related changes even after controlling for time. As stated previously, during brain development, there is a window of sensitivity where adolescents have a higher risk of developing mental disorders (Casey et al. 2010). Also during this period, adolescents tend to have a stronger preference towards eveningness. The current finding is consistent with previous studies demonstrating a strong relationship between evening chronotypes and affective disorders. Further longitudinal studies are required to investigate this across multiple mental disorders. We hypothesise that results would remain consistent across different disorders, with earlier chronotype shifters showing greater clinical improvement regardless of diagnosis.

4.3.3 The underlying neuro/chronobiology/development in mental disorders

A change in circadian rhythm from childhood to adolescence involves a sleep phase delay and a steady shortening of the sleep period (Crowley et al. 2007). Accompanying these changes is the developmental maturation of neuroendocrine systems such as melatonin, cortisol, and pubertal hormones that are associated with behavioural changes in circadian rhythms (Carpenter et al. 2015). The current study demonstrated that higher eveningness in youth with mental disorders correlated with symptom severity and that a shift from late to earlier chronotypes at follow-up co-occurred with improved mood and symptom profiles, presumably independently from developmental maturation. Our findings showed a significant association between earlier chronotype shifters from baseline to follow up. Furthermore, the results showed that, as time passed, a decrease in symptom severity was found in participants who shifted to earlier chronotypes.

Overall, our findings suggest that there is a link between chronotype and mental disorders. However, it would be interesting to gain insights into functioning of the SCN in these particular patients from baseline to follow-up. As mentioned earlier, there are many internal and zeitgeber factors affecting the SCN, some being the same factors affecting chronotype. This includes behavioural schedules, meal times, activity levels, melatonin, cortisol and core body temperature. Core body temperature is at its lowest in the second half of the sleep period, whilst the melatonin secretion is highest during this time (Shanahan and Czeisler 1991). Also, circulating cortisol levels peak in the morning and decline gradually over the day (Kudielka et al. 2007). Studies have demonstrated that diminished amplitude of core temperature, cortisol, and melatonin are significantly correlated with depression severity (Ehlers et al. 1993). Therefore, in the current study, at baseline, when both depression severity and eveningness were elevated, there may have been more pronounced abnormalities in the circadian rhythms of melatonin, cortisol and temperature, and at follow-up, these factors may have improved. Future longitudinal studies are required to examine further how the shift from eveningness to morningness is associated with dynamic changes in both internal circadian neurobiology as well as in relation to external stimuli.

4.3.4. Possible associations between treatment and clinical state

At stated previously, study 2 showed that a shift towards morningness was associated with improvements in clinical symptoms. Regardless of the direction of this association, which could possibly be bi-directional, restoring the sleep-wake cycle, circadian rhythms and shifting to earlier circadian preference is highly likely to improve general well-being. Circadian-based interventions known to shift circadian rhythms and/or the sleep-wake cycle may also shift chronotypes. Thus, while causality cannot be ascertained from this study, from a clinical and practical perspective, study 2 raises the question as to whether treatments such

a light therapy, melatonogeric treatment or sleep rescheduling, may improve clinical state by actively shifting morningness-eveningness preference earlier. The possibility that shifting chronotype earlier may improve symptom profiles, mood and behaviour is further supported by the observation that morning types have better mood than evening types (Randler 2008). There is a need to assess whether psychiatric symptoms in individuals with later chronotypes respond better to circadian-based interventions than those with earlier chronotypes. Different types of treatment methods are discussed in more depth in the sections below.

4.4 Intervention for Mental Disorders

The Australian National Survey of Mental Health and Wellbeing reported that 31% of adolescents under the age of 24 were diagnosed with a mental disorder or substance misuse disorder (Sawyer et al. 2000). The quality of psychological and social intervention is important; however, availability and access are just as important. In 2003, 10.1% of individuals in the US did not have access to health care services (Cohen and Nelson 2003). Husky and colleagues showed that 19.5% of 4,509 ninth grade students were at risk of developing a mental disorder and 73.6% of those children were not receiving treatment (Husky et al. 2011). Given these figures, there is a crucial need to develop accessible interventions to support young adolescents suffering from, or at risk for, mental disorders.

