Actigraph-derived Variables as Predictors of Bipolar Disorder
Traits and States: Theoretical and Empirical Considerations

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Bipolar disorder (BD) is a chronic and potentially disabling mood disorder that is characterised by recurrent episodes of mania and depression. Signature features of episodes include changes in sleep and psychomotor activity patterns. Research has also proposed that instability of the circadian system may be part of the neurobiological diathesis to the disorder. The aim of the current project was to investigate all of these features for associations with vulnerability to BD at both the trait and state level using actigraphy, a non-invasive measure of activity rhythms and sleep. The outcomes of the project were also expected to inform clinical practice on the usefulness of actigraphic monitoring for the purposes of episode prodrome identification. Three studies were conducted in pursuit of these aims. Study 1 investigated the trait vulnerability concept by conducting factor analysis of two prominent measures of vulnerability to BD – the 2-dimension GBI and the 5-dimension TEMPS-A – using a mixed sample of well participants and those with a self-reported history of depression and/or mania (N = 484). The results showed that two dimensions, characterized by vulnerability to depression and vulnerability to mania, provided the most parsimonious solution in this sample. Items from the GBI measure dominated the explained variance in the solution. In Study 2, the GBI measure was used to separate a sample of well participants into groups of higher and lower levels of trait vulnerability to BD (n = 35 for both groups). The groups were then compared across 7 days on a series of sleep and circadian activity variables derived from actigraphy. The higher vulnerability group had a significantly lower mean amplitude in the circadian activity rhythm compared to the lower vulnerability group, an indication of reduced circadian stability. There were no differences however, on other features of activity or sleep. Study 3 investigated the prospective association between sleep, activity, and mood deterioration on a daily basis (state vulnerability to BD) in a sample of outpatients with BD (N = 11). Actigraphy was again used to measure the sleep and circadian activity variables. Mood and additional sleep variables were measured using self-report. Multilevel regression analyses showed that self-reported sleep, but not actigraph-derived sleep, was a significant predictor of mood deterioration the following
day. The results also showed that daytime activity was a significant predictor of mood on the same day. There were no significant associations between instability of the circadian activity rhythm and mood deterioration. The following conclusions were made based on the findings of the three-study design of the current project; (i) a 2-dimension structure appears to provide the most theoretically consistent and parsimonious model of trait vulnerability to BD, (ii) the circadian instability hypothesis of trait vulnerability to BD is tentatively supported, (iii) daytime activity is the only measure derived from actigraphy to be prospectively associated with daily mood change in BD. The latter conclusion in particular provides impetus for suggestions of how actigraphic monitoring may be applied in the clinical setting, including limitations associated with such monitoring. Accurate identification of manic and depressive prodromes is essential for successful relapse prevention. The current project identified a limited number of suitable candidates for actigraphic monitoring of vulnerability to BD states, as well as a potential biomarker of trait vulnerability to BD (reduced stability of the 24-hour activity rhythm).
Acknowledgements

A large project such as this is not possible without the support of many people. First and foremost I would like to thank my PhD supervisor, Associate Professor Greg Murray, for pushing me well outside my comfort zone to complete this project. Greg’s help extended beyond the usual project-related guidance and thesis writing, to include research skills development and instilling confidence in my academic abilities that will serve me well for many years to come. I’d also like to thank the various staff members of the Statistics unit at Swinburne University of Technology who helped with some of the advanced data analysis aspects of the project, particularly Dr. Alec Stephenson. Finally, I would like to acknowledge the emotional and financial support selflessly provided to me by my family, without which I have no doubt this project would not have been completed. Thank you to Mum, Dad, Matt, and especially my wife Lucy, for all their patience and encouragement these past few years. And even though I know she can’t read, thanks to Maggie for keeping me company for all those lonely days at home while I was producing this final thesis.
Signed Declaration

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text. This thesis contains no material previously published or written by another person, except where due reference is made in the text.

Ben Bullock
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Chapter 1

Bipolar Disorder: Description and Diagnosis

1.1 Introduction and thesis overview

Bipolar disorder (BD) is a chronic and potentially disabling mental illness that is characterised by recurrent episodes of mania and depression. In the latter part of the 20th century, clinical and research interest in BD expanded greatly. Reasons for the renaissance in scientific interest for BD are myriad, although publication of the comprehensive scientific compendium of BD and related phenomena – Manic-Depressive Illness by Frederick K. Goodwin and Kay Redfield Jamison – in 1990, may claim to be a significant catalyst. Not only did this text bring together data from a burgeoning but disparate field, synthesising research from many sources, it reminded readers of BD’s historical roots (e.g., starting with Emil Kraepelin), and its place as a core ‘pillar’ of psychiatric enquiry. The recent publication (2007) of the expanded second edition of ‘Manic-Depressive Illness’ further highlights growth in interest in this multi-faceted mental illness.

The overarching aim of the project reported here was to advance the BD literature by improving understanding of the distinction between state- and trait-based conceptualisations of the disorder. In particular, the focus was on biological rhythm features associated with BD and how they may be used to improve the identification of state and trait vulnerability to the disorder. Disruption to biological rhythms may be useful for prodrome identification in the former, and determining the degree of risk for BD amongst well populations in the latter.

Chapter 1 of the thesis focuses on description and diagnosis of BD. The current approach to description and diagnosis of the disorder is strongly categorical, as illustrated in the latest revisions of the Diagnostic and Statistical Manual of Mental
Disorders (DSM-IV-TR; APA, 2000) and the International Classification of Diseases (ICD-10; WHO, 1992). However, concerns regarding the ecological validity of categorical diagnostic systems have led to the development of alternative approaches to BD description. First, the bipolar spectrum approach recommends broadening the scope of categorical descriptors of BD to incorporate several closely related illnesses that vary along a continuum. Second, the quantitative trait approach invests in the possibility that vulnerability to BD is a quantitative trait distributed throughout the population, with disorder states the extreme clinical manifestation of the trait. Section 1.2 describes the various approaches to the description and classification of BD in detail, including the DSM-IV approach (1.2.2), the bipolar spectrum approach (1.2.3), and the quantitative trait approach (1.2.4). The complex relationship between states and traits in vulnerability to BD are also briefly considered (1.3). Chapter 1 concludes with a review of BD phenomenology (1.4), epidemiological data (1.5), and prominent psychosocial treatment and relapse prevention strategies for the disorder (1.6).

Chapter 2 focuses on neurobiological theories of vulnerability to BD. In particular, the role of biological rhythm disturbances in BD etiology is explored. The two most prominent biological rhythm processes in humans, circadian rhythms (2.1) and sleep (2.2), are described in detail, as is the interaction between the two (2.3). Evidence supporting the association between biological rhythm disruption and BD is critically reviewed (2.4). Chapter 2 concludes by briefly describing other neurobiological theories of vulnerability to BD, including genetic theories (2.5.1), neurotransmitter theories (2.5.2), and motivation/reward system theories (2.5.3). The intention of the latter part of Chapter 2 is to situate the biological rhythm focus of the current project within the appropriate context by reinforcing the idea that the neurobiological systems underpinning these theories do not operate independently of each other.

Chapter 3 focuses attention on two aspects of the biological rhythm pathway to BD that have direct relevance for the current project. First, the most appropriate way to measure the pathway is considered (3.1). The 24-hour activity rhythm was deemed to be the most parsimonious biological rhythm output parameter, given the broad range of potentially important information it produces. The 24-hour activity rhythm is a gross
measure of the daily pattern in locomotor activity. It also incorporates a circadian signal as well as information relating to the 24-hour sleep/wake pattern. All of these processes have been shown to have strong associations with vulnerability to BD. The second key aspect of the biological rhythm pathway to BD to be considered in Chapter 3 is closely related to the first. The best way to capture 24-hour activity rhythm information is discussed within the particular circumstances of the current project (3.2). Actigraphy, an ambulatory activity monitoring device, is described as the most appropriate tool to capture the required information from participants. It adequately captures 24-hour activity rhythm information in an objective and non-intrusive manner. These characteristics of actigraphy were deemed essential components of the longitudinal study designs employed in the current project. The potential utility of actigraphy in prodrome identification for BD is discussed. In particular, the question of associations between daily mood change and activity rhythm parameters derived from actigraphy are addressed (3.3). Chapter 3 concludes by presenting a major goal of the current project; to investigate whether prodrome identification can be improved through non-intrusive monitoring of biological rhythm function (3.4).

Three studies were conducted in pursuit of the goals of the project. The first study, presented in Chapter 4, was designed to guide decision-making regarding the selection of a psychometric instrument to measure vulnerability to BD. Several measures of temperamental vulnerability to BD have been developed, with each demonstrating particular strengths and weaknesses. Study 1 examined the psychometric properties and combined factor structure of these measures to determine the most appropriate instrument for describing temperamental risk for BD. A complementary aim of Study 1 was to assess the psychometric correlates of vulnerability to BD. The data was used to augment current understanding of the under-researched trait vulnerability to BD concept.

Study 2, presented in Chapter 5, used the strongest measurement predictor of BD-related traits and temperaments identified in Study 1 to separate a well student sample into low and high groups based on their respective level of temperamental vulnerability to BD. The two groups were then assessed for differences on a series of variables.
derived from measurement of the 24-hour activity rhythm. The primary purpose of Study 2 therefore, was to investigate biological rhythm function in vulnerability to BD. Disrupted biological rhythm function is a neurobiological correlate of disorder states, and Study 2 investigated the role of such disruption from a stable trait vulnerability perspective. Complementary outcomes from Study 2 included assessment of actigraphy as a viable tool for measuring biological rhythm function, and further clarification of the trait vulnerability to BD concept by investigating cognitive schema and dysfunctional thought patterns associated with the trait.

The final study for this project, Study 3, is presented in Chapter 6. This study used actigraphy to prospectively monitor state-based associations between 24-hour activity rhythm variables and daily mood variations in a sample of participants diagnosed with BD. The aim of the study was to investigate these associations with a view to their potential utility in predicting the onset of manic and depressive episodes. The primary outcomes of interest were daily associations between activity, sleep, and mood; however the unexpected relapse into mania of one participant allowed a post hoc investigation of the 24-hour activity rhythm antecedents associated with episode onset.

Chapter 7, the final chapter of this thesis, integrates the findings from all three studies, and focuses on the state-trait continuum in vulnerability to BD. In particular, the usefulness of variables derived from the 24-hour activity rhythm in predicting both state- and trait-vulnerability to BD is addressed. How the findings might be applied for use in the clinical setting is also considered. The discussion includes limitations associated with the practical use of actigraphic technology in such settings. It is concluded that there are useful applications for the technology and multiple future directions for research into its use with BD populations.
1.2 Description and classification of Bipolar Disorder

1.2.1 Historical perspective

The earliest known attempts at description and classification of BD appeared in the writings of Greek physicians of the Classical period (490-323 B.C.) who described discrete syndromes of mania (elevated, euphoric mood) and melancholia (depressed, anhedonic mood). However, Jean-Pierre Falret (Marneros & Angst, 2000) is credited as being the first physician to describe the manic and melancholic syndromes as constituting a single disorder – folie circulaire. In this way, Falret emphasised the importance of the interval between the periods of mania and melancholia as part of the illness process, thereby making the ‘circular’ component of the illness explicit. Theories regarding the nature of BD based on this concept of ‘circular madness’ were plentiful over the next 100 years. Most notable were those of German psychiatrist Emil Kraepelin who in 1899 described the syndrome of ‘manic-depressive insanity’. Kraepelin’s theories on manic-depression continue to influence current thinking regarding description and classification of BD (Akiskal, 1996; Cassano et al., 1999; Cavanagh, 2004; Marneros & Angst, 2000; Widiger & Samuel, 2005).

1.2.2 DSM-IV

Current psychiatric classification of BD is conducted according to the Diagnostic and Statistical Manual of Mental Disorders (DSM; published by the American Psychiatric Association) and the International Classification of Diseases (ICD; published by the World Health Organization). The two systems describe BD in much the same

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1 Much debate exists over who was the ‘first’ to describe mania and depression as a single disorder entity – Falret or his colleague, and academic adversary, Jules Baillarger. An engaging historical review of the, at times vitriolic, correspondence between the two eminent physicians is presented in the paper by Pichot (1995). It seems that both presented their clinical findings at around the same time, within days according to Pichot.
way, so for simplicity, DSM is used to describe psychiatric classification of BD in this thesis. The latest edition of the Manual (DSM-IV-TR; APA, 2000) recognises four BD diagnoses – Bipolar Disorder I (BD-I), Bipolar Disorder II (BD-II), Cyclothymic Disorder (CD), and Bipolar Disorder Not Otherwise Specified (BDNOS).

Specific BD diagnoses are built on the presence of disordered mood states, namely Mania, Hypomania, Depression, and Mixed States. In DSM-IV, such states are referred to as episodes. A Manic Episode is defined by DSM-IV as one in which abnormally and persistently elevated, expansive, or irritable mood is present for at least 1 week. In addition, at least three symptoms, including inflated self-esteem, decreased need for sleep, and flight of ideas must be reported. A Hypomanic Episode is defined by DSM-IV in essentially the same way as the Manic Episode, except that the length criterion is reduced to 4 days. The symptoms of a Hypomanic Episode are the same as those for a Manic Episode, albeit with less severe manifestation ("mania Lite"; Youngstrom, 2009; p. 141). Mood during a Hypomanic Episode must also be clearly different from the usual nondepressed mood. A Mixed Episode is defined by DSM-IV as a distinct period of at least 1 week in which the criteria for both a Manic Episode and a Major Depressive Episode (MDE) are met. A MDE is indicated by a number of features including persistently depressed mood, anhedonia, and insomnia.

Correct diagnosis of BD is subject to several criteria as set out in DSM-IV. The specific criteria for BD-I and BD-II are presented in Table 1. The defining feature of BD-I is history of a Manic episode. For BD-II, the defining feature is history of a Hypomanic episode plus history (or presence) of a MDE. Several criteria assist in differential diagnosis of both BD-I and BD-II from other DSM-IV disorders with similar phenomenology (e.g., Schizoaffective Disorder).

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2 The key difference between DSM-IV and ICD-10 definitions of BD is that the former requires the presence of only one manic episode for diagnosis, whereas the latter requires the presence of two episodes.

3 See Appendix A for the full list of symptoms for both Manic and Major Depressive Episodes.
Table 1

*DSM-IV Diagnostic Criteria for BD-I and BD-II*

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<th>BD-II</th>
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<tr>
<td>A.</td>
<td>Criteria are currently (or most recently) met for a Manic, Hypomaniac, Mixed, or Major Depressive Episode.</td>
<td>A. Presence (or history) of one or more Major Depressive Episodes.</td>
</tr>
<tr>
<td>B.</td>
<td>There has previously been at least one Manic Episode or Mixed Episode.</td>
<td>B. Presence (or history) of at least one Hypomaniac Episode.</td>
</tr>
<tr>
<td>C.</td>
<td>The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
<td>C. There has never been a Manic Episode or a Mixed Episode.</td>
</tr>
<tr>
<td>D.</td>
<td>The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.</td>
<td>D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional disorder, or Psychotic Disorder Not Otherwise Specified.</td>
</tr>
</tbody>
</table>
E. The mood symptoms in Criteria A and B are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

For diagnosis of CD, hypomanic and depressive symptoms must have persisted for at least 2 years. Symptom-free periods during this time must be shorter than 2 months. In addition, the 2-year period must be free of Major Depressive, Manic, and Mixed Episodes. BDNOS is a ‘catch-all’ diagnosis that provides a diagnostic option for presentations that are in the BD domain, but which do not satisfy criteria for any of the three primary BD diagnoses.

Although mania is the essential feature of BD, depression is the clinical state most often observed during the course of the disorder. Patients experience three to five times more lifetime episodes of depression than mania or hypomania (Judd, Akiskal, Schettler, Coryell, Endicott et al., 2003; Judd et al., 2002). Depression is also the most common first-episode modality in BD (Berk, Berk, Moss, Dood, & Malhi, 2006). The majority of BD patients seeking medical assistance present to primary care settings with depressive symptoms and are diagnosed and treated on the basis of such presentations (Mynatt, Cunningham, & Manning, 2002).

It is perhaps not surprising that misdiagnosis of BD is common. A large study of BD support group participants reported that up to 69% of those surveyed were initially misdiagnosed (Hirschfeld, Lewis, & Vornik, 2003) with the most frequent misdiagnosis being Major Depressive Disorder (MDD). Such incorrect diagnoses delay appropriate
treatment and affect long-term outcomes. The consequences of misdiagnosis and associated treatments can range from moderate (e.g., reduced well-being; Awad, Rajagopalan, Bolge, & McDonnell, 2007) to severe (e.g., anti-depressant induced mania; Leverich et al., 2006). Clinical awareness of subtle BD indicators in depressive presentations is growing (Berk et al., 2006) and the dominant taxonomies may need to evolve in order to accommodate the developing expertise.

For the present project, especially the prospective investigation of mood state in BD (Study 3), it is important to underscore a core paradox in description of the disorder: deterioration in mood state in this complex condition can present as either movement towards more elevated mood or movement towards more depressed mood. This reality constitutes a core challenge for patients attempting to monitor their disorder (see Section 3.3). A further complication attached to this paradox is that, empirically, deterioration in mood typically manifests as shifts towards depression (Judd et al., 2002).

1.2.3 The bipolar spectrum

Among many contemporary researchers the term ‘bipolar spectrum’ is the accepted nomenclature to describe BD diagnosed using DSM-IV criteria (Akiskal, 1996, 2004; Angst, 1998; Cassano et al., 1999; Dunner, 2003; Ghaemi et al., 2005; Hirschfeld et al., 2000; Lara, Pinto, Akiskal, & Akiskal, 2006). This change in terminology represents a shift away from a traditional, categorical approach to classifying the Bipolar Disorders to one that recognises an underlying dimensionality to BD. Thus, while clinical BD states appear to be qualitatively distinct, they are assumed to share a common pathogenesis. The BD variants described in DSM-IV imply an order of severity, starting at the most mild end of the spectrum (CD) and increasing through BD-II up to the most severe diagnosis of BD-I. DSM-IV does not explicitly refer to the disorder variants as constituting a spectrum, however the ordering of diagnoses is consistent with a spectrum-like model.

The driving force behind the adoption of the BD spectrum concept was the difficulties associated with reliable diagnosis. The reality was that BD seldom
conformed to the categorical descriptors proposed by prominent diagnostic systems. Angst, for example, a key figure in the revival of interest in BD research, observed amongst his patients a “heterogeneity of bipolar disorders” (1978; p. 65), highlighting the diversity of clinical presentations of BD.

Most common approaches to describing the bipolar spectrum encompass the three primary DSM-IV diagnoses (BD-I, BD-II, and CD), as well as some or all of the following subcategories: MDE superimposed on a hyperthymic or cyclothymic temperament (Akiskal & Pinto, 2000), antidepressant-induced hypomania (BD-III; Akiskal & Pinto, 2000), recurrent depression with family history of BD and/or early onset of symptoms (Bader & Dunner, 2007), and various adaptations thereof (see Phelps, Angst, Katzow, & Sadler, 2008). There is little consensus however, on how these subcategories should be incorporated into diagnostic systems.

The most comprehensive proposal for the introduction of BD spectrum phenomena in future editions of DSM was recently published by the International Society for Bipolar Disorders Diagnostic Guidelines Taskforce (Ghaemi et al., 2008). Briefly, the taskforce recommended that two examples be added to the BDNOS category (subthreshold hypomanic episodes and multiple signs of non-manic bipolarity), as well as specifiers such as positive family history of BD in a first-degree relative, antidepressant-induced mania/hypomania, and recurrent depressive episodes characterised by early age of onset. The approach recognises the complexities associated with “carving nature at its joints” (Kendler, 2006; p. 1142), when no such natural boundaries between conditions exist. To this end, Ghaemi et al. concede that assessments of continuous biological traits are likely to form key modules in future diagnostic systems.

1.2.4 The quantitative trait approach

The quantitative trait approach to the description of BD is an attempt to identify the dimensions underlying vulnerability to the disorder. It is a further step removed from the DSM-IV categorical model and represents an extension of the notion of a bipolar
spectrum. While the bipolar spectrum concept recognises dimensionality in the underlying BD construct, categorical descriptors are applied to the phenotypic expressions of the disorder. The quantitative trait approach discards any notion of category and classification and instead describes BD as the clinical expression of a quantitative trait(s) distributed throughout the population (Kelsoe, 2003). Commonly argued under this approach is that sets of genes generate neurobehavioural traits that predispose an individual to overlapping phenotypes of similar clinical manifestation (e.g., BD and schizoaffective disorder). External factors, such as stress and environment, exacerbate the trait diathesis and create the necessary conditions for expression of disorder phenotypes. Studies have shown that not just BD, but a variety of mood disorder diagnoses occur at higher rates in families of BD probands (Camp et al., 2005; Gershon et al., 1982), supportive of a broad genetic diathesis to the disorder. BD-related temperaments, shown to aggregate in the non-ill members of these families (Evans et al., 2005; Savitz, van der Merwe, & Ramesar, 2008), again indicate that risk for BD may be subject to variation along a series of vulnerability dimensions.

The dimensional traits thought to underlie vulnerability to BD have yet to be identified, although several models have been proposed and some have received empirical support. A comprehensive model of trait vulnerability to BD was developed by Depue and colleagues (e.g., Depue & Iacono, 1989). They described a series of behaviours that were consistent with subsyndromal manifestations of hypo/mania, depression, and biphasia (fluctuation between hypo/mania and depression). The model proposes that subsyndromal behaviours differ from disorder states in quantity only, in that they are less frequent and are of shorter duration. The model is based on neurobehavioural theory in which a dopaminergic system motivates and directs behaviour towards rewarding environmental stimuli. Vulnerability to BD under the model is due to dysregulation of this system. According to Depue and Iacono therefore, the trait underlying vulnerability to BD is a single dimension characterised by under-(depression) and overactivation (hypo/mania) of the system. A comprehensive description of the neurobehavioural system that supports this theory is provided in Section 1.6.3.
Several researchers have proposed a two-dimensional trait structure for vulnerability to BD. For example, Murray, Goldstone, and Cunningham (2007) measured personality dimensions and traits related to BD in a well student sample and found that separate dimensions of trait depression and trait hypomania provided a good fit to the data using confirmatory factor analysis. They also found that bi-directional correlations between the two traits were moderate-to-strong. A one-dimensional model also provided a good fit to the data in their study, however the authors argued that the more complex two-dimensional model added valuable information to the representation of trait vulnerability to BD, particularly as the two vulnerability dimensions had different personality correlates (viz., neuroticism with trait depression, extraversion with trait mania). The findings of Murray et al. are consistent with twin study data from McGuffin et al. (2003). Their study of MZ and DZ twin pairs with either MDD or BD showed that a correlated liability model, in which mania and depression occupied separable dimensions, was a better fit to genetic concordance data than a 2-threshold model, in which mania and depression occurred along the same dimension. Indeed, almost three-quarters (71%) of variance in the liability to mania was specific to the manic syndrome. Also similar to the data of Murray et al. was the finding that loadings on the two dimensions were highly correlated ($r = .65$). Support from both clinical and non-clinical sources can therefore be found for separable dimensions of hypo/mania and depression in vulnerability to BD. It also appears likely that these dimensions are highly correlated.

Emphasising the variety of clinical presentations of BD, Akiskal and colleagues propose five temperament dimensions that increase vulnerability to BD. Akiskal and Mallya (1987), for example, describe extreme variation in temperaments labelled dysthymia, irritability, anxiety, hyperthymia, and cyclothymia increase risk for bipolar spectrum conditions. The two latter temperaments are described as particularly salient risk factors for BD. The hyperthymic temperament, manifesting as intermittent subsyndromal hypomanic features with infrequent euthymia, is proposed to underlie vulnerability to BD-I (Koukopoulos et al., 2006). The cyclothymic temperament, manifesting as intermittent short cycles of biphasic changes in mood and energy, is
proposed to underlie vulnerability to BD-II (Koukopoulos et al.). Psychometric investigation of the instrument used to measure the five temperament dimensions (TEMPS-A; Akiskal, Mendlowicz et al., 2005) has demonstrated that two higher order factors may underpin the five dimension structure. The first of these factors has been shown to consist of cyclothymic, dysthymic, and irritable temperament items, while the second factor has been shown to consist of hyperthymic temperament items. The two-factor structure has been found in both clinical (Akiskal, Kilzieh et al., 2006) and non-clinical populations (Maremmani et al., 2005; Rozsa et al., 2008). Thus, although five dimensions are proposed, empirical assessment of the model reveals that two underlying factors may be fundamental. Notably, these ‘super factors’ align closely with the two-dimensional approaches to the description of vulnerability to BD.

A distinctive feature of the Akiskalian five-dimensional model of temperamental vulnerability to BD is the manner in which it captures both between-person trait differences as well as within-person state variation (the "state-trait continuum"; Akiskal, Kilzieh et al., 2006; p. 30). According to the model, higher trait levels of temperaments relevant to BD increase the risk for expression of the disorder. This is not a unique proposition – Depue and colleagues (e.g., Depue & Monroe, 1978) also subscribe to this theory and it is a key feature of quantitative trait approaches to BD vulnerability. Where the Akiskal model departs from others is in the description of within-person manifestations of recurrent mood states within the bipolar spectrum. That is, expression of disorder-relevant states is also subject to influence from waxing and waning of temperament in the presence of salient environmental stressors. The relationship between states and traits is discussed in further detail in Section 1.3.

In sum, the balance of evidence would appear to favour a two-dimensional model of quantitative trait vulnerability to BD. Confirmatory factor analysis of a self-report instrument used to measure vulnerability to BD in a well student sample highlighted the usefulness of a two-factor solution (Murray et al., 2007). Exploratory factor analysis of another self-report BD vulnerability measurement instrument in a clinical population also revealed two ‘super factors’ of affective temperament (Akiskal, Akiskal, Haykal, Manning, & Connor, 2005). Perhaps the most compelling evidence supporting the two-
dimensional structure of vulnerability to BD comes from the study of twins by McGuffin et al. (2003) in which much of the genetic liability to mania was found to be unique to that variant of the illness. The high correlations between the two dimensions in the Murray et al. and McGuffin et al. studies is noteworthy. It indicates that it may be empirically difficult, and perhaps even unnecessary, to distinguish the two dimensions, particularly at the level of subsyndromal temperament. Nevertheless, it is of significant theoretical interest that separable, albeit highly correlated, dimensions of hypo/mania and depression in vulnerability to BD can be identified.

1.3 State versus trait perspectives on vulnerability to Bipolar Disorder

A fundamental difference between categorical and dimensional approaches to the description of BD is that the former is based on states (syndromes of mania and depression) while the latter is based on traits (dimensions of mania-proneness, for example). The distinction is important for the present project because biological rhythm correlates of both are investigated (Study 3 and Study 2, respectively). It is therefore useful to articulate the project’s assumptions about state-trait relationships.

The distinction between state-based (within-person variations) and trait-based (between-person differences) theories of personality represents a long-standing divide in the study of psychology and psychopathology (Fleeson, 2004). States, which vary longitudinally within people and across situations, are seen by some personality researchers to occupy a different level of personality abstraction than traits, which are assumed to be constant across situations (e.g., Cervone, 2005). Trait personality theorists believe that traits consistently direct individual behaviour at the state level. In other words, states are assumed to be transient displays of the underlying stable trait dimensions (e.g., McCrae, 2005).

There is evidence to support both perspectives on state and trait theories of personality. Borsboom, Mellenbergh, and Van Heerden (2003) for example, state that
“the connection between within-subject processes and between-subject variables [is] speculative” (p. 206) based on current data. As such, there are no compelling reasons as to why trait features should be assumed to influence behaviour at the individual state level. Alternatively, Schutte, Malouff, Segrera, Wolf, and Rodgers (2003) demonstrated acceptable fit between the Big Five trait model and transitory states using confirmatory factor analysis. Watson, Clark, and Tellegen (1988) showed that trait manifestations of positive and negative affectivity remained stable over an eight-week period, while state manifestations of positive and negative mood showed more variation but remained consistent with trait characteristics. Bi-directional pathways of influence between the psychologically active characteristics of situations (state theory) and reliable individual differences in behaviour (trait theory) have also been demonstrated (Fleeson, 2007).

The Akiskal model recognises the value of understanding vulnerability to BD from both state and trait perspectives. As described in Section 1.2.4, the Akiskal state-trait continuum theory incorporates both between-person (trait) and within-person (state) elements for the description of BD. Between-person differences in temperament are assumed to affect relative risk for the disorder. Within-person variation of symptoms are assumed to be influenced by temperamental waxing and waning, activated in the presence of stressful events. Thus, according to Akiskal, subclinical temperaments increase risk for BD, as well as influence the longitudinal course of symptoms (Akiskal, Kilzieh et al., 2006). By way of empirical support for such a model, Henry et al. (1999) showed that temperament not only influences vulnerability to BD, but also polarity of episodes (mania or depression) and other features of the clinical course.

The current project adopts a similar perspective to Akiskal and colleagues in the investigation of neurobiological processes associated with BD. That is, for the current project it was assumed that some neurobiological processes act as both between-subject (trait) and within-subject (state) vulnerability markers. There is precedent for the adoption of such a conceptualisation. Nuechterlein et al. (1992) investigated developmental processes amongst 106 patients with schizophrenia over the course of a 1-year period. They discriminated between stable vulnerability indicators and mediating vulnerability factors in the description of neurobiological processes associated with
disorder progression. The former characterisation refers to trait-like processes that can be used to identify schizophrenia-prone individuals. The latter characterisation is the one that provides precedent for the current project, and refers to processes that “show abnormalities during clinical remission” but which become “more severely deviant” during psychotic exacerbations (p. 388). The current project did not aim to study the neurobiological correlates of BD episodes. Nevertheless, the theoretical standpoint is clear – it is assumed that neurobiological processes can act as both between- and within-person vulnerability factors.

1.4 Phenomenology

To round out the discussion of BD description and classification, it is worthwhile briefly describing some of the common symptoms of manic and depressive states. This will assist in gaining some semblance of appreciation of the experience as lived by people with the disorder. The description of these states outside the clinical descriptors used in DSM-IV is therefore the primary focus of this section.

Mania is often described as the ‘up’ phase of BD. The manic phase typically presents in the form of expansive or irritable moods, and euphoric self-confidence. Mood during the up phase has been described in terms of “intensity, power, well-being, financial omnipotence, and euphoria” (Jamison, 1996; p. 67) sometimes involving a deep impression of “cosmic relatedness” (Jamison, 1996; p. 37). Milder, less grandiose states are more common however, where mood is described as “cheerful” and patients as of an “imperturbable good temper” (Kraepelin, 1921; p. 56). Sometimes the level of arousal associated with the manic state can be unpleasant. Mountain (2003), a doctor who wrote of her experiences with mania, describes this feeling as “the kind of irritability in which you want to crawl out of your skin” (p. 40). Cognitively, mania most commonly presents in the form of grandiose thinking, racing thoughts, and poor concentration (Goodwin & Jamison, 2007). In severe cases, delusions and hallucinations can also be present (Canuso, Bossie, Zhu, Youssef, & Dunner, 2008). Behavioural signs
of mania are often the key to early recognition of an episode, particularly sleep
disturbance (Jackson, Cavanagh, & Scott, 2003). Other commonly observed behavioural
cues to manic onset include hyperactivity, rapid/pressured speech, and hyperverbosity
(Goodwin & Jamison, 2007).

Depression manifests primarily as intense and persistent feelings of sadness,
hopelessness, and anhedonia. Jamison (1996) describes feeling like nothing was
“interesting or enjoyable or worthwhile” (p. 38) and that there was a “gray, bleak
preoccupation with death, dying, [and] decaying” (p. 38). Depression is often referred to
as the ‘black dog’, a metaphor attributed to Sir Winston Churchill (Storr, 1997) that
describes the stubborn and tenacious dark depression that stalks sufferers. The cognitive
signs of depression include melancholic rumination, difficulty organising thoughts, and
indecisiveness. Jamison described her brain as being as “cold as clay” (p. 38) during
these bleak times. Behavioural signs of depressive states are less recognisable than those
seen in manic states, as depressed mood tends to be the dominating feature.
Nevertheless, sleep disturbance (particularly hypersomnia), hyperphagia, and
psychomotor retardation are all commonly observed characteristics of the depressive
phase in BD (Mitchell, Goodwin, Johnson, & Hirschfeld, 2008).

1.5 Epidemiology

DSM-IV quotes lifetime prevalence rates of BD-I in community settings of between
0.4% and 1.6% (APA, 2000). Lifetime prevalence of BD-II in community settings is
estimated at approximately 0.5% (APA, 2000). Angst (1998) reported lifetime
prevalence rates for mania (BD-I) and hypomania (BD-II) of 5.5% in a large,
longitudinal community-based study in Switzerland. This figure is at the extreme upper-
end of estimates however, with lifetime rates for combined BD-I and BD-II in other
similar-sized studies more likely to emerge in the range 1.6% (in Norway; Kringlen,
Torgersen, & Cramer, 2001) to 3.5% (in Hungary; Szádóczky, Papp, Vitrai, Rühmer, &
Füredi, 1998). Lifetime prevalence of CD is reported to be between 0.4% and 1% (APA,
2000. It is unclear how much of this lifetime incidence of CD ‘overlaps’ with other BD diagnoses, as Cyclothymia is a likely precursor to BD-II (Brieger & Marneros, 1997). Community prevalence rates for BDNOS are not available, however Ozcan et al. (2003) reported that 9.0% of total community intakes in a specialist BD clinic were classified as BDNOS.

Prevalence estimates of bipolar spectrum conditions using non-DSM-IV nosologies demonstrate that such conditions are higher than DSM-IV estimates. Angst, Gamma, Benazzi et al. (2003) reported a community prevalence rate of 23.7% for lifetime incidence of bipolar spectrum conditions that included ‘soft’ bipolar expressions. The definition of bipolarity used by Angst et al. included recurrent depressions with subthreshold hypomanias. Akiskal, Akiskal et al. (2006), also using diagnostic criteria that included soft bipolar expressions, reported that 64.5% of \( N = 537 \) participants presenting with MDE were bipolar spectrum cases under the broader definition. The validity and reliability of non-DSM-IV diagnostic strategies has yet to be adequately tested. However, there is sufficient evidence to indicate that BD spectrum conditions are more pervasive in the community than what is reported based on DSM-IV classifications.

There is limited data on community prevalence rates for BD in Australia. Mitchell, Slade, and Andrews (2004) conducted the most comprehensive investigation. Using data from the Australian National Survey of Mental Health and Well-Being, a combined 12-month prevalence rate of 0.5% for BD-I and BD-II was found. Some methodological limitations in the Mitchell et al. study, particularly a lack of investigation into subthreshold manifestations of BD and irritable-type depressions (a potential indicator of BD mixed states; see Benazzi & Akiskal, 2005), may have led to an underestimation of true prevalence. Some sampling exclusions, including those in prisons, hospitals, and remote areas, may have also contributed to underestimation of true prevalence, as these populations in particular could reasonably be expected to have a higher than average rate of mental illness (e.g., Brinded, Simpson, Laidlaw, Fairley, & Malcolm, 2001). A more recent Australian survey employing a smaller sample and slightly less restrictive
diagnostic criteria estimated the lifetime prevalence of BD spectrum conditions at 2.5% (Fisher, Goldney, Grande, Taylor, & Hawthorne, 2007).

1.6 Psychosocial treatments and relapse prevention

BD is a relapsing and remitting condition. Effective treatment must be capable of stabilising the initial symptoms of mania and/or depression, and then preventing future relapse. Pharmacological intervention is the first line of treatment in acute BD episodes and is successful in the vast majority of cases (Yatham et al., 2009). Effective maintenance treatment is more problematic and involves a combination of medication and psychosocial intervention (Castle, Berk, Lauder, Berk, & Murray, 2009).

Long-term outcomes for pharmacological treatment of BD alone are unsatisfactory. Subsyndromal symptoms persist following recovery in many cases (Keck et al., 1998) and 5-year relapse rates into mania or depression have been estimated at 73% (Gitlin, Swendsen, Heller, & Hammen, 1995). In a comprehensive review of studies investigating lithium therapy, Fountoulakis et al. (2008) concluded that there was “unclear or conflicting scientific evidence” (p. 277) regarding its effectiveness for long-term prophylaxis.4 Carney and Goodwin (2005) summarise research suggesting that only a one-third reduction in relapse risk is apparent for those using lithium versus those using a placebo. Relapse rates for BD patients using other medications (e.g., valproate) were not significantly different to those found for lithium.

The limited effectiveness of pharmacological prophylaxis has led to the investigation of adjunctive psychosocial interventions in BD. Indeed, treatment guidelines for BD, including those of the Royal Australian and New Zealand College of Psychiatrists (Mitchell, 2004), the American Psychiatric Association (Bowden et al., 2002), and the Canadian Network for Mood and Anxiety Treatments (CANMAT; Yatham et al., 2009), recommend psychosocial interventions should begin as soon as is practicable after stabilisation of acute symptoms. Among the psychosocial interventions

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4 Lithium is a key mood-stabilizing medication for maintenance treatment of BD (along with lamotrigine, valproate, and olanzapine; Yatham et al., 2009).
to have empirically supported efficacy in the maintenance treatment of BD are psychoeducation (group and individual), systematic care, family therapy, interpersonal and social rhythm therapy, and cognitive-behavioural therapy (Miklowitz, 2008).

The large-scale Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; Sachs et al., 2003) collected treatment outcome data amongst 293 BD-outpatients receiving either intensive psychosocial treatment or standard collaborative care (Miklowitz et al., 2007). Both interventions included standard pharmacological treatment. The psychosocial treatment group were more likely to be consistently well, and recorded significantly shorter times to recovery as well as significantly higher year-end recovery rates than those receiving standard care. No significant differences in outcomes between the different psychosocial therapies were apparent. These data were consistent with an earlier meta-analysis of randomised control studies showing reduced 12-month relapse rates when psychological interventions were used in conjunction with standard psychiatric treatment versus medication or standard treatment alone (Scott & Gutierrez, 2004).

The mechanism by which psychosocial interventions act in preventing relapse in patients with BD is largely unknown. For the present project however, it is noteworthy that stabilisation of biological rhythms is a prominent feature of many successful therapies for BD (Suto, Murray, Hale, Amari, & Michalak, 2010). For example, stabilisation of sleep patterns and establishment of a regular routine are key components of both cognitive-behavioural therapy (CBT; Basco & Rush, 2005; Lam, Jones, Hayward, & Bright, 1999) and psychoeducation (PE; Colom et al., 2003) approaches to maintenance treatment of BD. Monitoring of mood changes on a daily basis, particularly around times of increased vulnerability to manic or depressive onset, are also part of the therapeutic strategy in CBT and PE. Concurrent monitoring of sleep/wake patterns and mood facilitates patient awareness of the link between these two biobehavioural parameters. Family-based interventions recognise the importance of establishing stable family routines in maintenance therapy for BD, even though it is not a central feature of the therapeutic process (see Morris, Miklowitz, & Waxmonskey, 2007).

5 The generic term ‘biological rhythms’ is used in the current project to refer to both circadian and sleep/wake processes.
Interpersonal and social rhythm therapy (IPSRT; Frank, Swartz, & Kupfer, 2000) features a strong emphasis on the circadian instability hypothesis in maintenance treatment of BD. Regulation of sleep/wake patterns and daily routines are signature features of the IPSRT therapeutic process. Behavioural monitoring of social rhythms, which includes recording the timing of daily ‘events’ (e.g., wake time, time of first contact with another person, dinner time, bed time), is a key self-report strategy of the therapy. The monitoring component serves a dual purpose – to encourage stability in social rhythms, and to identify social rhythm disrupting events as potential triggers for relapse. The therapy has proven to be effective in stabilising social rhythms (Frank et al., 1997) and preventing relapse in BD outpatients (Frank et al., 2005).

Effective maintenance treatment of BD is multi-modal, incorporating the use of pharmacological agents as well as adjunctive psychosocial interventions to prevent relapse (Yatham et al., 2009). Re-establishing stability of circadian, sleep/wake, and other biological rhythms is a prominent feature of many psychosocial maintenance treatments for the disorder. The hypothesis that instability of biological rhythms is etiologically important in BD has a long history (Murray & Harvey, in press). The present project shares this assumption, and biological rhythms are the primary focus of the review of BD pathogenesis in Chapter 2.

1.7 Summary of Chapter 1

The symptoms of BD are complex. Particularly difficult for researchers investigating the neurobiological underpinnings of the disorder are, (i) the contrasting mood syndromes that define the disorder, and (ii) the importance of both state and trait manifestations of BD vulnerability. The former emphasises the difficulty in modeling pathology that generates such contrasting extremes. The latter emphasises the need to consider both between-subject (trait) and within-subject (state) outcomes of putative neurobiological pathogenesis.
Chapter 2

Biological Rhythms and Bipolar Disorder

Five topics are reviewed in Chapter 2, the primary aim of which is to present an overview of the empirical data supporting the relationship between disturbed circadian and sleep/wake processes, and BD. Before summarising the relevant research a brief description of the interacting circadian (2.1) and sleep/wake (2.2) systems and how they are measured is provided. The two-process model of sleep regulation is also described (2.3). Evidence supporting the association between biological rhythm disturbances and BD is presented next (2.4). The evidence is organised according to four key areas, and includes observations of disturbed sleep and circadian function during manic and depressive states (2.4.1), predictive relationships between sleep changes and the onset of clinical episodes (2.4.2), the effectiveness of treatments for BD that impact biological rhythms (2.4.3), and evidence of biological rhythm abnormalities as trait phenomena in vulnerability to BD (2.4.4). Finally, a brief review of other theories describing pathogenic processes proposed to underlie BD is presented. Genetic (2.5.1), neurotransmitter system disruption (2.5.2), and brain reward system dysregulation theories (2.5.3) are described in order to provide sufficient context for consideration of the biological rhythm pathway to BD that is the focus of the current project. The interactions between these systems and the circadian system are also described with the intention of showing that the biological rhythm pathway is not independent of other recognised neurobiological pathways to BD.
2.1 Circadian rhythms

Virtually every organism on Earth is driven by a series of endogenous biological rhythms (Refinetti, 2006). In mammals the source of these rhythms are the suprachiasmatic nuclei (SCN), a dense collection of photic-dependent cells located in the anterior hypothalamus that are responsible for rhythmic regulation of various physiological and behavioural processes. Lesions to the SCN of animals have been shown to severely disrupt biological rhythmicity (Refinetti, Kaufman, & Menaker, 1994), while restoration of the SCN via surgical transplant re-establishes rhythmic processes (Ralph, Foster, Davis, & Menaker, 1990). These and other corroborating data (see Reppert & Weaver, 2002) confirm the SCN as the central pacemaker for biological rhythms in mammals.

The rhythmic expression of the SCN is regulated by a series of genes common to most mammalian species (Lowrey & Takahashi, 2004). These ‘clock genes’ (e.g., CLOCK, NPAS2, ARNTL, PER1, PER2, PER3, CRY1, CRY2) are key determinants of SCN function. Variations in clock gene expression can have an impact on species’ survival. Beaver et al. (2002), for example, demonstrated reduced reproductive fitness in *Drosophila melanogaster* bred with mutated clock genes. The diurnal rhythmic output of the SCN also confers adaptive advantage to all species. The SCN signal encourages interaction with the environment at times most likely to produce positive outcomes, such as feeding behaviour in mammals (Refinetti, 2006). The system also encourages withdrawal from the environment at times of potential danger to the organism (e.g., night time in day-active species). Organisms with defective SCN processes are therefore at an evolutionary disadvantage and less likely to survive and prosper (e.g., Kumar, Mohan, & Sharma, 2005).

The output of the SCN can be observed in the 24-hour rhythms in processes it influences. The word ‘circadian’, derived from the Latin terms ‘circa’ and ‘dias’, translates to ‘about a day’ (Refinetti, 2006), and reflects the (approximately) 24-hour period of these biological rhythms. Circadian rhythms have been observed in neurobiological (melatonin; Moore, 1996), physiological (core body temperature;
Refinetti & Menaker, 1992), and behavioural (activity; Ancoli-Israel et al., 2003) output mechanisms. In humans, the sleep/wake rhythm is regarded as the most important expression of SCN output (Czeisler, Buxton, & Khalsa, 2005), although there are qualifications to such a conceptualisation (see discussion of the ‘two-process sleep model’ in Section 2.3).

The SCN is not the sole contributor to circadian rhythmicity. Biological clock mechanisms in tissues external to the hypothalamus have been identified in several mammalian species (e.g., Zylka, Shearman, Weaver, & Reppert, 1998). These peripheral clocks exhibit limited self-sustaining oscillations and may contribute to the expression of rhythmic behaviour (Yoo et al., 2004). Being independent, the peripheral clocks can become desynchronised from each other, resulting in distortion of the ensemble output rhythm (Welsh, Yoo, Liu, Takahashi, & Kay, 2004). The job of the SCN is to coordinate the clocks in all tissues and cells of the body so that the level of desynchrony is regulated. Thus, rather than being an exclusive driver of circadian rhythmicity, the SCN is likened to being the “conductor of the circadian orchestra” (Davidson, Yamazaki, & Menaker, 2003; p. 110), synchronising the various clocks to produce harmonic output.

Classic experiments show that the free-running period of endogenous human rhythms is slightly longer than 24 hours (Aschoff, 1965; Czeisler et al., 1999). External cues, or zeitgebers (literally, time-givers) are therefore necessary to entrain the internal clock to a 24-hour rhythm. The presence or absence of light is a particularly strong entraining parameter for the circadian system (Czeisler, Allan, & Strogatz, 1986). Afferent nerve pathways leading directly from the retinal system to the SCN demonstrate the importance of photic cues in regulating the 24-hour oscillatory period. Non-photic cues are also essential for entrainment of circadian rhythms and include neurochemical input from the raphe nuclei and pineal gland (Refinetti, 2006). Environmental cues, such as food availability and ambient temperature (e.g., Saper, Lu, Chou, & Gooley, 2005), can also entrain the SCN.

SCN signals are also entrained by socio-behavioural feedback loops (Dijk & Franken, 2005; Mistlberger, Antle, Glass, & Miller, 2000). In humans particularly, social zeitgebers are important behavioural entraining factors for the circadian control of
the sleep/wake rhythm (Ehlers, Frank, & Kupfer, 1988). Aschoff et al. (1971) demonstrated that biological rhythms of core body temperature and urinary hormone excretion could be maintained by a rigorous schedule of bed and meal times in the absence of light/dark cues. The operation of the circadian system is therefore subject to a complicated organisational structure, with neurobiological timing from the SCN interacting with environmental and socio-behavioural cues (see Figure 1).

*Figure 1.* Input and output pathways of the SCN (central oscillator) that contribute to the rhythmic behaviour of an organism.


Quantitative appraisal of circadian rhythmicity is described in terms of three measurement parameters – phase, amplitude, and period (Nelson, Tong, Lee, & Halberg, 1979). The phase represents the point at which the rhythm reaches either its acme or nadir. This parameter is time-based, and expressed relative to 24-hour clock time. The amplitude of the endogenous rhythm is generally measured as the distance between the mean and the peak of the oscillation, although others have recommended that the entire range of oscillation (i.e. peak-to-trough difference) is a more reliable parameter (Van
Someren, Kessler, Mirmiran, & Swaab, 1997; Witting, Kwa, Eikelenboom, Mirmiran, & Swaab, 1990), particularly for the modelling of the circadian pattern in activity. The period of the endogenous rhythm represents the longitudinal peak-to-peak distance of the oscillatory pattern. Again, it is expressed relative to 24-hour clock time. Figure 2 presents the three measurement parameters schematically.

![Figure 2. Schematic representation of the sin curve used to model the circadian rhythm. The parameters used to describe the fundamental characteristics of the curve are also shown (see text for description).](image)

2.2 Sleep

Sleep, a key output rhythm of the circadian system, serves an important purpose in the survival and well-being of all mammalian species. Even though the specific adaptive function of sleep is not known, the behaviour is strongly conserved across all birds and mammals studied so far (Lesku, Martinez-Gonzalez, & Rattenborg, 2009), suggesting that sleep is essential for normal functioning. The negative consequences of sleep deprivation in humans, including physiological, neurocognitive, and behavioural deficits are well documented (Minkel, Banks, & Dinges, 2009) and provide further evidence of sleep’s importance to normal functioning.
Normal sleep is comprised of two distinct states (Pace-Schott, 2009). Rapid eye movement (REM) sleep, which is characterised by increased autonomic activity, muscle paralysis, and dreaming, and non-rapid eye movement (NREM) sleep, which is considered to be a more restorative state. The NREM sleep state is further divided into four stages. Stage 1 sleep is brief and consists mostly of theta brainwaves (as measured by electroencephalogram; EEG). Theta waves are slower than waking state alpha and beta waves, and mark the slowing down of mental activity in preparation for deeper sleep states. Drowsiness associated with Stage 1 sleep eventually makes way for the light sleep state of Stage 2 in which alpha waves disappear altogether. Stage 3 and 4, characterised by even slower delta brainwaves, indicate deep sleep. Much of the restoration of physical resources occurs here, as muscles relax and the rate of respiration decreases. The cycle of stages then reverses, from Stage 4 back to Stage 1, and culminates in a period of REM sleep. Each complete cycle, from Stage 1 through to Stage 4 and back again, lasts for approximately 90 minutes. As the sleep period progresses, deep sleep occurs with less frequency. In contrast, REM sleep states are maintained for longer intervals in the latter half of the sleep cycle.

2.3 The two-process model of sleep regulation

According to the most widely accepted model of the sleep/wake process – the two-process model (Borbely & Achermann, 2005) – sleep is regulated by two functionally distinct, but interacting neurobiological processes. Process C, the circadian component of the sleep/wake cycle, is under the direct control of the SCN and entrained, primarily, by the 24-hour cycle of light and dark (see 2.1 above). Process S is a non-circadian, sleep-debt process that is driven by a homeostatic need for sleep. Process S describes a biological need that increases in proportion to the time elapsed since the last period of sleep. The need then decreases during the sleep period. Figure 3 presents a schematic representation of the two-process model of sleep regulation, incorporating Process C and Process S.
Figure 3. Schematic representation of the two-process model of sleep regulation. Process S involves an increase in sleep pressure as elapsed time awake increases. Sleep pressure decreases during the sleep period. Process C is an internal clock-driven process that waxes and wanes according to the time of day.