Social factors affecting youth mental health include relationships, education, role models, media, drug availability and peer pressure. Negative experiences with these variables may be damaging, affect social and cognitive functioning, and decrease various opportunities as an adult (Stein 2006). Therefore, these factors must be recognised and targeted by mental health services in order to minimise and avoid adverse outcomes. Such mental health disruptions can be observed within Australia's mental health organizations such as the Youth Mental

Health Institute at the University of Melbourne and the Youth Mental Health services of the Brain and Mind Centre, Sydney. These facilities use different types of intervention strategies that target various aspects of youth mental health (Thomson et al. 2012; Addington et al. 2006). Part of the plan was to report relevant outcomes in research studies. For example, related studies have assessed the relationship between binge drinking and depression, with their associated range of neurocognitive deficiencies (Naismith et al. 2012b; Hermens et al. 2013; Hermens et al. 2011; Hickie et al. 2005). Other studies have observed stress and anxiety that is formed by self-loss (i.e. loss of identity and belonging) and external factors (Hickie 2008). Various biomarkers of mental disorders linked to sleep and circadian rhythms have also been investigated (Robillard et al. 2015b; Robillard et al. 2013b). In addition, studies have further assessed the potential mechanisms behind the association between circadian rhythms and mental disorders (Robillard et al. 2014; Hickie et al. 2013a).

The current thesis examined the association between circadian preference and mental disorders in outpatients recruited from the clinics of the Brain and Mind Centre. In line with previous studies, our findings suggest that youth with delayed chronotypes or evening preference may be at risk for mental disorders such as depression, anxiety, bipolar disorder and psychotic disorders (Willis et al. 2005; Randler 2011a; Merikanto et al. 2013; Muro et al. 2009; Ohayona and Roth 2003; Roberts et al. 2002). Previous studies have shown that evening types are associated with poor academic results, sleep fragmentation, depressive symptoms, anxiety, worse sleep disturbances, daytime tiredness, increased behavioural and emotional problems, decreased work functioning, higher levels of alcohol and drug consumption and higher suicide rates (Reavley et al. 2010; Murray et al. 2003; Germain and Kupfer 2008). By contrast, morning types appear to have better mental and physical health (Cavallera and Giampietri 2007). Beyond the longitudinal improvements in psychiatric symptoms observed herein, future studies should also evaluate whether potential

improvements in sleep duration/quality and shifts towards morningness preference may likely lead to improvements in factors such as physical health, drugs and alcohol consumption and cognitive functioning.

Internationally, various studies have highlighted the importance of teacher involvement and efficient mental health resources provided within schools (Ringwalt et al. 2010). One study showed that, across 49 schools in America, 40.8% of teachers were actively participating in mental health interventions (Franklin et al. 2012). It was also noted that much of teacher-based mental health involvement took place within classrooms. Similarly, another study highlighted that safe schooling and healthy climate shapes an individual's emotional and behavioural learning (Weist and Paternite 2006). Therefore, having mental health programs within schools may benefit some developmental outcomes (Weist and Paternite 2006). Furthermore, Adelman noted that the delivery of mental health prevention and promotion programs targeting psychological and behavioural problems based on early intervention strategies in schools reduced the prevalence of various psychological disorders (Adelman and Taylor 2010). Since such interventions are often quite simple, strategies to promote healthy sleep and circadian rhythms could be implemented directly in school and work settings.

The effectiveness of various interventions and treatment programs targeting substance abuse in adolescence has been evaluated. For instance, studies have found that such intervention programs resulted in a reduction of substance use during adolescence (Jainchill et al. 2000; Etheridge et al. 2001; Hser et al. 2001). Intervention programs have also been shown to increase quality of life and reduce criminal activities (Broome et al. 2001; Dennis et al. 2004; Grella et al. 2001). Strategies targeting substance abuse in youth may also impact on the interplay between clinical profiles and circadian preference since elevated rates of drug and

alcohol consumption are found in individuals with later chronotypes, as well as in young persons with mental disorders (Prat and Adan 2011).