The interaction between Process C and Process S in determining sleep/wake behaviour is complex and yet to be fully understood. While it is known that pathways between the two processes are bidirectional, and their interaction predicts the propensity and timing of sleep (Dijk & Franken, 2005), the neurobiological basis of the relationship is less clear. Fuller, Gooley, and Saper (2006) have proposed that the sleep/wake process
operates according to a system in which sleep active neurons in the ventrolateral preoptic nucleus and arousal circuits in the hypothalamus and basal forebrain are functionally connected. A process analogous to an “electronic flip/flop switch” (Fuller et al., 2006; p. 485) mediates the interaction between the sleep and arousal mechanisms to ensure that consolidated states of sleep and wake are maintained. Rapid alternation between the two states is facilitated by the switch process in order to avoid intermediate states. Circadian ‘alerting’ signals operate on one side of the switch to promote wakefulness, while circadian ‘hypnotic’ signals and homeostatic sleep drive processes operate on the other side of the switch to promote sleep. It is further proposed that neurons containing the excitatory neuropeptide orexin, located in the lateral hypothalamus and active during wakefulness, help to stabilise the switch (Saper, Scammell, & Lu, 2005).

The interaction between Process C and Process S makes it difficult to measure the separate influence of each on the timing of sleep and wake. Laboratory techniques that ‘decouple’ circadian and homeostatic influence on sleep/wake behaviour (Dijk & Czeisler, 1995) are useful in this regard. The forced desynchrony (FD) protocol imposes a 28-hour sleep/wake schedule that delineates homeostatic from circadian processes. Under FD conditions the homeostatic sleep component quickly adapts to the new sleep/wake schedule, while the circadian oscillator continues on a 24-hour cycle. The outputs of each process can therefore be evaluated independently of each other. The FD protocol requires a stable environment in which light, ambient temperature, and other entraining parameters are tightly controlled, hence the need for a laboratory setting. For naturalistic designs, it is not possible to parse circadian and homeostatic constituents of the sleep/wake rhythm. It is for this reason that the non-specific term ‘biological rhythm’ is prominent in the current thesis, to refer to sleep/wake processes where the locus of circadian and homeostatic influences are ill-defined.

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6 A 28-hour sleep/wake schedule is typical for the FD protocol.
2.4 Biological rhythm disturbances associated with Bipolar Disorder

This section provides a review of clinical and pre-clinical evidence for disturbed biological rhythms in BD. The evidence is organised according to four broad areas. The first source of evidence is derived from clinical observations of sleep and circadian disturbances during manic and depressive states in BD patients. The second source of evidence is derived from clinically useful predictive relationships between sleep, circadian rhythms and mood in BD populations. The third source of evidence concerns effective treatments for BD that have known associations with biological rhythm function. Finally, evidence of biological rhythm disturbances as features of trait vulnerability to BD, including those disturbances that persist during euthymia and those that are present in high BD risk populations, is presented.

Two types of evidence are presented within the broad areas described above. Cross-sectional evidence relates to associations between biological rhythms and BD, while evidence of prospective and treatment-related associations indicate a more causal mechanism. It is important to recognise that each type of evidence has a different bearing on interpretations of the link between biological rhythms and BD. Clearly, evidence that describes a causal mechanism is more useful for inferences of disturbed biological rhythms as diatheses of vulnerability to BD. Evidence of cross-sectional associations between biological rhythms and clinical states in BD provides more distal inference. Nevertheless, such associations are useful, especially as far as treatment is concerned. Outcomes for patients are improved if associations between sleep difficulties and state manifestations of disorder are addressed (Murray & Harvey, in press). Murray and Harvey also draw attention to the interdependency between circadian and sleep/wake processes, and that treatments targeting sleep may also positively affect the circadian system, and vice versa (see also Frank, Gonzalez, & Fagiolini, 2006). It is therefore important that both types of evidence for the association between disturbed biological rhythms and BD are reviewed.
It is pertinent at this point to also make a brief note regarding the terminology used to describe circadian-level disturbances associated with BD. Our current level of knowledge regarding the mechanistic processes involved in circadian system pathogenesis in BD does not permit the use of specific terminology. Disturbances have been described in all fundamental parameters of circadian rhythm analysis – phase, amplitude, and period (see Figure 2). For example, phase advance (Wehr, Sack, & Rosenthal, 1987), phase delay (Lewy, Sack, Singer, White, & Hoban, 1989), and reduced amplitude (Souetre et al., 1989) are common circadian rhythm variations found in BD. It is not clear what the mechanistic implications of these differences are at a deeper level of analysis. The non-specific term ‘circadian instability’ is therefore used often throughout the current thesis to refer to the circadian system’s role in BD pathogenesis. The concept of instability is used commonly in the extant literature to describe circadian disturbances associated with manic and depressive onset (e.g., Frank et al., 2000). While there are obvious limitations associated with using generic terms, the benefit is that it allows important research findings to be sufficiently described without getting mired in hypothetical debates regarding processes at deeper levels of analysis. The search for circadian-based mechanisms at the molecular level is a recent and potentially fruitful line of enquiry (see Benca et al., 2009). However, at this point in time, we must satisfy ourselves with description at the broader level and use ‘circadian instability’ with recognition of the attendant shortcomings of such an approach.

2.4.1 Changes in biological rhythms are associated with manic and depressive states in people with Bipolar Disorder

Sleep/wake disturbances are core features of the clinical presentation in patients with BD. During the manic phase the most commonly reported sleep disturbance is a perceived reduction in the subjective need for sleep (Harvey, 2008). Indeed, decreased need for sleep is one of the key diagnostic criteria for both manic and hypomanic episodes in DSM-IV (APA, 2000). Serretti and Olgiati (2005) reported that 98.7% of
BD-I participants and 96.7% of BD-II participants described a reduced need for sleep during mania. In a large general population survey of BD-I, Kessler, Rubinow, Holmes, Abelson, and Zhao (1997) showed that the only manic symptom profile that could be validly assessed with the structured Composite International Diagnostic Interview (CIDI; Robins et al., 1988) was characterised by euphoria, grandiosity, and “the ability to maintain energy without sleep” (p. 1079). This diagnostic profile, characteristic of approximately half of all people with clinically validated BD-I in the survey, provides further support for reduced sleep need during mania. In a smaller study, Monk, Buysse, Welsh, Kennedy, and Rose (2001) showed evidence of subclinical hypomanic symptoms in a group of naturally short sleepers. Shortened latency to REM sleep onset (Hudson, Lipinski, Frankenburg, Grochocinski, & Kupfer, 1988; Hudson et al., 1992), increased density of REM episodes during the sleep period (Hudson et al., 1988; Hudson et al., 1992), later sleep onset phase (Linkowski & Mendlewicz, 1993), and generally lower quality sleep (Hudson et al., 1988) have also been demonstrated amongst manic patients.

Sleep disturbance during the depressive phase of BD has also been reported. Hypersomnia appears to be the most commonly observed manifestation of sleep disturbance in this phase of BD (Mitchell et al., 2008). A large investigation of clinical patients presenting with a MDE revealed that hypersomnia during the index episode was one of the core characteristics of those who later developed BD-II (Hantouche et al., 1998). A more recent investigation (Forty et al., 2008) showed that hypersomnia during depressive episodes was reported significantly more often in retrospective clinical interview by patients with BD-I than patients with MDD. Insomnia and early morning awakening have also been reliably reported in BD depression (see Harvey, 2008). Riemann, Voderholzer, and Berger (2002) reported that many of the disturbed sleep features seen in the depressive phase of BD are similar to those observed in unipolar depression. A small number of sleep-related features however, may be useful in differentiating the two forms of depression. Specifically, significant reductions in sleep continuity and NREM sleep, as well as a significant increase in total REM density were observed in a sample of depressed BD patients compared to an age-, gender-, and
symptom severity-matched sample of MDD patients. Early morning awakening was also observed to be more pervasive in the BD group than the MDD group in this study.

Circadian rhythm instability has also been demonstrated in episodes of mania and depression (Jones, 2001). Salvatore et al. (2008) for example, reported reduced amplitude in the 24-hour activity rhythm of 36 BD-I patients in a manic or mixed state compared to an age- and gender-matched healthy control group. A phase advance in the activity rhythm of approximately 2 hours was also found in the patient group compared to the controls. Linkowski et al. (1994) reported earlier timing of the cortisol nadir and elevated nocturnal cortisol levels amongst their sample of eight male unmedicated manic patients, compared to a matched sample of healthy controls. Similarly, Cervantes, Gelber, Kin, Nair, and Schwartz (2001) demonstrated elevated 24-hour plasma cortisol profiles in a sample of 18 patients with BD-II. Cortisol levels were elevated compared to healthy controls for both the hypomanic and depressed BD subgroups. The timing of cortisol secretion is coordinated by the SCN (Buijs, van Eden, Goncharuk, & Kalsbeek, 2003) and elevated levels are associated with detrimental effects on psychological well-being (e.g., Walker, Mittal, & Tessner, 2008). The level of melatonin, a hormone involved in the timing of sleep (Brzezinski, 1997) and also coordinated by the SCN (Buijs et al., 2003), was reported to be lower amongst nine patients with BD compared to an unmatched sample of healthy controls (Kennedy, Kutcher, Ralevski, & Brown, 1996). The differences between patients and controls persisted across both manic and depressed phases of the illness. Souetre et al. (1988) demonstrated instability in the circadian rhythms of core body temperature and plasma thyrotropin in eight patients in the depressive phase of BD. Specifically, nocturnal temperature was increased and the usual nocturnal pattern of thyrotropin was blunted compared to a group of healthy control subjects. Moreover, these group differences disappeared upon clinical recovery in the BD group, indicating that these features of circadian disruption were specific to the depressive phase of BD.

Diurnal variation of mood symptoms in depression, including the BD variant, provides further evidence of circadian involvement in BD states (Wirz-Justice, 2008). In some depressed populations, mood during the depressive phase is worse in the morning
and improves towards the end of the day (e.g., Tolle & Goetze, 1987). Normal diurnal mood in healthy populations shows the opposite pattern, with mood deterioration occurring closer to bed time (Clark, Watson, & Leeka, 1989). In patients with BD specifically, Feldman-Naim, Turner, and Leibenluft (1997) reported greater rates of mood switching from depression to hypo/mania from morning to evening, and hypo/mania to depression from evening to morning over a 3-month period in a rapid-cycling population. These findings would appear to be consistent with the evening mood improvements shown in other depressed populations. A recent investigation showed that the evening improvement pattern of mood variation may be more common in BD depression than unipolar depression (Forty et al., 2008). The mood system, particularly those mechanisms that encourage positive engagement with the environment (see Watson, Wiese, Vaidya, & Tellegen, 1999), is thought to be partially driven by the SCN (Murray, Nicholas et al., 2009). Moreover, dysregulation of these positive mood components in depression (Clark, Watson, & Mineka, 1994; Murray, 2007) provide a theoretical basis for understanding circadian involvement in BD depression via the mood system.

Ghaemi (2007) introduced another dimension to the discussion surrounding the role of circadian pathophysiology in BD, proposing that distortion of time is central to the subjective experience of manic and depressive states. Mania involves a subjective feeling of time ‘speeding up’, while the experience of time in depression is often described by patients as a feeling of ‘slowing down’. Jamison (1996) describes feeling as though her “mind had slowed down” (p. 110) during a particularly disabling depressive episode, in contrast to the awareness that “life and mind were going at an ever faster and faster clip” (p. 68) during manic episodes. As well as these anecdotal reports, quantitative support for subjective distortions of time during manic-depressive episodes was been provided. Bschor et al. (2004) showed that a group of manic patients rated their subjective experience of the flow of time throughout an experimental procedure as significantly more ‘sped up’ than a group of healthy control participants. Conversely, a group of depressed patients rated their subjective experience of the flow of time significantly more ‘slowed down’ than the controls. The findings imply that
distorted experience of time may be a component of BD phenomenology. Distortion of
time experience, particularly discrimination of time duration, has been demonstrated in a
patient with damage to the SCN (Cohen, Barnes, Jenkins, & Albers, 1997). These data
add incrementally to the evidence for a circadian pathophysiology to BD.

The evidence presented here is broadly supportive of biological rhythm disturbances
in the diathesis to BD. It must be noted however, that much of the evidence relies on
self-reports of sleep, some of which are collected retrospectively. Self-reports are not
ideal indicators of sleep disturbance, particularly in populations where sleep problems
are often encountered. It is also noticeable that the findings supportive of an association
between biological rhythm disturbances and manic or depressive states are invariably
based on small clinical samples, perhaps limiting their generalisability. Small sample
size appears to be a common feature of clinical studies in BD, although large-scale
collaborative studies such as the STEP-BD program of research (Sachs et al., 2003) are
attempting to address this issue. The correlational design of many of the studies
reviewed here must also be considered in weighing up the quality of the evidence
presented. Such designs are unavoidable however, given the ethical considerations
associated with using clinical populations for experimental research.

2.4.2 Changes in biological rhythms can predict manic and depressive
relapse in Bipolar Disorder

Changes in sleep are key predictors of mood change into mania or depression in
people with BD. According to a systematic review of 73 studies, over 80% of patients
with BD are able to recognise at least one early symptom of manic and depressive onset
(Jackson et al., 2003). The review identified sleep disturbance as the most commonly
observed prodromal feature of manic onset. For depressive onset, it was the sixth most
common feature. Specific sleep/wake disturbances identified as early indicators of
manic onset by BD participants were lack of interest in sleeping and a perceived
reduction in the need for sleep (Lam & Wong, 2005). For depressive onset, interrupted
sleep was the most commonly reported sleep disturbance. Sleep disturbance is also considered a key component of the prodrome to first episode mania (Conus et al., 2008). Indeed, sleep changes are notoriously referred to as the “final common pathway in the genesis of mania” (Wehr et al., 1987; p. 201).

Barbini, Bertelli, Colombo, and Smeraldi (1996) demonstrated that reduced sleep was associated with increased manic symptoms the following day in 34 BD inpatients being treated for mania. Specifically, patients that slept less were more likely to display higher levels of uncooperative behaviour and irritability the next day. These findings suggest that sleep loss is not only a potential trigger for manic onset, but also a maintenance mechanism through which the intensity of manic symptoms are moderated.

Perlman, Johnson, and Mellman (2006) also investigated the prospective impact of sleep duration on depressive and manic onset. In a sample of BD-I patients who were currently experiencing manic (30%), depressed (43%), or mixed (20%) episodes, sleep duration was assessed once at baseline and again at 1-month and 6-months follow-up. They found that shorter sleep duration at baseline was associated with more severe depression 6 months later. No significant associations between sleep duration and mania at 1-month or 6-month follow-up were evident. The authors acknowledged that this latter finding may have been due to sample bias, with manic severity associated with greater drop-out rates amongst the participants. It is also possible that 1-month follow-up time is too far removed from the index sleep measurement, as manic reactions to sleep loss generally occur within days rather than weeks after a night of no sleep (Wehr et al., 1987).

There is limited evidence of circadian rhythm changes as precipitants of manic or depressive onset. An investigation of students with a lifetime history of Cyclothymia or BD-II found that reduced lifestyle regularity was a significant predictor of shorter time to mood episode onset (Shen, Alloy, Abramson, & Sylvia, 2008). High relapse rates in people with BD during the month of Ramadan, an Islamic religious obligation that disrupts the timing of meals and other social behaviours, have also been demonstrated (Kadri, Mouchtaq, Hakkou, & Moussaoui, 2000). Malkoff-Schwartz et al. (1998) retrospectively investigated social rhythm phenomena amongst a sample of BD
inpatients currently experiencing manic or depressive symptoms. Social rhythm disrupting events were reported to predict manic but not depressive episodes. A later study confirmed that social rhythm disrupting events were specific to the onset of mania (Malkoff-Schwartz et al., 2000). While such findings are important, more evidence is necessary, particularly from investigations with a prospective design, to delineate causal mechanisms in the relationship between lifestyle regularity and manic or depressive relapse.

The evidence presented here, given the prospective nature of many of the research designs, provides a strong basis from which to make causal inferences regarding the relationship between biological rhythm disturbance and vulnerability to BD. Nevertheless, the use of retrospective self-report data to support prospective associations limits the strength of the evidence base in many cases. Clinical observation of behavior and mood changes (as in the Barbini et al., 1996 study, for example) provides a more objective alternative to patient self-reports, although, purely from a scientific perspective, blind observations would be preferable.

### 2.4.3 Effective treatments for Bipolar Disorder involve manipulation of biological rhythms

Sleep deprivation is a powerful antidepressant treatment for BD. Barbini et al. (1998) for example, showed that mood was significantly improved for participants experiencing a MDE following total sleep deprivation. During a 7-day protocol, three cycles of no sleep on alternate days were administered to the patients. Each day of no sleep was followed by a recovery day. Significant improvements in clinician-rated mood were observed following the first night of sleep deprivation, and were maintained at the endpoint of the protocol. Mood improvements were particularly strong for those patients with a lifetime history of BD-I and BD-II. It is commonly observed that the antidepressant effect of sleep deprivation is typically lost upon resumption of normal sleep routines (Benedetti, Barbini, Colombo, & Smeraldi, 2007). There is evidence
however, that the effect can be maintained for longer periods using combination therapies, including those with a circadian mechanism of action, and timely administration of pharmacological agents (see Benedetti, Barbini et al.). Although the precise mechanism of therapeutic action in sleep manipulation is not known (Grassi Zucconi, Cipriani, Balgkouranidou, & Scattoni, 2006), its robust effect on depressed mood in BD populations implicates sleep/wake and circadian involvement in the disorder. It is noteworthy that deliberate sleep deprivation can induce mania in a significant minority of people with BD (Wehr, 1992), thus demonstrating the central importance of sleep/wake manipulations in both phases of BD.

Phototherapy is another effective anti-depressant strategy that involves deliberate manipulation of the sleep/wake cycle by introducing bright light at strategic phases of the sleep period (Terman, 2007). The mechanism of action in effective phototherapy appears to be associated with the timing of melatonin onset and offset, thus implicating circadian system instability in BD. The demonstrated capacity for bright light to induce symptoms of mania in vulnerable populations (Benedetti, Barbini et al., 2007) further reinforces the likelihood of circadian involvement in BD.

Effective pharmacotherapies for mania and depression provide further support for involvement of the circadian system in BD pathogenesis (see McClung, 2007, for review). Lithium is probably the most effective pharmacological agent used for acute treatment and prophylaxis of BD (Smith, Cornelius, Warnock, Bell, & Young, 2007; Smith, Cornelius, Warnock, Tacchi, & Taylor, 2007). Besides its obvious mood stabilising properties, lithium has been shown to stabilise the endogenous circadian rhythm (Healy & Waterhouse, 1995; Klemfuss, 1992). The efficacy of lithium in the treatment of BD may therefore be partly attributable to its capacity to normalise SCN output. Indeed, GSK3β, an enzyme involved in regulation of SCN processes (Iitaka, Miyazaki, Akaike, & Ishida, 2005), is also a molecular target of lithium (Klein & Melton, 1996). Some second generation pharmacotherapies for BD (e.g., valproate) have also been shown to have parallel circadian rhythm stabilising effects to lithium (Dokucu, Yu, & Taghert, 2005; Lemoine, Fondarai, & Fairev, 2000).
Finally, stabilisation of social rhythms is an effective treatment option for the management of BD (Frank et al., 2000). Social rhythm therapy (IPSRT; see Section 1.6) has proved efficacious in, firstly, stabilising the social rhythms in this population (Frank et al., 1997) and, secondly, preventing relapse (Frank et al., 2005). Social rhythmicity is an important entrainment parameter for the endogenous clock in humans (Ehlers et al., 1988), and may also be partly driven by the SCN (Grandin, Alloy, & Abramson, 2006). The effectiveness of the therapy is attributed to redressing circadian instability via better adherence to social zeitgebers.

Evidence supporting a disturbed biological rhythm diathesis in BD based on treatment outcome studies appears to be quite strong. Treatments involving a broadly defined circadian mechanism of action appear to be successful in treating and managing the disorder. The lack of clarity in determining the precise mechanism of action in circadian-based treatments for BD detracts from the strength of the evidence base somewhat, although better understanding of pharmacological action on both BD symptomatology and the outputs of the SCN are encouraging in this regard.

2.4.4 Biological rhythm abnormalities are associated with trait vulnerability to Bipolar Disorder

Two broad lines of evidence support abnormalities in the sleep and circadian rhythms associated with trait vulnerability to BD. Firstly, sleep and circadian abnormalities often persist beyond clinical recovery in patients with BD: the euthymic phase of the illness is characterised by fundamental differences in sleep and circadian processes compared to healthy control groups. Secondly, people at higher genetic risk of BD (e.g., children and healthy relatives of BD probands) sometimes show similar sleep and circadian abnormalities to those diagnosed with the disorder. The review of evidence is presented separately for sleep (2.4.4.1) and circadian (2.4.4.2) abnormalities, with the populations of interest considered together under each section.
2.4.4.1 Sleep

Sleep/wake disturbances associated with the euthymic phase in BD have been identified in numerous investigations. Harvey, Schmidt, Scarna, Semler, and Goodwin (2005) for example, assessed the sleep characteristics of 20 euthymic patients with BD using objective (actigraphy) and subjective (retrospective self-report) estimates. Compared to a control group of good sleepers, the BD group exhibited a significantly greater amount of total sleep time according to actigraphic estimates. Differences were also found in BD patients’ self-reported sleep onset latency (greater), subjective judgement of sleep quality (lower), difficulties in falling/staying asleep (greater), and most indices derived from the Pittsburgh Sleep Quality Index (i.e., subjective sleep quality, sleep onset latency, habitual sleep efficiency, sleep disturbances, and daytime dysfunction; sleep problems greater in the BD group across all indices). Indeed, self-reported sleep quality amongst the BD group had more in common with a comparison group of patients seeking treatment for primary insomnia than the healthy control group, indicative of a significant level of subjective sleep disturbance amongst this group.

Millar, Espie, and Scott (2004) also gathered self-reports and actigraphic estimates of sleep amongst 19 euthymic outpatients with BD-I and 19 age- and gender-matched healthy controls. Similar to the findings of Harvey et al. (2005), the BD group self-reported greater sleep problems than that indicated by actigraphy. In particular, differences between patients and controls in terms of sleep onset latency estimates were much greater for self-reported data than objective actigraphic data. The actigraphic estimates of mean sleep duration, sleep onset latency, sleep efficiency, and night waking time were not significantly different between the two groups. The BD outpatient group did, however, exhibit significantly greater variability in the amount of sleep each night and the amount of time spent awake at night, suggesting a more variable sleep/wake rhythm than the control group.

Jones et al. (2005) compared the sleep/wake features of 19 euthymic BD-I outpatients with 19 age- and gender-matched healthy control participants. Actigraphy was again used to objectively measure the sleep/wake rhythm across 7 days, while the
Social Rhythm Metric (SRM; Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990) was used by participants to self-report the regularity of their daily activities, including wake times and bed times, over the same period of time. Self-reported bed times and wake times were not significantly different between the outpatient and control groups in the Jones et al. study, according to scores on the SRM. However, significant differences in the median timing of activities other than bed time and wake time were apparent. The later timing of these mostly morning activities (e.g., first contact with another person, breakfast, going outside for the first time, starting school/work/housework/childcare) implicate phase delay in the behavioural routine of outpatients that normalises as the day progresses. It is possible that greater levels of social engagement amongst the control group may explain some of the variance in the timing of activities between the two groups, although they did not differ in employment status. According to the actigraphy measures, there were no differences between the two groups in terms of mean sleep onset latency, sleep duration, sleep efficiency, sleep fragmentation, or wake time after sleep onset.

Other sleep features associated with the euthymic phase of BD include higher density of eye movements during the first REM period and higher overall percentage of REM sleep (Sitaram, Nurnberger Jr, Gershon, & Gillin, 1982), and generally lower quality sleep (more frequent night-time arousals) compared to controls (Knowles, Cairns, & MacLean, 1986). Overall however, the main sleep abnormalities associated with the euthymic phase of BD are subjective estimates of sleep quality. The relative absence of abnormalities in objective estimates of sleep quality suggest that there may be a cognitive element to sleep disturbances in people with BD, similar to that observed in insomnia, that may respond to cognitive therapy (Harvey et al., 2005).

Sleep disturbances have also been shown to aggregate in relatives and offspring of people with BD (see Harvey, Mullin, & Hinshaw, 2006). Jones, Tai, Evershed, Knowles, and Bentall (2006) for example, reported that children of parents with BD had greater incidence of sleep disturbances and poorer overall sleep quality than children of parents with no history of mood disorders. More rapid sleep onset and a trend towards longer total sleep time were also observed in the BD group. Consistent with the findings
of the Jones et al. (2005) adult BD sample however, most of the differences in sleep quality apparent from self-report measures did not emerge strongly in the actigraphic assessment of sleep parameters. Stoleru, Nottelmann, Belmont, and Ron saville (1997) also assessed sleep problems in children of parents with BD. The relationship between a mother’s BD diagnosis and parent reports of greater sleep problems in their children was highly significant. The sleep problems were also more severe and persisted for a longer period of time compared to children of healthy control parents.

Meyer and Maier (2006) monitored duration and stability of sleep in 141 students deemed to be ‘at risk’ of mood disorder over a 4-week period. The group of participants at higher risk of BD (high scorers on the Hypomanic Personality Scale; Eckblad & Chapman, 1986) recorded a significantly higher level of variability in the amount of sleep per day than an age- and gender-matched ‘low risk’ control group. The group of participants at higher risk of MDD (high scorers on the Rigidity scale of the Munich Personality Test; Von Zerssen, Pfister, & Koeller, 1988) did not differ from the control group.