4.4.1 Sleep and circadian interventions for mental disorders

Early-morning awakening is a common symptom found in clinical depression, although this has mostly been reported in older aged individuals (Germain and Kupfer 2008; Srinivasan et al. 2009b; Srinivasan et al. 2009a). In addition, phase delay is commonly reported in individuals with mood disorders (Robillard et al. 2013b). This suggests that there may likely be an association between circadian rhythms and depressed mood (Malhi and Kuiper 2013; Pandi-Perumal et al. 2009). Treating sleep and circadian disturbances may add value to current classical interventions for mental disorders, notably due to their possible contribution to some of the underlying mechanisms linked to psychopathologies and to their typically rapid therapeutic effects. For instance, studies have demonstrated that classical antidepressant drugs, such as SSRIs, take 2 to 8 weeks to start having an effect. In fact, antidepressants do not act as direct mood enhancers but rather modify part of the brain chemistry thought to regulate the relative balance of negative to positive emotional processing (Harmer et al. 2009). Therefore, sleep and circadian-based interventions are highly important as they may have a faster effect than antidepressant drugs. However, there is currently not enough empirical data to certify this idea.

The current studies showed a shift in circadian rhythms from eveningness to morningness. This shift may in turn be hypothesised to reduce symptom severity, as has been suggested by one interventional study (Kasper and Hamon 2009). Furthermore, some studies in the past have found that actively inducing a phase advance in circadian rhythms is associated with improvements in depressive symptoms (Wehr et al. 1979; Souetre et al. 1987; Sack et al.

1985). Considering the close association between circadian rhythms and morningness-eveningness preference, it could be postulated that a shift toward morningness may improve symptomology. Future clinical research is required in this area to directly evaluate if actively inducing a shift in morningness positively influences clinical profile. If this is indeed the case, then interventions and treatment strategies that induce shifts towards morningness during adolescence have the potential to reduce the risk of emerging disorders and improve wellbeing.

4.4.2 Sleep deprivation

Sleep deprivation has been used to treat thousands of patients suffering from depression worldwide with numerous studies consistently reporting rapid reductions in depression symptoms in approximately 40–60% of depressed patients (Giedke and Schwarzler 2002). However, in adolescence during school, chronic and continuous sleep deprivation has a negative effect on an individual's cognitive functioning. This differs from the therapeutic effect which is acute and non-continuous. Usually, the procedure for sleep deprivation includes keeping the patient awake throughout the night in order to reach maximum sleep deprivation (Justice and Hoofdakker 1999). After a few days of normal sleep, roughly half of the patients suffering from depression experience a dramatic improvement in mood, although relapse does commonly occur after recovery sleep (Justice and Hoofdakker 1999). Recent findings have suggested that treatment response may likely be prolonged if sleep deprivation occurs in conjunction with other treatments such as antidepressant medications, mood stabilizers (e.g. lithium) or other chronobiological interventions (e.g. light therapy (Neumeister et al. 1996; Colombo et al. 2000; Benedetti et al. 2003). Studies have shown that even patients with high symptom severity may respond to sleep deprivation (Rosenthal et al. 1984; Shanahan and Czeisler 1991).