Overall, the findings strongly indicate poorer sleep quality amongst people at increased risk of BD, particularly when sleep was assessed by self-report. Poor sleep quality may be a stable feature of vulnerability to BD that persists regardless of symptomatic status.

### 2.4.4.2 Circadian rhythms

Circadian rhythm instability also appears to be a feature of vulnerability to BD. Jones et al. (2005) demonstrated that variability of activity rhythms, both within- and between-days, was significantly greater amongst their group of euthymic BD outpatients compared to the control group. A phase advance of the 24-hour pattern in activity was apparent in the manic/mixed BD-I sample of Salvatore et al. (2008) compared to the control sample. This phase advance persisted beyond symptomatic recovery in the BD patient group. Reduced stability and phase advance of the 24-hour pattern in activity appear therefore to be enduring features of vulnerability to BD.
Reduced lifestyle regularity, indicative of a potentially unstable circadian system (Grandin et al., 2006), has also been demonstrated in populations with increased risk for BD. Ashman et al. (1999) for example, studied the social rhythms of nine BD outpatients and compared them to nine age- and gender-matched control participants. The outpatient group had significantly lower regularity in their day-time activities than the control group across all mood states, including euthymia. There was an additional phase delay in the timing of morning activities amongst the outpatient group (see also Jones et al., 2005). Similarly, Shen et al. (2008) showed that students with a lifetime history of CD or BD-II reported significantly fewer regular activities than students with no history of mood disorder. In the Meyer and Maier (2006) study of students at risk of mood disorder, the group with higher vulnerability to BD exhibited lower regularity of daily activities over the 4-week assessment period than both the healthy controls and the group with higher vulnerability to MDD.

Further evidence of circadian instability as a potential diathesis for BD comes from studies showing reduced melatonin output and later timing of peak melatonin amongst euthymic BD patients (Nurnberger et al., 2000), and reduced amplitude of the core body temperature rhythm in recovered BD inpatients (Souetre et al., 1989). Ellenbogen, Hodgins, Walker, Couture, and Adam (2006) demonstrated significantly higher basal cortisol release, a hormonal process that is directly under circadian control (Hastings, O'Neill, & Maywood, 2007), in a cohort of adolescent offspring of BD parents compared to a low-risk (no family history of mental disorder) comparison group. Murray, Allen, Trinder, and Burgess (2002) showed that female students scoring high on the Neuroticism dimension of the NEO-PI-R (Costa & McCrae, 1992) exhibited significantly reduced amplitude in the unmasked core body temperature rhythm compared to female students scoring low on the same dimension. Neuroticism is a non-specific temperamental risk factor for BD (see Akiskal, Kilzieh et al., 2006; Clark, Watson, & Reynolds, 1995; Murray et al., 2007) so an association between reduced core body temperature stability and high scorers on this trait suggests circadian involvement in vulnerability to BD.
The evidence base supporting biological rhythm disturbances in trait vulnerability to BD is not strong. First, the definition of vulnerability to BD is ill-defined and differs between studies. Second, the measures used to operationalise circadian disturbance are often imprecise (e.g., lifestyle regularity). Third, the recurring problem of small clinical samples in correlational designs is evident. Nevertheless, the findings reported, taken in the appropriate context, serve to add incrementally to the overall evidence base supporting biological rhythm disturbance in the diathesis to BD.

In sum, a broad range of evidence has been presented that biological rhythm disturbances are found across all phases of BD. These disturbances appear also to characterise the circadian rhythms and sleep/wake behaviour of those at risk for BD. It is worth noting that although there is evidence demonstrating the prominence of circadian and sleep/wake disturbances in BD, the specific mechanisms associated with these disturbances are currently unknown. Disruption at all three levels of clock function (i.e., synchronising input mechanisms, regulatory output mechanisms, and molecular feedback loops in the clock itself) are all potentially causal (see Nievergelt et al., 2006).

Although a wide range of circadian and sleep variables have been implicated in BD pathogenesis, clarity on mechanistic hypotheses of circadian and sleep/wake disturbance in BD is not a feature of the current literature.

2.5 Other neurobiological theories of Bipolar Disorder pathogenesis

There are several neurobiological theories of BD pathogenesis that are complementary to the biological rhythm pathways already presented. Three prominent pathways with particular relevance to the current project are described below. Genetic investigations, including gene*environment interactions, are presented first. Next, dysregulation of neurotransmitter systems, particularly theories that describe disturbances of the dopaminergic system, are discussed. Finally, dysregulation of approach and reward systems as pathogenic processes in BD are reviewed. Interactions
between these pathways and the biological rhythm pathway are also described, in order to demonstrate that they do not operate independently of each other.

### 2.5.1 Genetic theories of Bipolar Disorder pathogenesis

An increasing spectrum of lifetime risk for BD based on genetic relatedness provides decisive evidence of robust genetic vulnerability to the disorder. A review of genetic concordance data by Craddock and Jones (1999) showed that twin siblings of BD probands have the highest risk of disorder, followed by first-degree relatives. Unrelated people have the lowest level of lifetime risk. Kraepelin (1921) observed that “about 80 per cent” of cases he observed were subject to “hereditary taint” (p. 165). A review of twin studies by Goodwin and Jamison (2007) assessing monozygotic (MZ) and dizygotic (DZ) twin pairs revealed mean heritability estimates of approximately .70. The genetic contribution to phenotypic expression of the disorder is therefore strong and comparable to schizophrenia (Owen, O'Donovan, & Gottesman, 2002) and greater than MDD (Sullivan, Neale, & Kendler, 2000).

Several potential linkage markers of BD-related phenomena have been identified. Middleton et al. (2004) demonstrated genomewide significant linkage for BD susceptibility at multiple loci, but particularly chromosomes 6q and 11p. McInnis et al. (2003) provided evidence for 16p as the key loci, with 20p, 11p, 6q, and 10p also close to demonstrating genomewide significance. Segurado et al. (2003), using ‘very narrow’ (i.e., BD-I only) and ‘narrow’ (i.e., BD-I + BD-II) definitions of bipolarity could not demonstrate genomewide significance for any single chromosome, although several loci approached significance, including 9p, 10q, and 14q. Finally, a thorough meta-analysis of 11 well-defined genomewide linkage scans, including that of McInnes et al., identified just two key candidates – 6q and 8q – showing genomewide significance in predicting BD-I and BD-II, respectively (McQueen et al., 2005). The genes associated with these linkages have not been identified.

Molecular science has revealed evidence for polymorphisms in genes encoding neurotransmitter systems (serotonin, dopamine) in BD patients. Brain-derived
neurotrophic factor (BDNF), disrupted in schizophrenia 1 (DISC1), D-amino acid oxidase activator (DAOA), peroxisome proliferators-activated receptor delta (PPARD), neuregulin 1 (NRG1), tryptophan hydroxylase-2 (TPH2) and catecol-o-methyl transferase (COMT) genes have also been indentified (see Barnett & Smoller, 2009, for review). However, none of these genes have been established as specific BD susceptibility candidates. Further advances in molecular technology have facilitated powerful genome-wide association studies, with similarly inconclusive findings. It would appear therefore, that there is no ‘gene for’ BD.

The consensual view is that the genetic etiology of BD involves interactions between multiple genes (Kendler, 2005). The quantitative trait loci model assumes that several genes of small to moderate effect interact to increase the likelihood of disorder. Schulze et al. (2004), for example, demonstrated that the combined contribution between chromosomal loci on 6q and 6p to BD susceptibility was significantly greater than either one alone. The genes already described are all likely to be involved in vulnerability to disorder, however they do not act independently of one another. The low levels of variance in BD phenotypes explained by single gene mutations reinforces the polygenic nature of risk for BD (Barnett & Smoller, 2009). For the moment, although there is broad acceptance that multiple genes interact to increase BD susceptibility, concrete evidence of specific interactions is lacking.

Incomplete phenotypic concordance between MZ twin pairs suggest that environmental effects account for a substantial amount of relative risk for BD (Goodwin & Jamison, 2007). Specific environmental effects that have demonstrated significance in the onset of manic and depressive episodes include alcohol and illicit substance use (Baethge et al., 2008), life stress and familial environment (Miklowitz & Johnson, 2009), and childhood trauma (Etain, Henry, Bellivier, Mathieu, & Leboyer, 2008; Leverich & Post, 2006). Circadian rhythm-disrupting life events are particularly prominent amongst theories of gene*environment interactions in manic and depressive onset (Grandin et al., 2006). Vulnerability to BD is therefore best conceptualised as the outcome of a complex interplay between multiple genes, including those involved in circadian regulation, and many environmental influences. Furthermore, the pattern of
gene*environment interactions is highly idiosyncratic within individuals (Barnett & Smoller, 2009).

Genes involved in the regulation of circadian processes also have demonstrated relevance to BD (Barnett & Smoller, 2009; McClung, 2007). Associations between the CLOCK gene and BD are the most commonly reported findings (Kripke, Nievergelt, Joo, Shekhtman, & Kelsoe, 2009; Shi et al., 2008). A particular CLOCK gene polymorphism has been associated with some well-known clinical features of BD, including sleep and activity alterations (Benedetti, Dallaspezia et al., 2007; Serretti et al., 2003) and illness recurrence (Benedetti et al., 2003). Animal models of BD also demonstrate associations with dysregulation of the internal clock. Roybal et al. (2007) showed that mice bred with CLOCK gene mutations displayed behaviour “strikingly similar” (p. 6406) to that of human mania, viz., hyperactivity, decreased sleep, lowered depression-like behaviour and anxiety, and increases in the reward value of cocaine, sucrose, and medial forebrain bundle stimulation. Moreover, chronic administration of lithium was found to reverse many of these behavioural effects. Support for associations between BD and other circadian gene polymorphisms have also been reported. PER3 (Artioli et al., 2007; Nievergelt et al., 2006), ARNTL (Mansour, Monk, & Nimgaonkar, 2005; Nievergelt et al., 2006) and TIMELESS (Mansour et al., 2005) have all been investigated for relevance to BD vulnerability. The molecular target of lithium, GSK-3β, also mediates the efficacy of this pharmacological agent via a circadian pathway (Yin, Wang, Klein, & Lazar, 2006). The findings linking circadian gene polymorphisms and BD are inconsistent and poorly replicated (Kishi et al., 2009; Sklar et al., 2008; Yang, Van Dongen, Wang, Berrettini, & Buatan, 2009), reinforcing the fact that genetic susceptibility to BD is subject to a complex developmental pathway. Nevertheless, there are sufficient grounds to suspect that circadian molecular processes have a role to play in susceptibility to BD (McClung, 2007).
2.5.2 Neurotransmitter dysregulation in Bipolar Disorder pathogenesis

Dysregulation of the brain monoamines as a pathogenic process in BD are prominent in the literature. Dopamine and serotonin are the two monoamine neurotransmitters that have received the most research attention (see Harvey, Murray, Chandler, & Soehner, in press). The primary functions of dopamine (e.g., motivation, reward processing, psychomotor activity, impulse control; Cools, 2008) and serotonin (e.g., attention, cognition, emotional processing; Cools, Roberts, & Robbins, 2008) have direct relevance to the clinical features of BD. The former has particular significance for manic manifestations, while the latter has particular significance for depressive manifestations. Interactions between the two neurotransmitter systems are probably relevant to psychopathology in general, and depression specifically (Esposito, Di Matteo, & Di Giovanni, 2008). The pathway from neurotransmitter dysregulation to BD is proposed to be mediated by a diathesis-stress mechanism, whereby the underlying vulnerability (diathesis) is activated by significant life events (stress; e.g., Seo, Patrick, & Kennealy, 2008). It is noteworthy that both positive and negative life events can activate BD episodes via monoamine pathways (see Urosevic, Abramson, Harmon-Jones, & Alloy, 2008).

Increased dopaminergic drive is proposed to underlie mania, while reduced dopamine is proposed to underlie depression. Berk et al. (2007) describe a model of dopaminergic dysregulation in BD that is characterised by an “endogenous homeostatic adaptive mechanism” (p. 42), whereby down-regulation of dopamine (depression) is enacted in response to sustained over-activation of the neurotransmitter in mania. The course of BD is supportive of such a model, as are data from animal studies showing behavioural hyperactivity in response to the administration of psychostimulants followed by depressive symptoms during withdrawal (see Berk et al., 2007). Additional evidence for the important role dopamine plays in BD is found in the clinical correlates of the manic state (Harvey et al., in press): addiction, pathological gambling, and hypersexuality are common comorbid conditions with BD that are likely to share dopaminergic pathways (Goodman, 2008). These and other corroborating evidence (see
Berk et al., 2007) support the prominence of dopaminergic dysregulation in BD pathogenesis.

A range of evidence links dysregulation of the serotonergic neurotransmitter system to BD (e.g., Drevets et al., 2007). Cannon et al. (2007) for example, demonstrated abnormalities in the binding potential of serotonin transporter function amongst depressed outpatients, compared to an age- and gender-matched control sample. In particular, the depressed outpatients with BD had significantly lower serotonin binding potential in the raphe nuclei than both the depressed outpatients with MDD and the healthy controls. Similarly, polymorphisms in genes encoding monoamine transmitter systems, including the serotonin transporter, have also been implicated in BD susceptibility (Lotrich & Pollock, 2004; Serretti, Calati, Mandelli, & De Ronchi, 2006). Many of the findings linking serotonin functioning to BD are weak-to-moderate in strength and are not specific to BD. Nevertheless, sufficient evidence exists to support disturbed serotonergic processes as a recognised pathway to depression, including that associated with BD (Carver, Johnson, & Joormann, 2008).

Neurotransmitter disturbances are also associated with circadian function. Dysregulation of dopaminergic pathways have been implicated in circadian irregularities (Aston-Jones, Chen, Zhu, & Oshinsky, 2001). Moreover, dopamine metabolism in circadian clock mechanisms has potential significance for mood regulation based on animal models of mood disorder (Hampp et al., 2008). Dopamine also plays an important role in the regulation of circadian processes, most likely via reward activation pathways (Harvey et al., in press). Murray, Nicholas et al. (2009) for example, showed that positive moods and reward motivation are subject to circadian influence, and suggest that the dopamine*circadian interaction is etiologically significant in BD. Dopamine is also suspected to be involved in the regulation of sleep/wake processes (Lima et al., 2008).

Bi-directional pathways between the SCN and several brain structures with serotonergic afferents may also be of etiological significance in BD (Mistlberger et al., 2000; Nestler et al., 2002). Of particular note is the finding that disruption to serotonergic systems in mammals (e.g., lesion to the raphe nuclei or chemical disruption
of 5-HT neurons) causes dysregulation of circadian rhythms, demonstrated by amplitude attenuation, phase advance and period lengthening (Morin, 1999; Prosser, 2000). Yuan et al. (2005), investigating circadian entrainment by light in *drosophila*, suggest that normal functioning of the circadian and serotonergic systems may be dependent on reciprocal regulation between the two systems. Sleep/wake processes also involve regulation of serotonin (Adrien, 2002; Fuller et al., 2006), further reinforcing the interaction between serotonergic, sleep/wake, and circadian systems in susceptibility to BD (see also Harvey et al., in press).

Finally, the HPA axis, dysregulation of which may have significance for BD pathogenesis (Watson & Mackin, 2006), also has a role in the coordination of circadian events (e.g., sleep/wake and appetitive drive; Buckley & Schatzberg, 2005). A reduction in the nocturnal nadir of cortisol is a commonly reported biological abnormality associated with BD (Cervantes et al., 2001) that may have adverse effects on sleep quality (Buckley & Schatzberg, 2005). The HPA axis pathway to both BD and circadian processes is a potentially fruitful line of investigation that provides further evidence of the link between biological rhythm disruption and BD.

### 2.5.3 Dysregulation of approach and reward systems in Bipolar Disorder pathogenesis

A neurobehavioural model of vulnerability to BD has also been proposed. Depue and Iacono (1989) postulate a motor/affective system that moderates appetitive motivation towards reward as pathogenic in BD. Variously termed the Behavioural Approach System (BAS; Gray, 1987), the Behavioural Facilitation System (Depue & Iacono), or the Behavioural Activation System (Fowles, 1988), the normally functioning BAS is hypothesised to regulate an organism’s approach behaviour towards reward and safety cues in the environment. BAS activation is strongly associated with dopaminergic activity in the ventral tegmental area of the midbrain (Depue & Iacono). It

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7 The three terms are effectively synonymous. The abbreviation ‘BAS’ will be used here.
is thus closely related to theories of pathogenic dysregulation of dopaminergic circuits in BD as described in Section 2.5.2.

Dysregulation of BAS, as is proposed in models of BD, manifests internally as hyper- and hypo-sensitivity to reward. According to this theory, locomotor initiation and incentive/reward motivation are the two major components of BAS. Abnormally elevated BAS activation initiates an intense locomotor response towards environmental reward, while abnormally subdued BAS activation is a barrier to active environmental engagement. BAS activity can therefore be quantified using locomotor activity monitoring techniques such as actigraphy. The mean level of locomotor activity during the daytime can be used to reflect BAS activation. A variety of other factors (including cognitive, affective, and social dynamics; see Urosevic et al., 2008) mediate the complex relationship between BAS activation and BD.

Similarities observed in symptoms associated with mania and depression, and BAS activation support the relevance of this brain reward system to BD. Changes in locomotor activity play key roles in the behavioural manifestation of manic and depressive states in BD. Increased psychomotor activation is one of the core symptoms of a manic episode as described in DSM-IV (APA, 2000) and is consistent with abnormally elevated BAS activation. Higher activity levels may also be a risk factor for hypo/mania. Klein, Lavie, Meiraz, Sadeh, and Lenox (1992) for example, showed that manic patients who relapsed after lithium discontinuation displayed a significantly higher daytime activity level than a comparison group of non-relapsers, both before and after lithium discontinuation. In a study of college students ‘at risk’ of bipolar spectrum symptomatology, higher self-reported BAS activation significantly predicted concurrent symptoms of subsyndromal mania (Meyer, Johnson, & Carver, 1999).

In the depressive phase of BD, psychomotor retardation is commonly observed (Mitchell et al., 2008). The low activity, anhedonic behaviour associated with the depressive state is consistent with abnormally low BAS activation. Moreover, this reduction in psychomotor activity during depression appears to be relatively specific to those with the BD-variant of mood disorder (or those who later convert to BD) compared to those with the MDD-variant of mood disorder who show normal or
sometimes increased activity levels (Mitchell et al.). There is also preliminary evidence indicating that lower levels of activity are related to depressed mood in non-psychiatric adults (Mendlowicz, Jean-Louis, von Gizycki, Zizi, & Nunes, 1999). Meyer et al. (1999) reported that low BAS activation significantly predicted concurrent symptoms of subsyndromal depression in their sample of college students.

The positive mood and reward motivation components of BAS are proposed to be subject to circadian regulation. In a series of studies, Murray, Nicholas et al. (2009) demonstrated that positive affect (PA) followed a distinct diurnal pattern that was (a) synchronous with the circadian pattern in core body temperature, and (b) parallel to a physiological measure of reward related arousal. Murray, Nicholas et al. concluded that the mechanism underpinning the circadian pattern in PA was the same as that underpinning reward motivation. The findings advance a novel hypothesis that has important consequences for the current project; that the subjective component of BAS can be measured in self-reports of positive mood. The stability of the circadian system may therefore be observable in daily patterns of mood via increases (unstable) and decreases (stable) in the deviation of PA from usual levels. The proposed link between circadian modulation of BAS activation and the relevance of BAS activation to BD further reinforces the fact that the biological rhythm pathway to BD that is the central focus of the current project, cannot be considered in isolation from other recognised pathways.

2.6 Summary of Chapter 2

Chapter 2 introduced a key relationship that forms the foundation of the current project; that between circadian rhythms and sleep, and vulnerability to BD. It was noted that circadian and sleep/wake processes are difficult to parse empirically, especially in vulnerable populations where the necessary laboratory protocols are not feasible. The term ‘biological rhythms’ was raised as a nonspecific alternative, and is used throughout
the current project whenever data are not strong enough to apportion variance to one or the other of these processes.

A range of evidence was presented suggesting links between biological rhythm function and (i) manic and depressive symptoms in BD, (ii) the onset of manic and depressive episodes in BD, (iii) traits associated with BD, and (iv) treatments that are effective for BD. Several alternative neurobiological theories of vulnerability to BD were described in Chapter 2, with the intention of showing that biological rhythm explanations are complementary to such theories.
Chapter 3

The 24-hour Activity Rhythm and the Goals of the Current Project

The previous chapter presented a broad range of evidence demonstrating the prominent role that biological rhythm pathways play in within- and between-person vulnerability to BD. Chapter 3 narrows the focus of the discussion to operationalisation of biological rhythm parameters. In the present chapter, the 24-hour activity rhythm is forwarded as a useful parameter that provides biological rhythm information with direct relevance to BD (circadian, sleep/wake, and daytime activity output processes; 3.1). Actigraphy is then discussed as the optimal tool for measuring the 24-hour activity rhythm, particularly in the context of naturalistic, longitudinal study designs such as that employed here (3.2). The clinical focus of the overall project is reinforced with a discussion of the potential application of activity rhythm parameters in prodrome identification (3.3). This section also addresses the issue of predicting daily mood change using 24-hour activity rhythm parameters. Finally, the goals of the current project are presented (3.4).

3.1 The 24-hour activity rhythm

The 24-hour rhythm in locomotor activity (hereafter referred to as the ‘24-hour activity rhythm’) is a common focus of animal research into circadian rhythms (Reinetti, 2006). In humans, the 24-hour activity rhythm is increasingly commonly used as a measure of the sleep/wake cycle under naturalistic conditions (Morgenthaler et al., 2007). This rhythm and the associated technology are fundamental to the present project and will be considered in detail. It is important to note that the 24-hour activity rhythm
is not a measure of circadian output per se. The 24-hour activity rhythm does contain a circadian signal, and evidence in support of this assertion will be presented in due course. However, the parameter is also driven by non-circadian processes that cannot be parsed. The drivers of the 24-hour activity rhythm and the output variables that have been inferred from it are presented in Figure 4.

Figure 4. Schematic representation of the drivers and variables that have been inferred from the 24-hour activity rhythm.

Figure 4 shows that there are four known drivers that contribute to the 24-hour activity rhythm. The SCN, the sleep/wake cycle, social rhythms, and the BAS modulate the 24-hour pattern of activity. Clearly, these four drivers are not independent. Interactions between circadian and sleep/wake processes are well-known (see Section
It is known that social factors also interact with circadian and sleep/wake processes to determine rhythms of rest and activity, particularly in humans (see Dijk & Franken, 2005). It is also apparent that circadian signals can be identified in BAS activation via reward motivation pathways (see Section 2.5.3). As such, the separate contribution of each driver to the 24-hour activity rhythm is impossible to determine. The 24-hour activity rhythm can thus be understood as a gross parameter that reflects non-specific biological rhythm function.

Figure 4 also shows that there are three distinct variables that have been inferred from the 24-hour activity rhythm. Information regarding circadian instability, daytime activity, and sleep can be inferred from the rhythm. Circadian instability is reflective of a weak circadian signal and poor entrainment to zeitgebers. Previous research has demonstrated the relevance of circadian instability to BD vulnerability (see Chapter 2). Daytime activity level is reflective of raw activity output during the day. Such activity level data is relevant to the study of BD, as changes in this variable can be a clinically useful indication of manic or depressive status (see DSM-IV symptom criteria in Section 1.2.2). The sleep variable reflects various qualities of the sleep experience, including length of the sleep period and sleep disruption, many of which have demonstrated relevance to BD vulnerability (see Chapter 2). It is reiterated here that these variables are clearly not independent. They reflect different ways of carving up the 24-hour activity rhythm, one or more of which may prove useful as a biomarker of vulnerability to BD. All three described here have direct relevance to the aims of the current project (see Section 3.4 below).

The 24-hour activity rhythm is a uniquely non-invasive variable which can be feasibly measured under long-term naturalistic conditions. It can also be tested as a biomarker of vulnerability to BD. The extant literature features designs that have used the 24-hour activity rhythm as a measure of circadian function in BD populations (e.g., Jones et al., 2005; Salvatore et al., 2008). Such studies support the usefulness of the 24-hour activity rhythm in measuring within- and between-person vulnerability to BD.

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8 Biomarkers are naturally occurring biological characteristics that can be used to identify the causes of developmental pathology. Biomarker is a term commonly used to refer to neurobiological processes involved in psychiatric illness (e.g., Phillips & Vieta, 2007).
3.2 Measuring the 24-hour activity rhythm using actigraphy

The 24-hour activity rhythm in humans is most commonly measured using actigraphy. The actigraph is a small wrist-worn device that measures changes in the speed and direction of movement via an omnidirectional accelerometer. Movement data is stored using onboard memory until the next opportunity for data retrieval. Data can be continually recorded and stored for up to 12 months. From the retrieved output, various indices of rest and activity can be estimated, including those related to the three variables of interest in the present project—circadian instability, daytime activity, and sleep (Ancoli-Israel et al., 2003).

Empirical evidence indicates that a circadian signal can be identified in activity data derived from actigraphy. Refinetti (1999), for example, demonstrated close synchrony between locomotor activity rhythms and core body temperature in several mammalian species. The phase of each daily rhythm was reached at the same time across all species and the highest correlation between the rhythms was achieved at time lags close to zero. In humans, the phase of the activity rhythm has been shown to correlate significantly with the phase of the 24-hour rhythm in urinary melatonin metabolites (Youngstedt, Kripke, Elliott, & Klauber, 2001). The phase and 24-hour period of the activity rhythm was also correlated with circadian features of melatonin onset and offset, as well as the 24-hour core body temperature rhythm in a small sample of healthy men (Middleton, Arendt, & Stone, 1996, 1997). Similar findings associating the activity rhythm and biological markers of circadian function in humans are apparent in other studies (see Ancoli-Israel et al., 2003, for review), even if the magnitude of agreement between these measures varies widely across participants and studies (Carskadon, Acebo, Richardson, Tate, & Seifer, 1997). Actigraphy thus provides useable output reflecting a circadian signal in activity that correlates with SCN-driven processes in naturalistic settings.

Actigraphy also has empirical support as a valid and reliable indicator of the sleep/wake cycle in humans. In a review of actigraph studies, Ancoli-Israel et al. (2003)

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9 Note that there is evidence to suggest that activity levels can influence the temperature rhythm (see Gander, Connell, & Graeber, 1986), so these findings must be treated with some caution.
demonstrated sufficient validity of actigraphy in differentiating sleep from wake compared to polysomnography (PSG), the gold standard of sleep recording methodologies. The review also showed that estimates of sleep length correlated well between the two techniques. Although actigraphy is unable to inform evaluations of sleep architecture (REM/NREM sleep – which are the exclusive domain of PSG), it has the advantage of being able to non-intrusively measure other sleep features over long periods. PSG, a predominantly laboratory-based technique, uses expensive and non-portable equipment. It also employs procedures, such as the attachment of multiple electrodes to various parts of the body, which may be uncomfortable from some participants. Actigraphy has been used to measure features of the sleep/wake cycle across many populations where the PSG technique may be either impractical or intolerable, or both (e.g., Monk, Buysse, & Rose, 1999; Van Someren, 1997; Werth et al., 2002).

Prospective self-reports of the sleep/wake process is a commonly used sleep monitoring technique (e.g., Spielman, Yang, & Glovinsky, 2005). Poor agreement however, is often found between self-report estimates and objective actigraphic estimates (e.g., Lockley, Skene, & Arendt, 1999). Differences between subjective and objective estimates of sleep are particularly prominent amongst populations manifesting sleep difficulties, including those with BD. Millar et al. (2004), for example, showed that their BD group subjectively overestimated sleep duration by approximately 39 minutes per day when compared to objective actigraph recordings. Similarly, 20 BD outpatients self-reported a mean total sleep time that was approximately 78 minutes lower than mean actigraphic estimates (Harvey et al., 2005). Discrepancies were also apparent in studies comparing actigraphic estimates of sleep length and self-report estimates in two sleep-disordered populations. Kushida et al. (2001) reported a mean discrepancy of approximately 60 minutes between the two recording methods, while Edinger, Means, Stechuchak, and Olsen (2004) reported a much greater mean discrepancy of approximately 108 minutes. The issues surrounding subjective versus objective measures of sleep are complex (e.g., Ancoli-Israel et al., 2003). Both methodologies possess unique properties with regards to the measurement of sleep, and
the source of error variance between them is unknown. It is recommended therefore, that whenever possible, self-report measures of sleep are monitored alongside actigraphic estimates.

Actigraphy also provides valid and reliable estimates of activity levels in human subjects (Ancoli-Israel et al., 2003). Indeed, that is the central purpose of the technology and it stands alone as an objective monitor of locomotor activity levels. Actigraphy has obvious applications in the monitoring of activity levels amongst clinical populations where changes in activity are prominent features of the disorder, such as BD.

In sum, three variables of theoretical interest can be drawn from the 24-hour activity rhythm as measured by actigraphy. Importantly, these variables cannot be parsed in the data: the circadian driver is inextricably confounded with the sleep process, and both are inextricably confounded with overall levels of activity. Nonetheless, separate investigation of these three perspectives on the data is warranted in an exploratory investigation. In the present project, Circadian Rhythm Instability, Sleep, and Total Daytime Activity are the names given to variables capturing these perspectives on actigraph data. Operationalisation of these three variables is described in 5.1 below.

### 3.3 Prodrome identification in Bipolar Disorder

Identification of manic and depressive episode prodromes is a primary goal of many manualised therapies for BD (e.g., Lam et al., 1999). A prodrome is a limited set of behavioural features known to be characteristic of an impending episode. Prodromes are highly idiosyncratic patterns of behaviour that remain remarkably consistent across mood-congruent episodes for individuals with BD (Sierra, Livianos, Arques, Castello, & Rojo, 2007). The intra-individual consistency of a prodromal ‘signature’ affords the opportunity for patients and clinicians to collaboratively monitor a small set of behaviours for signs of change. Monitoring of these episode precipitating behaviours has potential significance for relapse prevention. Significant changes in key prodromal
features can be recognised early and phase-appropriate intensive interventions can be enacted.

There is reason to believe that information derived from the 24-hour activity rhythm, measured by actigraphy, might provide useful and feasible markers of prodrome in at least some patients. First, changes in biological rhythms are key features of the prodromal phase for many people with BD. The fact that sleep disturbance is often referred to as the final common pathway to manic onset has already been noted (see Section 2.4.2). The prevalence of sleep/wake changes as precipitants of manic and depressive onset has also been reviewed. Disruption of lifestyle regularity was discussed as evidence of circadian instability in the prodromal phase of BD episodes. There is ample evidence that biological rhythm disruption is predictive of changes in clinical state in some people with BD (see also the review by Benca et al., 2009). Many of these biological rhythm features can be derived from the 24-hour activity rhythm, and measured using actigraphy as previously described.

Changes in activity level have also been shown to predict changes in the clinical state of people with BD. The limited review by Lam et al. (1999) showed that increased activity was apparent in the prodromal phase to mania in between 56% and 100% of people with BD. A similar range of patients with BD reported ‘psychomotor symptoms’ in the prodromal phase to mania in the review by Jackson et al. (2003). The ‘psychomotor symptoms’ reported in the Jackson et al. review of manic symptoms were assumed to be of the activation type, as opposed to the retarded type. Retarded psychomotor symptoms are more characteristic of the prodromal phase to depression in BD. Loss of energy, low motivation, and lack of interest in normal activities are common features of this phase that may be reflected in lower activity levels. Lam et al. (1999) reported these symptoms in between 45% and 86% of people with BD. Jackson et al. reported ‘psychomotor symptoms’ in a median of 41% of patients with BD. Activity level changes would appear to be more common in the manic prodrome than the depressive prodrome. From a clinical perspective, the changes are certainly more obvious in the former versus the latter and thus easier to identify and monitor (e.g., Perry, Tarrier, Morris, McCarthy, & Limb, 1999). Nevertheless, it is apparent that
activity level changes, as derived from the 24-hour activity rhythm and measured using actigraphy, may be a clinically useful predictor of both manic and depressive onset.

Monitoring of the 24-hour activity rhythm using actigraphy presents a methodology within which biological rhythm pathways to trait and state vulnerability to BD can be investigated. The actigraphic technique is theoretically sound and offers an optimal solution to the likely disruptive effects associated with more intrusive technologies, such as PSG. A further strength of actigraphy is that it does not rely on self-report, which is confounded by lack of insight in some phases of BD (Dell'Osso et al., 2002; Yen, Chen, Ko, Yen, & Huang, 2007). The investigation of relationships between biological rhythm disruption and vulnerability to BD at both the trait and state level may realise potentially important advances in effective relapse prevention for the disorder. This overarching aim of the current project is discussed in further detail in the next section, along with the other goals of the project.

3.4 The goals of the current project

The overarching aim of the current project was to advance understanding of the distinction between state- and trait-based conceptualisations of BD. Monitoring of the 24-hour activity rhythm using actigraphy was used to investigate the feasibility of using biological rhythms as biomarkers of trait vulnerability to BD and potential predictors of deterioration in clinical state amongst people with the disorder. The applied goal of the current project was to investigate whether prodrome identification can be improved through non-intrusive monitoring of biological rhythm function. The project therefore had a primary goal of informing clinical practice. Three studies were conducted in pursuit of the aims of the project. Figure 5 provides a schematic representation of the overall, three-study design of the project.

10 A program of research by the Signal Processing and Control Group of the University of Southampton has a similar aim. The Personalized Ambient Monitoring (PAM) program aims to develop activity-based algorithms that allow patients with BD to monitor their condition (Amor & James, 2008).
Figure 5 shows that the key assumption underpinning the project was that circadian instability is an important neurobiological abnormality associated with vulnerability to BD. Evidence from both empirical and observational sources has been presented in support of this assumption. Vulnerability to BD was considered in two separate, but related contexts (‘Research Foci’ in Figure 5). Trait-like vulnerability to BD, in which risk for the disorder is believed to be subject to a stable underlying diathesis, was the first context. Vulnerability to BD states was the second context.

The three studies of the current project contributed to the ultimate goal of improving prodrome identification in unique ways. Study 1 had two aims. The first, more theoretical aim, was to investigate the nature of the traits thought to underpin vulnerability to BD. The second, applied aim, was to guide decision-making regarding an appropriate psychometric instrument to measure vulnerability to BD. Selection of an appropriate measure is a necessary first step in experimental designs involving the investigation of ‘risk’ samples (Correll et al., 2007). In Study 1 therefore, several existing measures of temperamental vulnerability to BD were completed by a large sample of respondents in order to determine the most useful measurement predictor of BD-related traits and temperaments.11

The aim of Study 2 was to investigate the biological rhythm correlates of trait vulnerability to BD. The most useful predictor of BD-related traits and temperaments from Study 1 was used to separate a well student sample into groups of low and high vulnerability to BD. This is an acceptable research design for assessing the viability of novel concepts, and has been used in previous investigations (e.g., Meyer & Maier, 2006). The two groups in Study 2 were monitored for 7 days on variables derived from the 24-hour activity rhythm. Study 2 also provided the opportunity to assess the practicality of the actigraphic technique for monitoring these variables in a BD-relevant sample.

Study 3 was an entirely novel study which examined whether activity and sleep/wake variables were prospectively related to daily variation in mood states in an

11 Note that the intention of this section is to provide an indication of how the three-study design of the current project was used to address the stated goals. Information regarding specific hypotheses are not provided here, but are presented individually in their respective studies and within the context of their specific designs.
outpatient sample of people diagnosed with BD-I. The same activity and sleep/wake variables used in Study 2 were used in Study 3. Participants wore an actigraph and also self-reported their mood and sleep on a daily basis. This final study was designed to address the applied goal of the project, that variables derived from the 24-hour activity rhythm and measured using actigraphy, may act as clinically useful biomarkers of variation in clinical state in people with BD. Such information is intended to contribute to the improvement of prodrome identification in BD.

3.5 Summary of Chapter 3

The 24-hour rhythm of locomotor activity has the potential to advance understanding of BD. The 24-hour activity rhythm, as it is commonly known, has three main neurobiological drivers – circadian, sleep/wake, and BAS processes – which are unable to be parsed in the data. Three theoretically important variables relating to these drivers can, and have been, inferred from the output of the rhythm, as measured by actigraphy. Actigraphy was used to measure these variables – named in the current project as Circadian Rhythm Instability, Sleep, and Total Daytime Activity – because, compared to more direct measures of circadian, sleep, and BAS neurobiological processes, it is feasible for long-term use in a naturalistic setting. The present project sought therefore, to test actigraph variables as predictors of between-subject (trait) and within-subject (state) vulnerability to BD.
Figure 5. Schematic representation of the project’s three-study design

Study 1: Self-report measurement of vulnerability to BD

Study 2: Actigraphic correlates of vulnerability to BD

Study 3: Actigraph-derived Measures of Circadian Instability, Sleep, and Daytime Activity, and their Prospective Relationships with Mood Deterioration in BD
Chapter 4

Study 1: Exploration of Psychometric Properties and Factor Structures Underpinning Self-report Measurement of Vulnerability to Bipolar Disorder

The primary aim of Study 1 was to investigate the factor structure and psychometric properties of two prominent self-report instruments designed to measure trait-like vulnerability to BD. The two instruments – the General Behavior Inventory (GBI; Depue, Krauss, Spoont, & Arbisi, 1989) and the Temperaments Autoquestionnaire (TEMPS-A; Akiskal, Mendlowicz et al., 2005), and their psychometric correlates, are described in detail (4.1). In support of the study aims, the factor structure of these instruments was explored individually, and in combination, using data from a large sample of university students and internet respondents (4.2). The results showed that, individually, two- and five-factor solutions were appropriate for the GBI and TEMPS-A, respectively, as predicted by theory. Exploratory factor analysis of the two instruments in combination revealed three- and six-factor solutions, depending on the method of extraction used (4.3). The three-factor solution was identified as the most accurate representation of the dimensional traits underpinning vulnerability to BD, and the one most consistent with theory (4.4). The two-dimensional theory of temperamental vulnerability to BD was therefore only partially supported, as the third factor in the three-factor solution was not consistent with predictions. Possible explanations for the third factor are provided in 4.4, given the unique context of the instruments and sample used, as well as recommendations for the best self-report measurement predictor of trait-like vulnerability to BD.
4.1 Background and Overview of Study 1

The design of Study 1 assumed that risk for BD is subject to variation along a trait, or series of traits, that are distributed throughout the population. The current study therefore adopted the theoretical standpoint of a quantitative trait approach to BD vulnerability, as described in Section 1.2.4. Study 1 also assumed that the traits underpinning vulnerability to BD could be measured using self-report questionnaires. Self-report questionnaires are important tools because they can be used to identify BD-related temperaments that may be pre-clinical indicators of full syndromal BD (Depue & Klein, 1988).

The early identification of those vulnerable to BD facilitates longitudinal research into biological features that may have significance for the long-term course of the disorder. In addition, such features may serve as links between genotypic vulnerability to BD and the wide variety of phenotypic expressions associated with the disorder. Endophenotypes, as these features are known, ‘lie between’ gene and behaviour and are assumed to possess a simpler genetic structure than the complex, polygenic configurations associated with BD (Bearden & Freimer, 2006). At-risk populations identified by questionnaire self-report provide an opportunity for the investigation of candidate endophenotypes in a non-clinical setting. The attendant increases in statistical power associated with such settings (dimensional traits are more widespread than phenotypic expressions of disorder) is a significant advantage for research into low-frequency illnesses such as BD. Self-report inventories of trait vulnerability to disorder are one of the key strategies for identifying these at-risk populations.

The number and nature of the trait(s) thought to underpin vulnerability to BD are largely unknown. As described in Section 1.2.4, theoretical approaches describing one- (DSM-IV; APA, 2000; Schweitzer, Maguire, & Ng, 2005), two- (Depue & Klein, 1988), and five-factor models (Akiskal & Mallya, 1987) have been proposed.12 The DSM-IV description of BD suggests that vulnerability to the disorder is mediated by a single

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12 Although Depue and Klein (1988) describes one underlying system underpinning vulnerability to BD (under- and overactivation of the BAS; see Section 1.2.4), the model used to represent the system has two clear trait dimensions – mania and depression – that are highly correlated.
factor. Unlike the two- and five-factor models of vulnerability to BD, the DSM-IV approach to description of the disorder is not based on a dimensional model. However, the implication of the DSM-IV approach is that a single factor can explain vulnerability to BD. That factor is best described as ‘bipolarity’. Schweitzer et al. advocated a reconceptualisation of BD as manic disorder on the basis that clinical presentation is often one of sustained, elevated mood rather than mood swings as the name ‘bipolar’ might suggest. They proposed that although depression is often co-morbid with mania, the two syndromes are separable, and mania is specific to the diagnosis of BD.

The two-factor model of vulnerability to BD describes two underlying dimensions – a depressive dimension and a hypo/manic dimension. The two-factor model is commonly measured using the GBI (Depue et al., 1989), a 73-item self-report inventory of BD-related experiences that incorporates elements of intensity, duration, and frequency of symptomatology. Two subscales, measuring the depressive and hypo/manic dimensions, respectively, form the structural basis of the instrument. Subsyndromal manifestations of cyclothymia are also incorporated into the instrument as part of the hypo/manic subscale. Total GBI score, and vulnerability to BD, is derived from a linear combination of scores on the depressive and hypo/manic subscales.

Psychometric investigation of the latent factor structure of the GBI instrument has confirmed two factors. The two-factor structure has been demonstrated in clinical populations (Depue & Klein, 1988), nonclinical populations (Depue & Klein, 1988; Murray et al., 2007), youths presenting at an outpatient research centre (Danielson, Youngstrom, Findling, & Calabrese, 2003), and adolescent offspring of parents with BD (Reichart et al., 2004). A parent-report version of the GBI also demonstrated a two-factor structure (Youngstrom, Findling, Danielson, & Calabrese, 2001). Item content of the factors in all solutions is consistent with the depressive and hypo/manic dimension surface structure. In all cases a strong positive correlation was found between the two factors (and/or dimensions). A modified teacher-report version of the GBI produced a four-factor solution, with one depression factor, and three mania-related factors (Youngstrom, Joseph, & Greene, 2008). Moderate to strong positive correlations characterised the relationship between the depression factor and each of the mania-
related factors. Overall however, the two-factor structure of the GBI appears to be the most parsimonious solution and the one most commonly identified, particularly amongst investigations of the self-report version of the instrument.

The five-factor model of vulnerability to BD describes five underlying temperament dimensions – Dysthymic Temperament (DT), Cyclothymic Temperament (CT), Hyperthymic Temperament (HT), Irritable Temperament (IT), and Anxious Temperament (AT). The TEMPS-A (Akiskal, Mendlowicz et al., 2005) is a self-report instrument that is used to measure the five temperaments. It is a shortened, self-rating version of the clinician-administered TEMPS interview (Akiskal & Mallya, 1987) which was primarily used for identifying vulnerability to affective disorders in clinical populations. The TEMPS-A however, has been used to assess affective temperaments in both clinical populations and the general community.

Psychometric investigation of the TEMPS-A commonly finds less than five latent factors in the instrument. As described in Section 1.2.4, exploratory factor analyses in both clinical and nonclinical populations have demonstrated that the TEMPS-A can be described in terms of two higher order factors. Factor 1 has been shown to consist of cyclothymic, dysthymic, and irritable temperament items, while Factor 2 has been shown to consist of hyperthymic temperament items (Akiskal, Akiskal et al., 2005; Maremmani et al., 2005; Rozsa et al., 2008). Thus, the TEMPS-A displays a structure that is generally consistent with the 2-factor structure of the GBI. The item content of the two factors for each instrument is slightly different, with the cyclothymic temperament seemingly misplaced in Factor 1 for the TEMPS-A according to the GBI factor structure. Nevertheless, the broad consistency in factor structure across both clinically-derived measures is noteworthy. It is somewhat surprising that relationships between the two closely-aligned instruments have yet to be fully investigated.

The psychometric correlates of vulnerability to BD were also explored in the current study, in order to further develop understanding of the trait vulnerability concept. Three measures were employed to act as external correlates of the traits underpinning vulnerability to BD – the Five-Factor Model of normal personality (FFM; Digman,
1990), the Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000), and the “ups and downs” trait item of Angst, Gamma, and Endrass (2003).

The Big Five personality traits of Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C) are proposed to underlie all manifestations of human personality (Digman, 1990). N is the most pervasive domain of personality and represents a trait feature of emotional stability (Eysenck, 1981). Not surprisingly, high levels of N (low emotional stability) are strongly associated with a general vulnerability to psychopathology (Widiger & Trull, 1992), including BD-II (Akiskal, Kilzieh et al., 2006). The E dimension is characterised by personality features such as sociability, optimism, and energy (Eysenck). High levels of E have been shown to be specifically associated with BD-I in some studies (e.g., Bagby et al., 1997). E was significantly higher amongst BD outpatients from a tertiary care centre compared to subgroups of other internalising disorders (i.e., those associated with mood, affect, and anxiety; Tackett, Quilty, Sellbom, Rector, & Bagby, 2008). High levels of N and E have both been implicated in the predisposition to BD amongst a non-clinical community sample (Murray et al., 2007). The dimensions of A (associated with personality features such as altruism and empathy; Costa & McCrae, 1992), C (associated with reliability and determination; Costa & McCrae), and O (associated with imagination and novelty seeking; Costa & McCrae) are outside the normal range of variation in some BD populations. Higher levels of O (Nowakowska, Strong, Santosa, Wang, & Ketter, 2005; Tackett et al., 2008), and lower levels of A (Murray et al.) and C (Lozano & Johnson, 2001) may be associated with BD, although these findings need further replication. Psychoticism, a personality trait characterised by features of impulsivity, aggressiveness, and egocentricity (Eysenck) and considered to be conceptually equivalent to low levels of A and C in the FFM (Eysenck, 1992), has been implicated in general vulnerability to psychopathology (Eysenck & Eysenck, 1976). Overwhelmingly, the evidence appears to favour high levels of N (depression) and high levels of E (hypo/mania) in vulnerability to BD. Other personality traits have been inconsistently associated with vulnerability to BD.
The MDQ (Hirschfeld et al., 2000) measures self-reported history of the presence (or absence) of hypo/manic symptomatology. The instrument is primarily used to screen for clinically-relevant BD-spectrum conditions in the general community (Hirschfeld, Calabrese et al., 2003). In the current study, the degree of self-reported hypo/manic symptomatology on the MDQ was used to measure BD vulnerability. The MDQ has been shown to demonstrate moderate sensitivity and excellent specificity in detecting BD-II in general community settings (Hirschfeld, Holzer et al., 2003).

The ups and downs trait item (Angst, Gamma, & Endrass, 2003) is a measure of the propensity for an individual to experience mood swings. Thus, the ups and downs correlate of vulnerability to BD, particularly BD-II, was assessed according to the presence of trait mood lability. The ups and downs item has been shown to have a good balance of sensitivity and specificity in detecting BD-II (Benazzi, 2004) and has also been shown to be a stronger predictor of general BD diagnoses than positive family history of mania (Angst et al.). The ups and downs item appears therefore to be positively correlated with vulnerability to BD-II.

4.2 Hypotheses for Study 1

Based on previous research it was expected that two dimensions would provide the best representation of the latent structure of trait vulnerability to BD. Two factors – one representing a depression-like trait, and one representing a manic-like trait – were expected to be prominent in principal components analysis (PCA) of the combined GBI and TEMPS-A instruments. The one-factor and five-factor solutions were not expected to represent trait vulnerability to BD with the same degree of parsimony and heuristic utility. Given the two dimensional surface structure of the GBI, it was expected to be the best measure of trait vulnerability to BD and the preferred instrument for selecting participants in Study 2. The strong clinical focus of the TEMPS-A parent instrument (viz., the TEMPS interview) was expected to limit the usefulness of TEMPS-A for identifying vulnerability to BD in a predominantly well sample.
Several hypotheses regarding the external correlates of vulnerability to BD were also proposed. First, the dimensions of N and E were expected to correlate positively with the Depression and Hypo/mania scales of the GBI, respectively. Positive correlations between N and the CT, DT, IT, and AT scales of the TEMPS-A, and between E and the HT scale of the TEMPS-A were also expected (see Bloink, Brieger, Akiskal, & Marneros, 2005). Second, total MDQ score was expected to correlate positively with GBI-Hypomania score. A positive correlation between the MDQ and the CT scale of the TEMPS-A was also expected based on scale content and previous findings (Bowen, Baetz, Hawkes, & Bowen, 2006). Finally, the ups and downs item was expected to correlate positively with Total GBI score and the GBI-Hypomania score, as well as with the CT scale of the TEMPS-A.

4.3 Method for Study 1

4.3.1 Participants

Participants were recruited through a variety of avenues, including press releases to local newspapers, mental health information websites, and through approved internal University subject recruitment avenues. Respondents were informed that completing the questionnaire implied voluntary consent for their data to be used in the study. No identifying data was collected, and so participation was entirely anonymous. A total of 540 respondents participated in the online survey, however 56 (10.4%) participants failed to respond to more than half of the survey and were excluded from further analysis. Thus, a total of 484 completed surveys were retained for analysis.

The final sample for analysis consisted of 377 female (77.9%) and 102 male (21.1%) participants. Five respondents (1.0%) did not record their gender. The mean age of the sample was 29.31 years ($SD = 12.83$) with the youngest respondent being 16 and the oldest 86 years of age. Country of residence was predominantly Australia (96.7%), with two participants from New Zealand (0.4%), and eight living in “Other” countries (1.7%). Six respondents (1.2%) did not complete this question.
4.3.2 Materials and procedure

Participants completed an online questionnaire that consisted primarily of four psychometric instruments – the GBI, TEMPS-A, MDQ, and NEO-FFI. A copy of the complete questionnaire can be found in Appendix B. Demographic questions (i.e., age, gender, country of residence) and the ups and downs item (Angst, Gamma, & Endrass, 2003) were also included.

The 73-item GBI consists of two subscales – depression and hypomania + biphasia. The depression subscale includes 46 items (e.g., “have there been times of several days or more when you really got down on yourself and felt worthless?”) that measure respondents’ tendency to depression. The hypomania subscale consists of 27 items (e.g., “have there been periods of several days or more when your thinking was so clear and quick that it was much better than most other people’s?”) that measure hypomanic tendencies. Items are responded to on a 4-point scale including “never or hardly ever”, “sometimes”, “often”, and “very often or almost constantly”. A deliberate conceptual gap between the two middle responses allows items to be “case-scored”. That is, participants who select one of the first two responses receive a score of 0 for that item, which effectively equates to a ‘no’ response. Participants who select one of the latter two responses receive a score of 1, effectively a ‘yes’ response. This case identification scoring strategy is the most commonly employed and is the one originally intended for use with the GBI. However, the 4-point Likert-type scale affords the opportunity for a dimensional scoring strategy that allows increased sensitivity to subtler variations in hypomaniac and depressive symptomatology. This latter scoring strategy was the one employed in Study 1. The GBI has proved to be psychometrically sound and has demonstrated adequate sensitivity to identify a full range of both syndromal and subsyndromal affective intensities, in both clinical and non-clinical populations (e.g., Depue and Klein, 1988; Reichart et al., 2004). The GBI was successfully used as the initial screening tool for potential bipolar spectrum conditions in the large longitudinal study.