4.4.3 Bright light therapy

Bright light therapy is an effective treatment for mental disorders, such as seasonal affective disorders. Bright light influences circadian rhythms by activating the SCN, inhibiting corticotrophin releasing hormone and suppressing hypothalamic, pituitary and adrenal activity (i.e. suppressing melatonin) (Golden et al. 2005; Van Someren et al. 1999). Impairments in the activation of the hypothalamic–pituitary–adrenal axis results in behavioural changes that may influence sleep, motivation, pleasure, appetite and concentration, all of which are symptoms commonly found in individuals with mood disorders (Esseveldt et al. 2000). Bright light therapy has seen to be the new antidepressant treatment for patients with depression showing significant clinical improvements after the use of light therapy in various studies (Dallaspezia et al. 2012; Deltito et al. 1991; Labbate et al. 1995; Martensson et al. 2015). For instance, a study using three weeks of light therapy in 70 in patients with depression showed significant improvements in clinical profile (Dallaspezia et al. 2012). Studies have also shown that light exposure improves the symptoms of recurrent depression in many patients (Martensson et al. 2015). In addition, light therapy is one of the commonly used means of phase shifting circadian rhythms. Accordingly, a controlled study found that bright light therapy for adolescents with delayed sleep phase disorder is effective for improving multiple daytime and sleep impairments (Gradisar et al. 2011). In addition, a study in patients with winter depression who have abnormally delayed circadian rhythms found that bright light therapy is beneficial as it provides a phase advance correction (Sack et al. 1990). This supports the notion that some of the therapeutic mechanisms of light therapy may include shifts in the timing (phase) of circadian rhythms.

4.4.4 Melatonin-based therapies

Other options for advancing circadian rhythms include the use of exogenous melatonin. In humans, the melatonin hormone is known to promote sleep and has phase shifting properties which can aid in resynchronizing and realigning circadian rhythms. Studies using novel melatonin-based therapies have found that it has a soporific effect, successfully facilitating sleep onset, as well as advancing circadian rhythms (Kostoglou-Athanassiou 2013). Such melatonin-based therapies, such as agomelatine, have significant antidepressant effects in patients with mood disorders (Hickie and Rogers 2011). Another study found that melatonin was effective in improving sleep in outpatients with major depression (Dolberg et al. 1998). With regards to age-related sleep and circadian changes, Echerberg and team examined healthy students over five weeks and found that students slept earlier and longer when using melatonin, making them more alert during school (Eckerberg et al. 2012). Additionally, one group showed that treatment with agomelatine compared to sertraline, an antidepressant, significantly improved the sleep-wake cycle and the amplitude of the circadian rest-activity cycle as well as decreased anxiety and depressive symptoms (Kasper and Hamon 2009). In addition, ramelteon, another novel MT1 and MT2 melatonergic agonist, has effects on receptors that influence melatonin in the SCN (Srinivasan et al. 2009b), and has been shown to promote sleep in animals, such as cats and monkeys (Srinivasan et al. 2009b; Pandi-Perumal et al. 2007). Both ramelteon and melatonin promote sleep by regulating the sleep/wake cycle through their actions on melatonergic receptors in the SCN (Srinivasan et al. 2009b).

The correlation between longitudinal shifts towards morningness and better mood in affective disorders provides valuable insights for the prevention and treatment of these disorders. To extend the positive findings of sleep and circadian based treatments mentioned above, it is crucial to: (i) determine whether changes in morningness-eveningness preference take place

during the course of mental disorders other than depression and bipolar disorders, (ii) to investigate whether seep rescheduling, light therapy or melatonegeric treatment may induce a shift in morningness-eveningness preference, and if so, (iii) whether this is associated with clinical improvement. Furthermore, there are some indications that chronotype may predict antidepressant response to these treatments. Therefore, there is a need to further investigate changes in morningness-eveningness preference across the course of mental disorders and their relation to treatment outcomes over a longitudinal period.

4.5 Limitations

Some limitations inherent to the design of our studies need to be considered. Firstly, in study 1, the control group was significantly older (23.5 years old on average) than the clinical subgroups (averages ranging from 19.4 to 22.0 years old). This is a complex issue since the current sample's age range is at the cross-roads of multiple age-related changes in morningness-eveningness preference. Chronotypes shift towards more morningness during the twenties, but this is after shifting towards more eveningness during adolescence. In the current study, 4.5% of the controls were aged between 12-16 y.o. as opposed to 21.9% in the patient subgroups. In this age range, morningness is still more prevalent when compared to 17-24 y.o., an age group constituting 53.7% of our control group. From this angle, an age-related shift towards more 'eveningness' in the control group could result from the lower proportion of children and younger adolescents. We however acknowledge that the younger age of our patients compared to controls is also driven in part by a higher proportion of patients in the 16-25y.o. age range relatively to the 25-30y.o. range, which could pull chronotypes in towards more eveningness in patients groups and counterbalance the effect previously mentioned. The current study attempted to limit the influence of age by controlling for time and age statistically. Another limitation unfortunately, is missing data across the different scales, diagnostic subgroups and sex subgroups limited the sample sizes precluding the use of regression modelling. In study 1, we used a cross-sectional approach to assess chronotype across multiple mental disorders; however, the results may be a reflection of symptom progression over time rather than the association of eveningness and clinical changes long-term. Indeed, symptom severity varies over time and this raises the question as to whether morningness-eveningness preference could be potentially influenced by individual traits as well as transient clinical states. This influence could have affected the results from study 1.