13 Note that the hypomania + biphasia subscale will be referred to simply as hypomania for the remainder of the thesis. Biphasia is not a term commonly used in the literature. Previous research has adopted this clarification in terminology (e.g., Murray et al., 2007).
investigation run through Temple University and University of Wisconsin (Alloy, Abramson et al., 2009). The GBI was shown to have good predictive validity of bipolar spectrum conditions in this large study.

The TEMPS-A (Akiskal, Mendlowicz et al., 2005) is a 39-item self-report measure of temperamental characteristics that is particularly suited for use with non-clinical populations. As described earlier it contains 5 subscaled dimensions, DT (8 items; e.g., “people tell me I am unable to see the lighter side of things”), CT (12 items; e.g., “I get sudden shifts in mood and energy”), HT (8 items; e.g., “I have abilities and expertise in many fields”), IT (8 items; e.g., “when angry, I snap at people”), and AT (3 items; e.g., “I am often fearful of someone in my family coming down with a serious disease”). It has been used in clinical studies to assess affective temperaments in both its short (Akiskal, Mendlowicz et al.) and long forms (Placidi et al., 1998). Items are responded to on a dichotomous (yes/no) scale according to whether they “apply to (the respondent) for much of (their) life”, thereby emphasising the lifetime trait aspect of the subscale dimensions. The psychometric properties of the TEMPS-A are typically strong with alpha coefficients ranging from 0.67 to 0.91 for the five dimensions (Akiskal, Mendlowicz et al.).

The Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000) is a 15-item self-report measure of lifetime history of manic/hypomanic symptoms. The first 13 items relate to respondents’ experience of symptoms as derived from DSM-IV criteria and the clinical experiences of the scale developers. It includes items such as increased self-confidence and heightened sexual interest which are responded to on a dichotomous (yes/no) scale. The 14th item asks whether any of the reported symptoms occurred during the same period of time (i.e., in a cluster) and again requires a yes/no response. The 15th item requires respondents to rate how much of a problem the symptoms caused in their day-to-day life on a 4-point Likert scale ranging from ‘no problem’ to ‘serious problem’. Items 14 and 15 are qualifying questions designed to avoid over-diagnosis of bipolar spectrum disorders. A minimum of seven symptoms is required for the secondary stage of diagnosis – the clustering of symptoms – to be considered. In turn, this item must be responded to in the affirmative before respondents rate how much of a
problem their symptoms have caused them. Finally, a ‘moderate’ or ‘serious’ problem must be reported to receive a diagnosis of a bipolar spectrum disorder. If respondents do not achieve these benchmarks a diagnosis is not given.

As a diagnostic tool, the MDQ has been shown to have good sensitivity and excellent specificity amongst psychiatric outpatients (Hirschfeld et al., 2000) and the general community (Hirschfeld, Holzer et al., 2003). Sensitivity was considerably lower in the community study than the outpatient study, and reflects the difficulty in using structured clinical interviews to diagnose low frequency mental disorders such as BD-II in community settings. Most importantly however, the specificity of the MDQ in the community setting was of similar magnitude to the outpatient setting, reducing the possibility of false positive errors in diagnosis. The full MDQ also demonstrates adequate internal consistency (Hirschfeld, Holzer et al.; Hirschfeld et al.). The factor structure of the MDQ is seemingly robust, with two studies demonstrating a 2-factor structure amongst both clinical (Benazzi & Akiskal, 2003) and community (Mangelli, Benazzi, & Fava, 2005) populations. The two factors derived in these studies are broadly labelled as ‘hyperactivity’ and ‘irritability’.

The NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992) was used to measure the five normal personality dimensions of the FFM. Sixty items were used to measure the five dimensions of N (12 items; e.g., “I often feel tense and jittery”), E (12 items; e.g., “I like to be where the action is”), O (12 items; e.g., “I have a lot of intellectual curiosity”), A (12 items; e.g., “I would rather cooperate with others than compete with them”), and C (12 items; e.g., “I am a productive person who always gets the job done”). The NEO-FFI consistently performs well psychometrically across a range of age groups and cultures (e.g., Costa & McCrae, 1992; Egan, Deary, & Austin, 2000; Rolland, Parker, & Stumpf, 1998; Schmitz, Hartkamp, Baldini, Rollnik, & Tress, 2001). Factor analyses of the NEO-FFI parent measure (NEO PI-R; Costa & McCrae) reliably find five factors that are consistent with the five subscales of the instrument. The 5-factor structure has been replicated in both normal samples (Costa & McCrae) and psychiatric patient samples (Bagby et al., 1999).
Assessment of the ups and downs item (Angst, Gamma, & Endrass, 2003) is made by asking the question “Would you say you were one of those people who have frequent ups and downs?”, to which respondents answer “yes” or “no”.

Analysis of questionnaire data was conducted using SPSS 16.0 for Windows (SPSS, Inc., Chicago, Illinois).

4.3.3 Data reduction and analysis

Principal components analysis (PCA) was conducted separately for the GBI and the TEMPS-A in the first instance. PCA was also conducted for the two instruments together. The number of factors to extract in each analysis was investigated using four methods. The Kaiser-Guttman criterion (Kaiser & Caffrey, 1965) uses eigenvalues to determine the number of factors to extract. Eigenvalues represent the amount of variance explained by a component. Components with eigenvalues greater than 1 are considered for extraction. The Kaiser-Guttman criteria often overestimates the number of factors to extract, especially in larger samples such as that employed in the current study (Tabachnick & Fidell, 2007). However, it was included here for the sake of completeness and statistical transparency. The scree criteria (Cattell, 1966) uses a plot of eigenvalues against the number of components arranged in descending order to aid the factor extraction process. The recommended number of factors to extract using this technique is determined by visual inspection of the plot for the point at which the fitted slope line changes angle. Parallel analysis (Horn, 1965) uses a three-step process to guide factor extraction. A randomly generated data set with the same number of cases and variables is created. A series of PCA’s using the random data set is conducted and eigenvalues from each iteration averaged and compared to the eigenvalues from the PCA on the real data set. The number of factors to extract is indicated at the point where the eigenvalues from the real data set no longer exceed the averaged eigenvalues from the random data set. The Minimum Average Partial (MAP; Velicer, 1976) test also uses a series of PCA’s to guide factor extraction. A one-component PCA is run, followed by a two-component PCA, followed by a sequential series of PCA’s where one component
is added for each new analysis. At each iteration the mean squared partial correlation is computed until such point that the minimum squared partial correlation is identified. This point determines the number of factors to extract. SPSS algorithms for parallel analysis and the MAP test were derived from O’Connor (2000).

Determining the number of factors to extract was the key element of the analytic strategy for Study 1. As such, all methods used to guide decision-making were considered equally likely to provide a parsimonious solution and the number of possible factors was not restricted for any of the methods used. However, given the strong theoretical basis for only a small number of components (maximum of five; see Akiskal & Mallya, 1987; Depue, Krauss, & Spoont, 1987), decision-making regarding the most appropriate number of components to extract was biased towards solutions recommending the extraction of less than 6 components.

Rotation of extracted factors was used to improve factor interpretability. The Direct Oblimin (oblique) rotation method was preferred for all solutions in Study 1, as orthogonality of the personality dimensions used in the study could not be theoretically justified (e.g., Depue et al., 1989). Orthogonal rotations are often applied in PCA’s of the TEMPS-A (e.g., Akiskal, Akiskal et al., 2005; Akiskal, Mendlowicz et al., 2005). However most research demonstrates that these dimensions are highly correlated (e.g., Rozsa et al., 2008), so an oblique rotation was indicated, on both statistical and theoretical grounds. Item content of the extracted and rotated factors was used to determine factor labels.

4.4 Results for Study 1

4.4.1 Assumption testing

Four hundred and eighty-four participants completed the online questionnaire, comfortably above the minimum of 300 cases recommended by Tabachnick and Fidell (2007) for statistically sound PCA. The 56 excluded surveys had extensive missing data
in the latter part of the survey, indicative of failure to finish the survey. In all excluded cases at least 50% of the online questionnaire had not been completed.

Missing data was minimal across the completed questionnaires, with mean missing items per respondent equal to 0.68 ($SD = 1.78$). Missing responses on the GBI were replaced with the within-subject series mean of their respective subscale dimension. Missing responses on the TEMPS-A and the MDQ were replaced with a ‘0’, equivalent to a “no” response. Missing responses on the NEO-FFI were replaced with a score of ‘3’, equivalent to a “neutral” response, as recommended in the scoring manual (Costa & McCrae, 1992). Extreme univariate outliers (values greater than three times outside the interquartile range of the standard boxplot) were replaced using the same methods as described above.

Distribution of scores for each variable was assessed for normality. The Kolmogorov-Smirnov (KS) statistic for all scales except the NEO-C scale was significant, indicating that the assumption of normality was violated for these scales. This is not an unexpected outcome in large samples, especially those measuring low frequency domains such as depression and hypomania and the subsyndromal traits associated with these clinically-relevant manifestations of disorder. An inspection of the frequency histograms revealed a strong positive skew in all GBI, TEMPS-A, and MDQ subscales, reinforcing the expected non-normal distribution of these low frequency constructs. Inspection of histograms for the domains of the NEO-FFI revealed near-normal distribution for all scales, with the possible exception of the N scale which showed a slight negative skew. PCA solutions can be degraded by violations of distributional assumptions (Tabachnick & Fidell, 2007). Transformation of scores on variables with non-normal distributions is a possible solution to violation of such assumptions. However, given that the scores on each variable emerged in a manner consistent with distributional expectations in a normal population, no raw data transformations were performed.

Multivariate normality amongst some linear combinations of variables were also assessed via inspection of scatterplots. Due to the large number of possible pairings between variables, only the small number of combinations most likely to show evidence
of nonlinearity were investigated. Scatterplots showing the relationship between N (slight negative skew) and positively skewed variables HT, IT, MDQ, and GBI-Hypomania were inspected. No curvilinear relationships were found, so transformation of raw data was not necessary.

4.4.2 Preliminary analyses and data description

Internal reliability, assessed by Cronbach’s alpha, was good to excellent for all subscale and total scale dimensions of the GBI ($\alpha = .94 - .98$), the NEO-FFI ($\alpha = .69 - .90$), and the MDQ ($\alpha = .87$). For the TEMPS-A, alpha coefficients were within the recommended range for all subscales ($\alpha = .71 - .87$) except for the AT subscale ($\alpha = .64$). However, inter-item correlations were adequate ($r = 0.28 – 0.53$) for a subscale of this size (i.e., three items). Mean subscale scores for the total sample are presented in Table 2 below. Subscale scores classified by gender are also presented in Table 2. Data are presented to show that mean scores in the sample were generally consistent with normative data and gender specific distributions from previous investigations.

Mean subscale scores for the NEO-FFI in the current sample were within ±1 SD of the gender-specific norms described by Costa and McCrae (1992). The mean number of symptoms identified on the MDQ in the sample was lower than that recorded by Udachina and Mansell (2007), but was also within 1 SD. Mean subscale scores for the TEMPS-A were greater than 1 SD higher than mean scores reported for the normal controls in Mendlowicz, Jean-Louis, Kelsoe, and Akiskal (2005), except for the HT subscale which was more than 1 SD lower. Scores on the Likert-scored GBI were higher than those reported by Murray et al. (2007), although still within 1 SD.

Table 2 shows that significant gender differences were only apparent for the A scale of the NEO-FFI ($\alpha$ adjusted for multiple comparisons). This finding was consistent with previous studies that have shown the trait of agreeableness to be a female-oriented domain (Costa & McCrae, 1992; Stemmler & Petersen, 2005). Nonsignificant trends for gender differences on HT, AT, and N were found in the current sample, and this is also consistent with previous research (Akiskal & Akiskal, 2005; Costa & McCrae, 1992;
Perugi et al., 1990; Stemmler & Petersen, 2005). Endorsement of the ‘ups and downs’ item was evenly distributed for both genders, with 49.0% of males and 48.7% of females responding “yes” to this item.

Table 2

Means and Standard Deviations for Scale Scores on the GBI, TEMPS-A, NEO-FFI, and MDQ for the Total Sample and Grouped by Gender

<table>
<thead>
<tr>
<th>Measure</th>
<th>Domain</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
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<th>p</th>
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<tr>
<td>GBI</td>
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<td>46.2</td>
<td>30.9</td>
<td>42.6</td>
<td>27.6</td>
<td>47.4</td>
<td>31.8</td>
<td>1.48†</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypomania</td>
<td>19.4</td>
<td>14.3</td>
<td>21.1</td>
<td>12.8</td>
<td>19.1</td>
<td>14.7</td>
<td>1.29 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>65.6</td>
<td>42.3</td>
<td>63.8</td>
<td>37.4</td>
<td>66.4</td>
<td>43.7</td>
<td>0.62†</td>
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<td>3.7</td>
<td>5.2</td>
<td>3.6</td>
<td>5.2</td>
<td>3.8</td>
<td>0.02 ns</td>
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<tr>
<td></td>
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<td>2.5</td>
<td>2.2</td>
<td>2.5</td>
<td>2.5</td>
<td>0.32 ns</td>
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<tr>
<td></td>
<td>HT</td>
<td>3.7</td>
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<td>4.1</td>
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<td>3.6</td>
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<td>2.08 ns</td>
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<tr>
<td></td>
<td>IT</td>
<td>2.2</td>
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<td>2.3</td>
<td>2.0</td>
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<td>0.39 ns</td>
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<td></td>
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<td>2.95 ns</td>
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</tr>
<tr>
<td></td>
<td>E</td>
<td>25.0</td>
<td>8.3</td>
<td>24.4</td>
<td>7.5</td>
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<tr>
<td></td>
<td>O</td>
<td>29.6</td>
<td>6.1</td>
<td>29.1</td>
<td>5.4</td>
<td>29.7</td>
<td>6.2</td>
<td>0.84 ns</td>
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<td></td>
<td>A</td>
<td>30.4</td>
<td>6.3</td>
<td>27.8</td>
<td>5.6</td>
<td>31.1</td>
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<td>4.81 &lt;.001</td>
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<tr>
<td></td>
<td>C</td>
<td>28.4</td>
<td>7.6</td>
<td>27.1</td>
<td>7.6</td>
<td>28.7</td>
<td>7.6</td>
<td>1.85 ns</td>
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<td>MDQ</td>
<td>Symptoms</td>
<td>5.5</td>
<td>3.9</td>
<td>5.9</td>
<td>4.1</td>
<td>5.4</td>
<td>3.8</td>
<td>1.22 ns</td>
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<td></td>
</tr>
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</table>

†Levene’s test was significant for these comparisons, violating the homogeneity of variances assumption; df adjusted accordingly.

Pearson correlation coefficients were computed to explore bivariate relationships (Table 3). Some subscales were expected to correlate strongly in a positive direction (e.g., TEMPS-DT and GBI-Depression), and some strongly in a negative direction (e.g.,
TEMPS-IT and NEO-A), while others were not expected to show strong correlations (e.g., NEO-O and GBI-Depression).

Table 3

_Correlation Coefficients Between Scales of the GBI, TEMPS-A, and NEO-FFI_

<table>
<thead>
<tr>
<th></th>
<th>GBI</th>
<th>TEMPS-A</th>
<th>NEO-FFI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dep</td>
<td>-</td>
<td>.72*</td>
<td>.97*</td>
</tr>
<tr>
<td>Hyp</td>
<td>-</td>
<td>.86*</td>
<td>.73*</td>
</tr>
<tr>
<td>Tot</td>
<td>-</td>
<td>.71*</td>
<td>.55*</td>
</tr>
<tr>
<td>CT</td>
<td>-</td>
<td>.49*</td>
<td>.10</td>
</tr>
<tr>
<td>DT</td>
<td>-</td>
<td>-.20*</td>
<td>.42*</td>
</tr>
<tr>
<td>HT</td>
<td>-</td>
<td>.08</td>
<td>.07</td>
</tr>
<tr>
<td>IT</td>
<td>-</td>
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<td>.33*</td>
</tr>
<tr>
<td>AT</td>
<td>-</td>
<td>.35*</td>
<td>-.16*</td>
</tr>
<tr>
<td>N</td>
<td>-</td>
<td>-.58*</td>
<td>.05</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>.08</td>
<td>.26*</td>
</tr>
<tr>
<td>O</td>
<td>-</td>
<td>.09</td>
<td>.01</td>
</tr>
<tr>
<td>A</td>
<td>-</td>
<td>.27*</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < .01

N = 484

Table 3 shows that there were a large number of moderate to strong correlations between subscales of the instruments used in Study 1. The Depression scale of the GBI correlated significantly with all scales except NEO-O. All relationships were in the expected direction based on scale descriptors and relevant theory (see Akiskal & Mallya, 1987; Costa & McCrae, 1992; Depue et al., 1989). The correlation between the Hypomania scale of the GBI and the MDQ was stronger than that between the Depression scale of the GBI and the MDQ.
Relationships between the subscales of the TEMPS-A, NEO-FFI, and the MDQ were as expected based on item content (see Akiskal & Mallya; Costa & McCrae; Hirschfeld et al., 2000). The CT scale of the TEMPS-A demonstrated the highest correlation with the MDQ. The binary ‘ups and downs’ trait item (not shown in Table 2) correlated in the expected direction with the TEMPS-CT ($r_{pb} = .63, p < .01$) and GBI Total scales ($r_{pb} = .49, p < .01$).

It is also apparent from the correlation coefficients displayed in Table 2 that there are aspects of the TEMPS-A which are not captured in the GBI. The AT scale and, particularly, the HT scale of the TEMPS-A did not correlate strongly with either of the Depression or Hypomania scales of the GBI.

A logistic regression analysis was performed to assess the prediction of MDQ hypo/mania diagnosis by the two subscales of the GBI and the five subscales of the TEMPS-A. One hundred and sixty-three participants (Female $n = 127$) recorded a positive diagnosis of hypo/manic history on the MDQ. The chi-square statistic for the model with all variables entered, including the constant, was significant, indicating improved fit of the full model compared to the constant only model; $\chi^2 (7) = 285.44, p < .001$. Table 4 presents the full model output parameters.

Table 4

<table>
<thead>
<tr>
<th>Variables</th>
<th>$B$</th>
<th>SE</th>
<th>Wald Chi-square</th>
<th>df</th>
<th>$p$</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPS-CT</td>
<td>.028</td>
<td>.056</td>
<td>.255</td>
<td>1</td>
<td>.61</td>
<td>1.029</td>
</tr>
<tr>
<td>TEMPS-DT</td>
<td>.025</td>
<td>.072</td>
<td>.125</td>
<td>1</td>
<td>.72</td>
<td>1.026</td>
</tr>
<tr>
<td>TEMPS-IT</td>
<td>.088</td>
<td>.083</td>
<td>1.110</td>
<td>1</td>
<td>.29</td>
<td>1.092</td>
</tr>
<tr>
<td>TEMPS-HT</td>
<td>-.052</td>
<td>.069</td>
<td>.571</td>
<td>1</td>
<td>.45</td>
<td>.949</td>
</tr>
<tr>
<td>TEMPS-AT</td>
<td>.018</td>
<td>.136</td>
<td>.018</td>
<td>1</td>
<td>.89</td>
<td>1.018</td>
</tr>
<tr>
<td>GBI Hyp</td>
<td>.028</td>
<td>.016</td>
<td>2.977</td>
<td>1</td>
<td>.08</td>
<td>1.029</td>
</tr>
</tbody>
</table>
Table 4 shows that the Depression scale of the GBI was the strongest and only significant predictor of Hypo/mania diagnosis according to the MDQ. Trait vulnerability to depression appears therefore to be strongly associated with the presence and/or history of hypo/mania. A nonsignificant trend for the prediction of hypo/mania by the GBI hypo/manic trait was also apparent.

### 4.4.3 Exploratory factor analysis – GBI

The latent factor structure of the GBI was investigated using PCA. Factorability of the data was good, as shown by a significant Bartlett’s test of sphericity \( p < .001 \) and high Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy (.975). Table 5 presents the number of components to be extracted from PCA of the GBI as recommended by the four extraction methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of components</th>
<th>Variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scree plot</td>
<td>2</td>
<td>49.82%</td>
</tr>
<tr>
<td>Parallel Analysis</td>
<td>3</td>
<td>52.26%</td>
</tr>
<tr>
<td>MAP test</td>
<td>8</td>
<td>61.20%</td>
</tr>
<tr>
<td>Kaiser-Guttman</td>
<td>9</td>
<td>62.69%</td>
</tr>
</tbody>
</table>

Note: R-square value for the model is .618 using the Nagelkerke formulation (Nagelkerke, 1991).
The scree plot and parallel analysis recommended extraction of two and three factors, respectively. The MAP test and Kaiser-Guttman criteria recommended the extraction of eight and nine factors, respectively. Two or three factors were considered to be the most consistent with both the theory underpinning the instrument and previous research. One factor was not recommended by any of the extraction methods. Forced two- and three-factor solutions were ordered and oblique rotation applied. It is sufficient in this preliminary part of the analysis to recognise that 43 of the 46 items that loaded above .3 on Factor 1 were from the Depression scale of the GBI. The other three items loading on Factor 1 were from the GBI Biphasia subscale. Factor 2 was predominantly GBI Hypomania items (17 out of 22 items loading above .3). The other five items loading on Factor 2 were from the GBI Biphasia subscale.

The forced three-factor solution with oblique rotation did not substantially change the structure of the two-factor solution. The third factor consisted of one item – item number 25, a Depression item that did not load above .3 on either factor in the two-factor solution. The most parsimonious solution for the latent factor structure for the GBI in Study 1 would therefore appear to include two factors – one strongly characterised by Depression items and the other strongly characterised by Hypo/mania items.

4.4.4 Exploratory factor analysis – TEMPS-A

The latent factor structure of the TEMPS-A was also investigated using PCA. Factorability of the data was good, as shown by a significant Bartlett’s test of sphericity ($p < .001$) and high KMO measure of sampling adequacy (.884). Table 6 presents the number of components to be extracted from PCA of the TEMPS-A as recommended by the four extraction methods.
Table 6

Recommended Number of Components to Extract and Variance Explained for Each Extraction Method for the TEMPS-A

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of components</th>
<th>Variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scree plot</td>
<td>3</td>
<td>34.10%</td>
</tr>
<tr>
<td>Parallel Analysis</td>
<td>5</td>
<td>42.41%</td>
</tr>
<tr>
<td>MAP test</td>
<td>3</td>
<td>34.10%</td>
</tr>
<tr>
<td>Kaiser-Guttman</td>
<td>9</td>
<td>54.26%</td>
</tr>
</tbody>
</table>

Extraction of three components was recommended by the scree plot and MAP test. Extraction of five components was recommended by the parallel analysis technique. Both recommendations, but particularly the latter, would appear to be consistent with the theory underpinning the structure of the TEMPS-A instrument and previous research. Extraction of nine components, as recommended by the Kaiser-Guttman criteria, is not consistent with theories of the TEMPS-A latent structure. Forced three- and five-factor solutions were thus ordered and oblique rotation applied.

Factor 1 in the three-factor solution consisted of the 12 CT items from the TEMPS-A. Factor 2 consisted of the eight HT items from the TEMPS-A. Factor 3 included the eight items from the DT subscale, the three items from the AT subscale, and four of the items from the IT subscale. The remaining four items from the IT subscale did not load above .3 on any of the extracted factors. It would appear then, based on a three-factor latent structure, the CT and HT subscales were adequately defined in the current sample, while the third factor was a combination of items from the other three subscales of the TEMPS-A instrument.

For the five-factor solution, the 12 items of the CT subscale again formed the first factor. Factor 2 consisted of seven HT items. The eighth HT item moved to Factor 3 which consisted mostly of DT items. Six of the eight DT items from the TEMPS-A loaded on this Factor. Of the remaining two DT items, one did not load above .3 on any
factor, and one loaded on Factor 4. Factor 4 included all of the IT items from the TEMPS-A. Factor 5 included the three AT items exclusively. The five-factor solution found in the current sample was therefore consistent with the theory underpinning the TEMPS-A and the latent factor structure defined by previous investigations of the instrument.

4.4.5 Exploratory factor analysis – combined GBI and TEMPS-A

The combined latent factor structure of the GBI and TEMPS-A instruments was investigated using PCA. Factorability of the data was good (Bartlett’s test of sphericity was significant and the KMO measure of sampling adequacy was .962). Table 7 presents the number of components to be extracted from the combined PCA of the GBI and TEMPS-A as recommended by the four extraction methods.

Table 7

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of components</th>
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</tr>
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<tr>
<td>Parallel Analysis</td>
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<td>53.64%</td>
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<tr>
<td>Kaiser-Guttman</td>
<td>20</td>
<td>64.10%</td>
</tr>
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</table>

The MAP test and Kaiser-Guttman methods recommended the extraction of 10 and 20 factors, respectively. The large number of factors recommended for extraction using these methods was not consistent with what could reasonably be expected in a PCA of the GBI and TEMPS-A instruments. The theory underpinning these two measures also
does not support such a large number of factors. In addition, the small amount of additional variance explained by these solutions, and the difficulties associated with interpreting components in large, multi-factor solutions, meant that these models were not investigated further. Note also that the Kaiser-Guttman criteria in particular often overestimates the number of factors to extract when applied to large samples (see Section 4.2.3).

The scree plot recommended the extraction of three factors and parallel analysis recommended the extraction of six factors. Given that three- and six-factor solutions were more consistent with what was expected in the current PCA, based on theory and previous research, only these solutions were investigated. Oblique rotation was applied to the extracted factors in both solutions in order to aid interpretation. The scree plot showing three factors for extraction is presented below in Figure 6. It is immediately followed by Table 8 showing the item content of the three-factor solution.

Figure 6. Scree plot of eigenvalues for the unrotated factor solution for PCA of the combined GBI and TEMPS-A
<table>
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</thead>
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<td>GBI14</td>
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<td>GBI59</td>
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<td>F3</td>
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<td>Dysthymia</td>
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% Variance 31.89 6.65 3.34
Cum. Variance 31.89 38.54 41.88

*Note.* Given the large number of items included in this PCA only factor loadings above .55 are shown in the table, in order to aid factor interpretation. Comrey and Lee (1992) recommend that items with factor loadings above .55 are considered ‘good’ contributors to their respective factors.
Factor 1 in the three-factor solution is clearly a depression-related factor. The content is dominated by GBI-Depression items. Thirty-seven out of the 38 items that loaded above .55 on Factor 1 were from this scale. The remaining item came from the DT scale of the TEMPS-A. Factor 2 in the three-factor solution is clearly a hypomania-related factor. All of the items loading above .55 on this factor were derived from the GBI-Hypomania scale. Factor 3 included only one item loading above .55. This single item was from the IT scale of the TEMPS-A instrument. Thus, the two strongest factors derived from a forced three-factor PCA of the combined GBI and TEMPS-A measures can be defined as Depression and Hypomania. The first factor in the current sample can be defined as the tendency to experience depression on a lifetime or trait basis, and the second factor can be defined as the tendency to experience hypo/mania on a lifetime or trait basis. The smaller third factor was characterised by behaviours associated with an irritable temperament. The number of non-redundant residuals in the reproduced correlation residuals matrix for the three-factor solution was 1217, or 19.0% of the total number of reproduced correlations.

A six-factor model was forced on the data, as recommended by the parallel analysis technique, and an oblique rotation applied. The item content of the six-factor solution is presented in Table 9 below.

Table 9

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*Note:* Only factor loadings above .55 are shown in the table.

Factor 1 in the six-factor solution is, again, clearly a depression-related factor. Thirty-five out of the 36 items loading above .55 on this factor were from the GBI-
Depression scale. Item number 17 from the TEMPS-A, a dysthymia item, was again the only non-GBI item to load strongly on the first factor. Factor 2 was clearly a hypomania-related factor, with all items loading above .55 on this factor coming from the GBI-Hypomania scale. Factor 3 was dominated by IT items from the TEMPS-A and Factor 4 was dominated by HT items from the TEMPS-A. The negative loadings for the items loading strongly on Factor 5 indicate a low CT factor. The sixth factor is difficult to interpret, as it includes only two strongly loading items – one from the AT scale of the TEMPS-A and one from the DT scale of the TEMPS-A. The number of non-redundant residuals in the reproduced correlation residuals matrix for the six-factor solution was 867, or 13.0% of the total number of reproduced correlations.

It would appear then that the two-factor structure of the GBI and the five-factor structure of the TEMPS-A can both be found in the six-factor solution. The Depression and Hypo/mania scales of the GBI are prominent in the solution and account for a substantial amount of the variance. The Depression scale is particularly strongly represented in the solution and probably accounts for much of the variance that would usually be associated with the DT scale of the TEMPS-A. The IT, HT, and CT scales of the TEMPS-A are represented by their own factors in the six-factor solution, suggesting that they capture elements of vulnerability to BD that are not adequately explained by the GBI.14

4.5 Discussion for Study 1

The primary aim of Study 1 was to investigate the factor structure and psychometric properties of the GBI and TEMPS-A, two prominent self-report measures of trait-like

14 Exploratory factor analysis was also conducted for the portion of the sample that, according to the MDQ diagnostic self-report, had not experienced a previous hypo/manic episode (n = 321). The ‘scar hypothesis’ proposes that previous mood episodes may cause neuropsychological scarring that permanently alters temperament (Akiskal, Hirschfeld, & Yerevanian, 1983; Lewinsohn, Steinmetz, Larson, & Franklin, 1981), so it was prudent to investigate BD-related temperaments in this part of the sample free of potential scarring. For this additional analysis, the number of factors to extract was identical to that recommended for the whole sample. The item content of the factors was very similar to that reported for the whole sample.
vulnerability to BD. The psychometric correlates of vulnerability to BD were also investigated in order to further understand this under-researched construct. With regards to the primary aim, it was expected that a two-factor solution would emerge as the most accurate representation of the latent structure of trait vulnerability to BD when the GBI and TEMPS-A were investigated in combination. The factors were expected to consist of depression-like items on one factor and mania-like items on a second factor. With regards to the secondary aim, N was expected to correlate positively with GBI-Depression, and the CT, DT, IT, and AT scales of TEMPS-A. E was expected to correlate positively with GBI-Hypomania and the HT scale of TEMPS-A.

The first hypothesis, that two factors would be the most accurate representation of the dimensional traits underlying vulnerability to BD, was only partially supported. In fact, three- and six-factor solutions were recommended by PCA of the combined GBI and TEMPS-A instruments. The three-factor solution consisted of a depression-like dimension, a mania-like dimension, and an irritability dimension. The first three factors in the six-factor solution were virtually identical to those in the three-factor solution. The remaining three factors in the six-factor solution were virtually identical to those in the three-factor solution. Notably, a single-factor solution was not recommended by PCA.

The dominance of the first two factors in both the 3- and 6-factor solutions is broadly consistent with previous research. A two dimension structure of depressive- and
manic-like tendencies is consistent with many recent models of the affective domain, including those of Depue et al. (1989; see also Reichart et al., 2005; Youngstrom et al., 2001), the two ‘super factors’ of affective temperament (a general mood disturbance factor with neurotic features and a hyperthymic factor; Akiskal, Akiskal et al., 2005; Rozsa et al., 2008), internalising vs. externalising disorders (Krueger, 1999; Slade & Watson, 2006), anger vs. fear traits (Lara et al., 2006), and the positive/negative affectivity dimensions described by Watson and Tellegen (1985). While the labels attached to each dimension vary between investigations, it is clear that a two dimension structure is prominent in explanations of vulnerability to mood disorders generally, and BD specifically.

The correlated liability model using genetic concordance data from MZ and DZ twin pairs with BD (McGuffin et al., 2003; see Section 1.2.4) also supports the two-dimension structure of vulnerability to BD. According to the findings from Study 1, this conceptualisation of liability to affective disorder may also be applicable to the traits of depressive and hypo/manic tendency. The moderate to strong, positive correlations between dimensions measuring depressive tendencies and dimensions measuring hypo/manic tendencies in the current study is also supportive of the correlated liability model.

The emergence of irritability in Study 1 as a third factor underlying vulnerability to BD was an unexpected finding. Irritable temperament often arises as a separate factor (usually third strongest) in factor analyses of the TEMPS-A instrument (e.g., Akiskal, Mendlowicz et al., 2005; Karam, Mneimneh, Salamoun, Akiskal, & Akiskal, 2005; Rozsa et al., 2008). While the predicted two-factor model was expected to include some items from the IT scale of the TEMPS-A, most likely within the depression-like factor, a separate factor of irritability was not anticipated. The small amount of variance explained by the irritability factor reduces the potential importance of this factor. That only one item loaded strongly on this factor further reduces the explanatory power that can be attributed to this factor. Nevertheless, the fact that a separate irritability factor emerged in an exploratory factor analysis of instruments measuring trait vulnerability to BD necessitates further discussion.
The emergence of a separate irritability factor suggests that this construct may not be adequately captured by the GBI instrument. Irritability is a prominent feature of depression and mania in many people with BD (Goodwin & Jamison, 2007). The GBI includes nine items (3, 14, 27, 29, 34, 39, 44, 53, 54) that are intended to measure irritability, most often in conjunction with other depressive mood descriptors. Only two of the items describe irritability in the context of hypo/manic mood patterns, while one item describes irritability in the context of cyclothymic mood patterns. It is possible therefore, that a weakness of the GBI is the inability to adequately capture irritability associated with hypo/manic and cyclothymic mood manifestations. The TEMPS-A achieves this aim, which results in items from the IT scale of this instrument emerging as a third factor in combined PCA of the two instruments.

A similar argument can be attributed to the emergence of the fourth factor in the six-factor solution from the combined PCA. The fourth factor was populated exclusively by HT items from the TEMPS-A, suggesting that the GBI may not adequately capture moods arising from a hyperthymic disposition. That the GBI does not capture hyperthymic moods is perhaps not surprising, given that the overarching aim of the instrument is to describe broadly distributed dimensions of mood that are associated with bipolarity. Subclinical hypo/manic moods, as described in the GBI, would appear to be more common amongst the general population. Hyperthymic moods may be less widely distributed, especially as the hyperthymic temperament appears to be a specific predictor of the less common, but more serious, variant of bipolar illness, BD-I (Koukopoulos et al., 2006). The clinical focus of the TEMPS-A parent instrument may mean that the hyperthymic construct is better captured in the TEMPS-A than the GBI. This argument however, must be considered in the context that relatively small amounts of variance were explained by Factors 3-6 (including the irritability and hyperthymia factors) in the six-factor solution.

No items from the GBI and TEMPS-A instruments describing the tendency to ‘mood lability’ were found to load strongly on either the hypo/mania or depression factors in either the three- or six-factor solution. This was despite the presence of numerous items describing this tendency on scales used in this study (e.g., TEMPS-CT;
GBI-Biphasia). The tendency to labile moods is commonly associated with BD (Evans et al., 2005; Mendlowicz et al., 2005; Solomon et al., 1996), and is particularly relevant to the BD-II variant (Akiskal, Kilzieh et al., 2006; Angst, Gamma, & Endrass, 2003; Hantouche & Akiskal, 2006). However, in the present study no mood lability items were found to be strongly associated with the hypo/mania or depression dimensions.

The two-factor surface structure of the GBI would appear to be most consistent with the latent factor structures described in the current investigation. Although three- and six-factor structures are not commonly associated with the GBI, the clear dominance of two latent factors – depression and hypo/mania – in both solutions suggests that this instrument provides the best balance of parsimony and heuristic utility for measuring vulnerability to BD. In addition to the strength of the first two factors in both solutions, items from the GBI dominated the item content of both factors. There were very few strong loading items on the depression and hypo/mania factors that were not from the GBI, further reinforcing the usefulness of this instrument. The strong psychometric properties of the GBI provide supplementary motivation for recommending this instrument for measuring vulnerability to BD. Finally, the Likert scoring method applied to the GBI lends itself to more precise measurement of dimensional constructs by allowing subtle variations in temperament and subjective experience to be assessed. This is something that the dichotomous response format of the TEMPS-A is unable to achieve with similar acuity.

Relationships between the GBI and TEMPS-A, and the instruments used for external correlation performed largely as expected. N correlated positively and strongly with the Depression scale of the GBI. N also correlated positively with the Hypo/mania scale of the GBI, but at a much lower level. The strongest predictors from the NEO-FFI of Total GBI score were N (positive), E (negative), A (negative), and C (negative). These findings are broadly consistent with those of Murray et al. (2007) who employed a similar sample and experimental design to that of the current study. Positive correlations between N and the CT, DT, IT, and AT scales of TEMPS-A were also supported by the data. Not surprisingly, the strongest positive correlation was found
between N and DT. Again, these findings were broadly consistent with previous research (Bloink et al., 2005).

The predicted relationships between E, GBI-Hypomania, and the HT scale of TEMPS-A were partially supported. E and HT were positively and moderately correlated as expected. The correlation between E and GBI-Hypomania however, was negative and small. We argue that such a relationship further reinforces the notion that the GBI instrument is not a good measure of the hyperthymia construct. The GBI is better suited to identifying subsyndromal cyclothymia and BD-II, manifestations of mood that include an element of instability. By extension, the GBI may not be suitable for measuring risk for BD-I, although (Depue et al., 1989) present some data to suggest that it can identify BD-I cases on a lifetime basis. The TEMPS-A instrument includes a better measure of hyperthymia and may be a more useful indicator of BD-I.

Intercorrelations between the GBI and TEMPS-A instruments also showed that the hyperthymia construct was not adequately captured by the GBI. Correlations between the HT scale and the Depression (negative) and Hypo/mania (positive) scales of the GBI were the lowest of all the correlations between these instruments. Indeed, the correlation between HT and Total GBI score was less than .10, and the only nonsignificant relationship out of 15 correlations between the various subscales of these instruments. Based on the results of the factor analysis it might also have been expected that the IT scale of TEMPS-A would not correlate strongly with the GBI. However, this was not the case.

The MDQ instrument and the ‘ups and downs’ item, both putative measures of vulnerability to BD-II specifically, correlated positively and strongly in the expected direction with the GBI and the CT scale of the TEMPS-A. These findings support relationships demonstrated in previous research (e.g., Bowen et al., 2006). In circumstances where there are no published data (i.e., to our knowledge there are no previous investigations of the relationship between ‘ups and downs’ and the CT scale of the TEMPS-A), the findings are consistent with expectations based on scale descriptors and item content.
Overall, investigation of the external correlates of vulnerability to BD support a trait conceptualisation that has separable, but correlated dimensions that are best described as hypo/manic- and depressive-like, respectively. Correlations of different magnitude between subscales of the GBI and the external correlates support the separable nature of the two dimensions. Specifically, differences in the magnitude of the relationships between the two dimensions and the traits of N and E from the NEO-FFI are instructive. Dimensions of irritability and, particularly, hyperthymia, deserve further scrutiny for their role in vulnerability to BD. Items describing the trait of hyperthymia may need to be added to the GBI, especially if the goal is to identify vulnerability to, and case history of, BD-I.

4.5.1 Limitations

The key findings of Study 1 must be considered in light of some limitations in the correlational design. Firstly, a high percentage of respondents received a positive diagnosis of hypo/manic history according to scores on the MDQ. Given the potential for temperamental scarring amongst these participants (Akiskal et al., 1983; Lewinsohn et al., 1981), it is possible that the overall findings may have been affected. When factor structures of the combined GBI and TEMPS-A were analysed separately for those with no history of hypo/mania, similar findings to those of the whole sample emerged. Nevertheless, a desirable improvement to the design would be to definitively exclude those with a history of hypo/mania. Although the MDQ has demonstrated excellent specificity in detecting BD history amongst nonclinical populations (Hirschfeld, Holzer et al., 2003), future studies may wish to employ a more comprehensive screening procedure (e.g., structured or semi-structured interview, or medical record review).

Closely related to this issue is the fact that current mental health status of respondents was not ascertained via the online questionnaire. With a relatively high proportion of respondents reporting previous experience of hypo/mania on the MDQ it was possible that some of these respondents were currently experiencing mood symptoms, which may have affected their responses. Previous studies have shown that
current depressive (Hirschfeld, Klerman, & Clayton, 1983) and manic states (Lumry, Gottesman, & Tuason, 1982) can influence scores on trait measures of personality, although the evidence is not conclusive (Costa, Bagby, Herbst, & McCrae, 2005; Santor, Bagby, & Joffe, 1997). In any case, recording of current mood episode status would have allowed the question of affective state-dependence on personality assessment to be addressed.

Several measures of trait vulnerability to BD were not included in the battery of questionnaires for Study 1. The Hypomanic Personality Scale (HPS; Eckblad & Chapman, 1986), a self-report measure of subsyndromal manic symptoms, was not used because it does not assess the depressive aspects of vulnerability to BD. Depression is the most common manifestation of BD, particularly at the less severe end of the bipolar spectrum (Judd, Akiskal, Schettler, Coryell, Endicott et al., 2003). It was important that subsyndromal manifestations of depression within the vulnerability to BD construct were adequately measured. It was for similar reasons that the Hypomania Checklist (HCL-32; Angst et al., 2005) was not used in Study 1.

Finally, counterbalancing of the order of presentation of the scales would have been a desirable addition to the methodology. Randomising the presentation order of the various psychometric scales used in Study 1 may reduce the possibility of response sets. Set responding due to fatigue and boredom may arise in long surveys, affecting in particular those scales that appear towards the end of the survey. The impact of response sets on data integrity in the current study was not assessed.

4.5.2 Conclusions and future directions

In conclusion, the two-factor structure of temperamental vulnerability to BD was tentatively supported in Study 1. Although the two-factor structure was only partially supported, it was the one most consistent with theory, and the one with the greatest level of heuristic utility. The GBI was shown to be the best measure of the highly correlated but separable dimensions of hypo/manic and depressive traits. The GBI contains many
of the necessary attributes as a tool for this purpose, particularly in research contexts where markers of hypo/manic and depressive tendencies are sought.

The length of the GBI, both in number of items and the long-winded descriptive nature of the items themselves, would seem to detract from its effectiveness as an assessment tool in clinical practice. Indeed, the unwieldy nature of the instrument was one of the motivations behind the construction of the 39-item TEMPS-A (Akiskal, Akiskal et al., 2005). An interesting future direction, given the GBI’s strong psychometric properties and sound theoretical construction, may be to create a brief version of the GBI based on the factor loadings found in Study 1. The psychometric performance of the briefer GBI could then be assessed against similar brief instruments such as the TEMPS-A and MDQ. A dedicated study aimed at developing a briefer version of the GBI is indicated and may permit application of the GBI in clinical settings to assist the process of BD diagnosis. Such a study is timely considering the current debate concerning the importance of recognising latent bipolarity amongst ‘apparently unipolar’ cases (e.g., Benazzi & Akiskal, 2008; Dunner, 2003).

4.6 Summary of Chapter 4

Investigation of two self-report instruments designed to measure temperamental vulnerability to BD found that both were psychometrically sound. The two-factor structure of the GBI and the five-factor structure of the TEMPS-A were both supported using PCA, and internal reliability was adequate for both instruments. The two-factor structure of the GBI, and the high correlation between dimensions of hypo/mania and depression on this instrument, appears to be particularly consistent with previous research and the two-dimensional theory of vulnerability to BD. The external correlates of both instruments, measured using the NEO-FFI, MDQ, and the ups and downs item, were also broadly consistent with theory and previous investigations.

Combined PCA of the GBI and TEMPS-A instruments revealed two large factors – one that can be described as hypo/mania and one that can be described as depression.
Items from the GBI dominated the content of both factors. Several smaller factors, in particular those describing irritable and hyperthymic tendencies, indicate that the TEMPS-A may add valuable information to the interpretation of GBI scores for identifying vulnerability to BD. Nevertheless, it was concluded that the two-dimension GBI provides the most psychometrically reliable, interpretable, and parsimonious measure of trait-like vulnerability to BD.
Chapter 5

Study 2: Actigraphic Correlates of Vulnerability to Bipolar Disorder

The aim of Study 2 was to investigate aspects of biological rhythm function in BD as potentially useful biomarkers of trait vulnerability to the disorder. Previous research has shown that biological rhythm disturbances can be found in those ‘at risk’ of disorder. Such findings underline the importance of quantitative trait and endophenotype approaches to the investigation of BD (5.1). Using the findings from Study 1 as justification, the GBI was used in the current study to identify levels of vulnerability to BD (5.2). Characteristics of circadian rhythm instability and sleep were derived from actigraphy to represent biological rhythm function, with three measured variables representing each process (5.3). Also in 5.3, the operationalisation of total daytime activity as a measure of BAS dysregulation is described. Total daytime activity was also measured using actigraphy. Cognitive style was investigated in order to build on the findings from Study 1 regarding the psychometric correlates of vulnerability to BD and further develop understanding of the trait vulnerability concept (5.5). Hypothesised relationships between circadian instability and sleep disruption, and increased vulnerability to BD were framed based on data from clinical BD samples (5.6). There were no predictions made regarding the relationships between vulnerability to BD, and total daytime activity or cognitive style. Hypothesis testing revealed a significant association between only one of the three circadian rhythm instability variables – the amplitude of the 24-hour activity rhythm – and greater vulnerability to BD (5.8). There were no significant associations between the sleep variables or the total daytime activity variable and vulnerability to BD. It was concluded that reduced amplitude of the 24-hour activity rhythm may be a useful biomarker of increased vulnerability to BD (5.9).
5.1 Background and Overview of Study 2

The endophenotype approach to the study of risk factors for psychiatric disorder involves the investigation of biological features that mediate the gap between genotypic vulnerability to disorder and phenotypic expression of disorder states. The approach assumes that the mediating features are less genetically complex than overall disorder genotypes, thus providing a means for decomposition of the factors that contribute to the phenotype into more manageable chunks (Bearden & Freimer, 2006; see also Section 4.1 above).

Biological rhythm disturbances have been investigated as candidate endophenotypes for BD. In Chapter 2, specifically Section 2.4.4, the evidence supporting a role for some of these biological rhythms in risk for BD was presented. Gene polymorphisms involved in circadian function are sometimes associated with the BD phenotype. Sleep disturbances and instability of the circadian system are sometimes found in populations at higher genetic risk of BD (e.g., healthy relatives of BD probands, well students with cyclothymic personality traits). While the evidence is limited at this stage, there is a growing body of data supportive of trait disturbances in biological rhythm function amongst those vulnerable to BD. The current study aimed to advance research in the field of biological rhythms and BD by investigating circadian rhythm instability and sleep disturbances in a non-clinical sample at varying degrees of risk for BD. In particular, non-invasive methods for measuring biological rhythm disturbances that are suitable for longitudinal, naturalistic study designs were used.

The investigative approach employed in Study 2 provided an additional benefit to the study of biological risk factors in BD. A prominent issue in such studies, and indeed in studies of many psychiatric illnesses, is the potential for the disease process to permanently alter the biological feature being investigated. For example, it is an open question as to whether sleep problems are characteristic of the years preceding the first episode of mania or depression. There is increasing evidence that sleep problems may precede the first-episode of mania or depression, however more evidence from longitudinal and prospective designs is needed (see Harvey et al., in press).
risk’ of BD, or does the onset of the illness cause difficulties in sleep. In particular, are there specific features that characterise the sleep behaviour of people who eventually develop BD? In studies of people already manifesting disorder states in BD questions such as these are difficult to answer due to the potential for changes in sleep caused by the onset of the illness. The quantitative trait approach to the description of BD adopted in Study 2 offers an alternative method of investigating biological risk factors associated with the disorder that is free of these potential complications.

5.2 Operationalisation of trait vulnerability to Bipolar Disorder in Study 2

In the current study, vulnerability to BD was operationalised from a continuous trait perspective. Vulnerability to BD was therefore defined as a quantitative trait distributed throughout the population (see Section 1.2.4). Using the outcomes of the exploratory factor analysis in Study 1, the two-dimension GBI (Depue et al., 1989) was determined to be the most parsimonious measure of trait-like vulnerability to the disorder. Although a continuous trait approach was used to operationalise vulnerability to BD, two extreme groups of high and low scorers on the GBI were ultimately used for hypothesis testing in order to maximise power in the study design (see Section 5.6.2.1 below for GBI scoring procedure).

5.3 Operationalisation of biological rhythm function in Study 2

The 24-hour activity rhythm was described in Chapter 3 as a feasible and informative biomarker of biological rhythm function for investigations under naturalistic conditions. Figure 4 showed that three output variables with direct relevance to the aims of the current project can be inferred from the 24-hour activity rhythm – circadian
instability, total daytime activity, and sleep. All three output variables are potential biomarkers of between- and within-subject vulnerability to BD. The operationalisation of each variable inferred from the 24-hour activity rhythm is described below.

5.3.1 Circadian rhythm instability

Circadian rhythm instability was operationalised using a nonparametric method of activity data analysis. Circadian data is commonly modeled using a 1-cycle-per-day, cosinor curve fitting technique (Nelson et al., 1979). However, modeling based on cosinor functions often provide a relatively poor fit when applied to activity data.16 The 24-hour pattern in activity appears to approximate more closely a square-like wave than a cosinor function. Van Someren et al. (1999) developed a nonparametric method of data analysis that does not rely on the assumptions associated with cosinor curve fitting (see also Van Someren et al., 1996). This method of activity data analysis has been applied across a wide range of populations, including patients with Alzheimer’s disease (Van Someren et al., 1999), healthy ageing populations (Huang et al., 2002), patients with seasonal affective disorder (Winkler, Pjrek, Konstantinidis et al., 2005), and patients with BD (Jones et al., 2005). For the present study nonparametric variables describing the 24-hour pattern in activity were used for hypothesis testing. Given the significant concerns regarding the suitability of cosinor model fitting to 24-hour activity data, these curve parameters were not used for hypothesis testing.