In study 2, a longitudinal design was used to investigate possible state influences on morningness-eveningness preference by assessing how eveningness preference relates to the course of mental disorders. However, in this second study, there was insufficient data for some primary diagnostic groups and thus, we only evaluated the depression and bipolar groups. Also, in this longitudinal study, having a longer interval between baseline and follow-up may have allowed for further clinical changes to occur, which may have strengthened our findings. In addition, there was not enough data on the SOFAS and K10 to determine if there were changes in social and occupational functioning or psychological distress levels. It would have been interesting to see if the morning shifters who improved clinically also improved in their social behaviour and general level of distress.

Another limitation of both studies was that the clinical scales used may have had potentially low sensitivity to anxiety and psychotic symptoms, and therefore other scales would aid in future studies. Also, the clinical subgroups were defined according to primary diagnoses and did not take into account comorbidity or current medication taken. The medications used at baseline (table 2), over time could have changed depending on the patients clinical state. Patients were continually monitored by their clinician, some patients may have needed higher dosage; others may have needed to change the type of medication. If any changes were made this was done in the best interest of each individual patient, decided by their clinician. While most psychotropic medications influence sleep and possibly circadian rhythms, they may also have an impact on morningness-eveningness preference, and could possibly have influenced the present findings. During the longitudinal study, there was an improvement in symptom profile, some patients may have improved due to treatment and passage through time or from a change in lifestyle or a patient could have spontaneously remitted. In both studies 1 and 2, the addition of measures to characterise endogenous circadian rhythms, such as melatonin, cortisol and core body temperature, could have clarified how morningness-eveningness

profiles linked to more severe depression severity relate to objective circadian patterns. Dim light melatonin onset (DLMO) measures could have provided us information on the participant's melatonin rhythm and whether there had been a difference between patients and controls melatonin levels across night. This test could have also shown if there were any changes in melatonin levels for the patients that shifted from eveningness to morningness during follow-up. In addition, actigraphy measures would have allowed us to determine the exact sleep and wake times of patients and would have given us information on their sleep timing, quality and quantity, as well as at what times their physical activity levels peaked. Actigraphy measures would have strengthened the current findings and helped us to determine if there was a difference in sleep patterns and physical activity from baseline to follow-up in study 2.

4.6 Conclusions

The current body of work supports the notion that mental disorders are associated with higher eveningness. The higher rates of late chronotypes in patient groups compared to controls is interesting, particularly in light of work suggesting an aetiological link between circadian rhythms and the development, perpetuation and recurrence of depressive features (Benedetti et al, 2003). This thesis also incorporated the rare opportunity for longitudinal analysis of chronotypes, and for the first time demonstrated that chronotypic preference is closely tied to clinical symptom severity, and likely to be influenced by 'state' variations. That is, chronotypes are not simply hard-wired during adolescence but are rather malleable, and can shift alongside variations in clinical states. The implications of this work for clinical practice are notable, with data supporting a role for chronobiotic therapies. From this perspective, the application of both pharmacological and non-pharmacological chronotherapies for mental disorders warrants further attention. Future work should aim to address the utility of such interventions in similar groups of young people with emerging mental disorders. Firstly, chronotherapies may improve clinical symptoms. Secondly, broader and longer-term outcomes may include prevention of symptom progression before full-threshold symptoms are apparent. Finally, it is likely that circadian-focused interventions will have extended benefits in terms of optimising educational, vocational and psychosocial functioning.

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