Three measures of circadian rhythm instability can be derived from the nonparametric technique described by Van Someren et al. (1999) – Relative Amplitude (RA), Intradianly Variability (IV), and Interdaily Stability (IS). RA describes the strength of the activity rhythm based on the difference between the most active 10-hour period (the period of 10 consecutive hours within the 24-hour day with the highest average

16 In the current study, preliminary model-fitting of activity data showed that the cosine function explained an average of only 15.07% (SD = 0.07%) of the variance in 24-hour activity patterns. The addition of a second-order harmonic explained, on average, 2.49% more variance (M = 17.56%, SD = 0.07%) in the 24-hour pattern. Visual inspection of the raw activity data confirmed the poor fit of a cosine function to 24-hour activity records.
level of activity; M10) and the least active 5-hour period (the period of 5 consecutive hours within the 24-hour day with the lowest average level of activity; L5), relative to an estimation of total activity (i.e., M10 + L5). A higher ratio indicates a stronger and more stable rhythm. The difference between M10 and L5 is expressed relative to an estimation of total activity in order to standardise between-person differences in activity levels. Individual preferences for different types of activities (e.g., running vs. playing chess) mean that standardised amplitude is a more valid reflection of activity rhythm strength. Vigorous types of exercise can increase the level of activity and amplify the raw amplitude independent of an improvement in rhythm strength and stability. The equation for computing RA is presented in Appendix C (see also Van Someren et al., 1999).

IV provides an indication of rhythm fragmentation, reflecting the frequency of rest/activity transitions in a given 24-hour period. It is calculated as the ratio of the mean squares of the difference between consecutive hours and the mean squares around the 24-hour mean. A higher IV ratio indicates greater rhythm fragmentation and reduced stability of the activity rhythm. The algorithm for computing IV is provided in Appendix C and is also available in the paper by Van Someren et al. (1999).

IS provides an indication of the strength of coupling between the activity rhythm and the presumed 24-hour exogenous zeitgeber pattern. It is calculated as the ratio between the variance of the average 24-hour pattern around the mean and the variance of the overall activity pattern across multiple days. A lower IS ratio indicates reduced stability in the activity rhythm. The computational algorithm for IS is also available in Appendix C and in the paper by Van Someren et al. (1999).

5.3.2 Sleep

Naturalistic, longitudinal investigations of sleep behaviour in BD commonly focus on three sleep variables – total sleep time (TST), sleep efficiency (SE), and wake after

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17 Note that M10 and L5 are presumed to represent periods of day and night, respectively, although there are no constraints placed on where these periods are located within the 24-hour pattern during analysis.
sleep onset (WASO). WASO is defined as the number of minutes spent awake after sleep onset and is expressed in minutes. TST is calculated as the total number of minutes spent asleep and is also expressed in minutes. SE is expressed as the percentage of minutes spent asleep during a given sleep period. A higher percentage indicates more time spent asleep during the sleep period. All three operationalisations of sleep were used in Study 2.

5.3.3 Total daytime activity

A single variable was used to measure total daytime activity. The 10 consecutive hours within the 24-hour day with the highest average level of activity (M10) provides an output variable that can be used to monitor changes in BAS activation. Higher levels of M10 are indicative of greater BAS activation and lower levels are indicative of reduced BAS activation. The M10 variable, also used in the computation of RA, was thus employed as a measure of BAS activation.

5.4 Summary of operationalised variables in Study 2

Contained in Figure 7 is a schematic representation of the relationships investigated in Study 2 between predictor (Vulnerability to BD) and outcome (Sleep, Circadian Rhythm Instability, Total Daytime Activity) variables, and how they were operationally defined.
5.5 Cognitive style correlates of vulnerability to Bipolar Disorder

In addition to the core purpose of Study 2, external correlates of trait vulnerability to BD were investigated. Specifically, cognitive styles were measured in order to

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Figure 7. Schematic representation of relationships between predictor and outcome variables in Study 2.
improve understanding of the vulnerability concept. Cognitive styles refer to the typical ways in which people perceive, interpret, and react to life events (Alloy, Bender, Wagner, Abramson, & Urosevic, 2009). The information on cognitive styles was used to build on the findings from Study 1 regarding the psychometric correlates of vulnerability to BD.

According to cognitive theories of BD, dysfunctional thought patterns and maladaptive cognitive schemas are commonly found amongst those with the disorder. Such dysfunctional and maladaptive cognitive styles appear to persist throughout the hypo/manic (Goldberg, Wenze, Welker, Steer, & Beck, 2005), depressive (Mansell, Colom, & Scott, 2005), and euthymic (Lam, Wright, & Smith, 2004) phases of the illness (see also Alloy, Reilly-Harrington, Fresco, Whitehouse, & Zechmeister, 1999). Cognitive factors have also been implicated in the longitudinal course of BD, with negative cognitive styles associated with greater chance of relapse (e.g., Scott & Pope, 2003). In addition to the dysfunctional cognitive styles amongst those already with BD, several studies have demonstrated similar patterns amongst those at putative risk of the disorder. Knowles, Tai, Christensen, and Bentall (2005) for example, showed that high temperamental risk of BD was associated with greater levels of dysfunctional cognitions. Carver and Johnson (2009) reported similar findings amongst their high risk group. Dysfunctional and maladaptive cognitive styles therefore appear to be stable characteristics of vulnerability to BD.

Specific cognitive styles that demonstrate particular significance for BD include perfectionism, autonomy, self-criticism, goal-striving, and approval seeking. Alloy, Abramson et al. (2009) for example, found that these dysfunctional styles were significantly more pervasive amongst individuals with bipolar spectrum disorders. They also found that such dysfunctional cognitive styles predicted the likelihood of hypo/manic and depressive onset over a 3-year period. The cognitive styles assumed to be most relevant to the BAS brain reward system were the strongest predictors of episode onset. The cognitive styles assumed to be most relevant to the BAS brain reward system were the strongest predictors of episode onset. Such findings support the BAS dysregulation theory of vulnerability to BD, and suggest a key role for this brain reward system in the longitudinal course of the disorder.
5.6 Research questions and hypotheses for Study 2

Instability of activity rhythms has been demonstrated in both euthymic and illness phases of BD (Jones et al., 2005; Salvatore et al., 2008; see Section 2.4 above). Ankers and Jones (2009) showed that unstable activity rhythm could also be found in a sample of well-participants at high-risk of BD. Based on these findings, it was predicted in the current study that high scorers on the GBI instrument (greater risk for BD) would display greater instability in their circadian activity patterns compared to low scorers (lower risk for BD). Group differences were expected to be reflected in lower amplitude (RA) and interdaily stability (IS), and higher intradaily variability (IV) amongst the ‘high risk’ group compared to the ‘low risk’ group.

Sleep disturbance also has demonstrated significance in trait vulnerability to BD (Harvey et al., 2006; Jones et al., 2006; see Section 2.4 above). In addition to these findings in clinical samples, general sleep disturbances have been demonstrated in student samples deemed to be at increased temperamental risk of BD (Ankers & Jones, 2009; Meyer & Maier, 2006). An alternative measure of trait vulnerability to BD was used in the current study in an attempt to replicate these findings. Therefore, it was expected that the ‘high risk’ group in the current study would display greater sleep disturbance than the ‘low risk’ group. Specifically, the ‘high risk’ group was expected to exhibit decreased sleep efficiency (SE) and increased wake after sleep onset (WASO). No predictions were made regarding total sleep time for which no between-subject predictions can be drawn from the literature.

Changes in daytime activity levels are prominent features of BD states (Mitchell et al., 2008; Salvatore et al., 2008; Serretti & Olgiati, 2005) as well as being potential predictors of relapse (Klein et al., 1992; see Section 2.5.3 above). The BAS dysregulation hypothesis of BD provides a neurobiological basis for considering the role of activity level changes in the episodic course of the disorder (Urosevic et al., 2008). It is unclear however, how this neurobiological hypothesis translates to the between-subject trait perspective. No specific predictions were made therefore, regarding day-
time activity level (M10) differences between the ‘high risk’ and ‘low risk’ groups in the current study.

5.7 Method for Study 2

5.7.1 Participants

A screening sample of 358 participants were recruited through advertising on University noticeboards and websites and through the Research Experience Program for first-year psychology students at Swinburne University of Technology in Melbourne, Australia. All participants completed a questionnaire from which criterion groups of high and low vulnerability to BD were identified (see Section 5.7.2.1). This subsample of 120 participants, consisting of 60 ‘High GBI’ and 60 ‘Low GBI’ individuals, were then assessed for adherence to the prescribed exclusion criteria.

Preliminary exclusion criteria included age (restricted to 18-30 years old only), not currently employed in a working environment that requires night-shift hours, and the absence of physical conditions that might impact on the measurement of locomotor activity. The latter two criteria were designed to limit compromises in data quality due to exogenous influences on activity patterns, while restricting the age range of participants allowed greater control over age-related changes in sleep behaviour and circadian activity patterns (Huang et al., 2002). Seventy-eight participants met inclusion criteria and were invited to attend a series of information and screening sessions. Prior to screening, five participants withdrew from the study due to changes in their personal circumstances and, after screening to exclude participants with a past history of mania (screening procedure described below), a final sample of 72 participants were invited into, and agreed to participate in, the study proper.\(^\text{18}\)

Current depressive and/or hypo/manic symptomatology was also an exclusion criterion. No participants accepted into the study proper showed evidence of current

\(^\text{18}\) One participant (female, 23 years-old) was excluded from further participation in the study due to a previous manic episode reported on the CIDI-Auto.
depressive and/or hypo/manic diagnostic indicators based on responses to the Composite International Diagnostic Inventory (CIDI-Auto; Robins et al., 1988).

Participants’ history of clinically-relevant mood episodes was also assessed, with hypo/manic history an exclusion criterion. It has been suggested that manic episodes can have neuropsychological ‘scarring’ effects in people with mood disorders, potentially causing relatively stable changes in associated temperaments (Akiskal et al., 1983). A well population with no history of mania can be assumed to provide a more pure measure of subaffective temperament, with no complications arising due to ‘scarring’ from previous episodes. MDE history was not an exclusion criteria in Study 2 because a balance was sought between generating a sample unscarred by previous mood episodes and the goal of generating a sample exhibiting an adequate range of temperamental vulnerability to BD. Based on previous studies, MDE history was expected to be more common in participants with elevated vulnerability to BD (Cassano et al., 2004). Excluding all participants who reported a previous MDE may therefore have severely limited the temperamental heterogeneity of the sample.

5.7.2 Materials and equipment

5.7.2.1 Self-report instruments

Hypo/manic and depressive tendencies were measured on the GBI (Depue et al., 1989). Scoring and administration of the GBI was identical to that described in Study 1 and these details are not repeated here. The strategy used for identifying High GBI and Low GBI groups in the current study was based on Total GBI score, incorporating scores on both the hypomanic and depressive subscales of the GBI measure. High and low scores for Total GBI score were used to identify High GBI and Low GBI group participants, respectively.

The Big Five personality dimensions were measured using the Australian Personality Inventory (API; Murray, Judd et al., 2009). The 50-item API has been shown to have adequate psychometric properties and high convergent correlations with
NEO-FFI domain scores (Murray, Judd et al.). The Big Five personality dimension scores derived from the API are therefore considered to be conceptually equivalent to the dimensions of the NEO-FFI and, like the NEO-FFI, provides separate scores for the N, E, O, A, and C dimensions. The API was used for the purpose of providing corroborating evidence for Study 1 regarding external correlations of vulnerability to BD using the GBI.

The TEMPS-A (Akiskal, Akiskal et al., 2005) was used to assess the temperamental characteristics of study participants. Scoring and administration of the TEMPS-A was identical to that used in Study 1 and these details are not repeated here. Associations between GBI scores and TEMPS-A scores in the current study were evaluated for their consistency with those found in Study 1. Similarly, the MDQ (Hirschfeld et al., 2000) and ‘ups and downs’ (Angst, Gamma, & Endrass, 2003) instruments were measured for their consistency with the findings of Study 1.

Two self-report instruments were used to assess the cognitive style correlates of vulnerability to BD – the Dysfunctional Attitudes Scale – 24-item version (DAS-24; Power et al., 1994) and the Young Schema Questionnaire – Short Form (YSQ-SF; Young, 1998). Both instruments draw heavily from Beck’s (1972) cognitive model of depression and are designed to identify maladaptive assumptions and schemas proposed to underlie cognitive vulnerability to mood disorder.

The DAS-24 (Power et al., 1994) is a subscaled version of the original DAS developed by Weissman and Beck (1978). It is a shorter, 24-item, 3-subscale version (Achievement, Dependency, Self-control) that includes items from both Form A and Form B of the original 40-item DAS instrument. The new version is psychometrically sound and shows a theoretically consistent 3-factor structure using confirmatory factor analysis. The 3-factor structure of the DAS-24 was supported in a large sample of BD-I and MDD outpatients (Lam et al., 2004). The 24-item, subscaled version of the DAS was used in this study. Responses to the DAS-24 were made on a 7-point Likert scale ranging from “Totally disagree” to “Totally agree”.

The YSQ-SF is a 75-item version of the original YSQ (Young, 1994). The instrument measures cognitive vulnerability to depression on 15 subscales (one less than
the full YSQ. Sample subscales from the YSQ include Abandonment, Social Undesirability, and Emotional Inhibition. Items from each subscale are measured on a 6-point Likert scale ranging from “Completely untrue of me” to “Describes me perfectly”. The YSQ-SF has shown comparable reliability and validity with the original YSQ in both clinical and nonclinical populations (Stopa, Thorne, Waters, & Preston, 2001; Waller, Meyer, & Ohanian, 2001). Adequate internal consistency has also been shown in a range of populations and cultures (Baranoff, Oei, Cho, & Kwon, 2006) and the factor structure of the instrument is typically strong, although slight variation in the number of derived factors is evident in some studies (e.g., Baranoff et al., 2006).

Participants’ current mood disorder status and history of clinically relevant mood episodes were evaluated using the CIDI-Auto, a computerised version of the original CIDI (Robins et al., 1988). The CIDI provides a valid and reliable diagnosis of mood disorder based on DSM-IV and ICD-10 criteria. Validation studies of the CIDI-Auto have reported adequate sensitivity (range .39-.92) and specificity (range .67-.91; Komiti et al., 2001; Peters & Andrews, 1995) for MDE diagnoses. While no studies have reported the validity of the CIDI-Auto in diagnosing hypomania or mania, the interviewer administered CIDI has been shown to display high diagnostic concordance with the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) for BD (Kessler et al., 2006). Adequate sensitivity (range .41-.79) and excellent specificity (range .99-1.00) in diagnosing BD was also apparent in this large validation study involving over 9,000 community-dwelling respondents.

5.7.2.2 24-hour activity rhythm

The 24-hour activity rhythm was measured via actigraphic monitoring of locomotor activity. The actigraph employed in the current study was the Respironics/Mini-Mitter Actiwatch-L (Respironics, Inc., Bend, Oregon) and activity data was uploaded using the Respironics/Mini-Mitter ActiReader device (Respironics, Inc., Bend, Oregon). The software program Actiware 5.0 (Respironics, Inc., Bend, Oregon) was used to view and analyse the activity data. Actiwatches were configured to record movements in 1-minute
epochs. Sleep-wake transitions were operationalised using the criterion that epochs with an average activity count of 41 or more (based on the current epoch and the two immediately before and two immediately after) were scored as awake and those below this cut-off were scored as sleep.

The actigraph can be placed on multiple parts of the body (e.g., ankle, torso) if activity levels across different planes of movement are sought. Multi-site applications of actigraphy reveal moderate correlations for activity level across multiple body sites (Middelkoop, Van Dam, Smilde-Van Den Doel, & Van Dijk, 1997). Attachment to the non-dominant wrist however, is the most common site for activity-based measurement (Middelkoop et al., 1997), and this was the methodology employed here.

5.7.3 Procedure

Participants selected for the study proper completed a questionnaire including the API, TEMPS-A, DAS-24, YSQ-SF, MDQ, and the ups and downs item in small groups of 8-10. The computerised CIDI-Auto was also completed by participants at this session. Training in use and care of the Actiwatch was given and participants were booked into a trial. Trials consisted of 8-10 participants balanced for group (High GBI or Low GBI) with each trial running for 7 consecutive days. Participants were instructed to wear the Actiwatch continuously throughout the 7-day protocol, removing it only when there was the possibility of damage to the device (e.g., contact sports).

5.7.4 Data preparation and analysis

5.7.4.1 Self-report instruments

Questionnaire data were entered into SPSS 17.0 for Windows (SPSS, Inc., Chicago, Illinois) for statistical analysis. Five missing values on the API and seven missing values on the YSQ-SF, representing less than 0.01% of all possible responses on each measure,
were replaced with the series mean of their respective subscale dimensions. There were no missing values on the GBI, TEMPS-A, or DAS-24 scales. There were also no extreme outliers (i.e., values greater than 3 times outside the interquartile range of the standard boxplot) on any scales. Distribution of scores was normal for all scales, except for the CT, DT, IT, and AT scales of the TEMPS-A which were all positively skewed. Transformation of scores using square root and logarithmic functions did not improve the shape of the distribution for any variables. Raw scores were thus used for all group comparison procedures. T-tests are reasonably robust with respect to violations of the normality assumption, especially in large enough sample sizes (e.g., > 30 cases; Gravetter & Wallnau, 2000). Nevertheless, the consequences of violating the normality assumption in t-tests are duly acknowledged in the outcomes of these statistical procedures.

5.7.4.2 24-hour activity rhythm

Activity records were screened for missing data and spurious recordings. Missing data exclusion criteria were based on Van Someren et al. (1999) who recommend that periods over 60 minutes without movement, even during sleep, are extremely unlikely to occur naturally. They further recommend that the entire 24-hour period within which the missing data is found be excluded from further analysis. A total of 29 days of data were excluded from the next stage of analysis, equivalent to 4.9% of total possible days of data, using the Van Someren et al. criteria. The average length of missing data periods across the entire sample was 251 minutes, with the smallest period of missing data being 61 minutes. Two actigraph records had extensive missing data for more than three out of seven days of recording. The extent of missing data meant that the entire actigraph records of these two participants were excluded from further analysis, leaving a sample of \( N = 70 \) for the analysis of the 24-hour activity rhythm. No obviously spurious recordings appearing outside the realistic range of possible activity values were identified in the remaining activity records.
The distribution of scores for the IV, IS, and M10 variables were normal or near normal. The distribution of scores for the RA variable was negatively skewed. An extreme univariate outlier was present in the RA data series (case number 48; RA = 0.46). This value was replaced with the mean of RA (0.84) for the High GBI group to which the case belonged. The distribution of scores remained negatively skewed so a reflected log transformation was applied. The distribution of the transformed variable was closer to normal. However, there was no difference in the outcome of the t-tests comparing the High GBI and Low GBI groups on raw and transformed RA variables so the raw data was used in all analyses reported here.

The distribution of scores on the TST and WASO variables was normal or near normal. The distribution of scores on the SE variable was negatively skewed. An extreme outlier in the SE variable (case number 4 with an SE value of 57.13) was replaced with the mean of the Low GBI group (77.54) to which this participant belonged, however the negative skew of the distribution remained. A log transformation of the reflected raw data produced a distribution closer to normal. There was no substantial difference in the outcome of the t-tests comparing the High GBI and Low GBI groups on SE for both raw and log transformed data so the raw data was used in all subsequent analyses.

5.8 Results for Study 2

5.8.1 Sample characteristics

The screening sample consisted of 358 participants (age $M = 22.3$, $SD = 4.5$; 72.9% female). Table 10 presents the mean GBI scale scores for the screening sample. Data pertaining to the psychometric performance of the GBI are also presented for comparison purposes with previous investigations.
Table 10

Means, Standard Deviations, Range of Scores, and Scale Characteristics for the GBI at the Screening Phase

<table>
<thead>
<tr>
<th>GBI Score</th>
<th>Likert scoring</th>
<th>Case scoring</th>
<th>α coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hyp Dep Total</td>
<td>Hyp Dep Total</td>
<td></td>
</tr>
<tr>
<td>358</td>
<td>18.1 33.9 52.0</td>
<td>0-27 0-46 0-72</td>
<td>.94 .97 .98</td>
</tr>
<tr>
<td></td>
<td>(13.9) (25.6) (37.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Hyp = GBI Hypomania subscale score, Dep = GBI Depression subscale score, Total = GBI Total scale score.

Scores on the GBI in this sample were comparable to those reported by Murray et al. (2007), the only other published investigation to employ a dimensional scoring strategy in a nonclinical population. Murray et al. reported mean scores of 15.0 (SD = 12.7), 29.8 (SD = 24.2), and 44.7 (SD = 35.4), for the GBI Hypomania, GBI Depression, and GBI Total scale scores, respectively. The range of case scores on each dimension of the GBI in the present study were also consistent with those reported previously by Depue and Klein (1988; 0-26, 0-42, and 0-68, for the GBI Hypomania, GBI Depression, and GBI Total scale scores, respectively). Cronbach alpha coefficients for the three scales of the GBI indicate excellent internal consistency in the data. These figures also compared favourably with those quoted by Depue and Klein, who reported alpha reliability statistics of 0.89, 0.95 and 0.96 for the scales of GBI Hypomania, GBI Depression, and GBI Total score, respectively.

The post-screening sample consisted of 72 participants. Thirty-six participants formed the ‘High GBI’ group (age M = 22.3, SD = 2.9; 69% female) and the remaining 36 participants formed the ‘Low GBI’ group (age M = 21.0, SD = 2.3, 75% female). The age difference between the groups was significant; t (70) = 2.01, p = .048. The group difference in gender balance was not significant according to the Pearson Chi-square
value (incorporating Yates’ Correction for Continuity for a 2 x 2 analysis); \( \chi^2 \) (1, 72) = 0.27, \( p = .60 \).

GBI score was the key criterion measure for the allocation of participants to High and Low GBI groups. As intended, the difference in mean total GBI score between the two groups (\( M = 108.0, SD = 26.4; M = 10.4, SD = 6.2 \); for the High GBI and Low GBI groups, respectively) was significant according to an independent groups t-test; \( t (70) = 21.59, p < .001 \). Figure 8 displays the distribution of GBI case scores for the two groups as a function of the hypomanic and depressive dimensions of the GBI. Data is presented graphically in the form of case scores to permit comparison with previous investigations (Depue & Klein, 1988). The distribution of GBI case scores for those not selected for the study proper, including those who did not meet inclusion criteria, are also represented in Figure 8. A clear delineation between the High GBI and Low GBI groups can be observed. The High GBI group showed a greater level of heterogeneity in terms of GBI dimension scores.\(^{19} \) The strong relationship between the two dimensions of the GBI was indicated by the linear distribution of scores (\( r = .83, p < .001 \)). This distribution of scores compares favourably with the distribution of GBI scores for the nonclinical group in Depue and Klein (1988).

\(^{19} \) Note that due to the low heterogeneity of GBI dimension scores in the Low GBI group it is not possible to label all participants’ scores in Figure 4. Therefore, for the Low GBI group, one ‘dot’ or label may represent several individual scores.
Figure 8. Distribution of GBI case scores as a function of the hypomanic and depressive dimensions for the High-GBI group (Hi), Low-GBI group (Lo), and participants not selected for the study proper (no label).

As expected, MDE history was significantly different between the two criterion groups ($\chi^2 = 14.66, p < .001$, odds ratio = 13.6, Cohen’s $d = 1.44$). A significantly greater proportion of the High GBI group (44%) reported a positive lifetime history of MDE’s than the Low GBI group (6%), as shown in Table 11.
Table 11

Crosstabulation of Group by History of MDE

<table>
<thead>
<tr>
<th></th>
<th>Positive history</th>
<th>Negative history</th>
</tr>
</thead>
<tbody>
<tr>
<td>High GBI</td>
<td>16 (44%)</td>
<td>20 (56%)</td>
</tr>
<tr>
<td>Low GBI</td>
<td>2 (6%)</td>
<td>34 (94%)</td>
</tr>
</tbody>
</table>

Note. Positive history = at least one MDE, Negative history = no MDE.

Self-reported history of hypo/manic behaviour, as assessed by the MDQ, was also significantly different between the two groups ($M = 10.0, SD = 1.9; M = 3.5, SD = 2.4$, for the High and Low GBI groups, respectively; $t (70) = 12.77, p < .001, d = 3.00$), as was self-reported ‘ups and downs’ ($\chi^2 = 43.11, p < .001$, odds ratio = 80.5, Cohen’s $d = 2.42$). In raw data terms, 29 of the High GBI participants (82.9%) endorsed the ‘ups and downs’ item compared to two of the Low GBI participants (5.6%). One participant in the High GBI group failed to respond to the ‘ups and downs’ item. Significant differences in personality and temperament between the High and Low GBI groups were also apparent.

Table 13 presents the mean API and TEMPS-A scores for the two groups. It shows that the High GBI group reported significantly higher levels of N ($t(70) = 7.43, p < .001, d = 1.74$), and significantly lower levels of A ($t(70) = 4.96, p < .001, d = 1.17$) than the Low GBI group on the API. No significant differences between the two groups on the dimensions of E, O, and C were found. There were significant differences between the two groups on the CT ($t(70) = 12.40, p < .001, d = 2.96$), DT ($t(70) = 4.93, p < .001, d = 1.11$), IT ($t(70) = 5.37, p < .001, d = 1.26$), and AT ($t(70) = 4.38, p < .001, d = 1.16$) subscales of the TEMPS-A. The High GBI group reported higher mean scores on all subscales. No significant group differences were found on the HT subscale.
### Table 12

**Distribution of Scores on the API and TEMPS-A Scales for the High GBI and Low GBI Groups**

<table>
<thead>
<tr>
<th></th>
<th>High GBI</th>
<th>Low GBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>M (SD)</em></td>
<td><em>M (SD)</em></td>
</tr>
<tr>
<td><strong>API†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N*</td>
<td>31.8 (5.9)</td>
<td>21.6 (5.8)</td>
</tr>
<tr>
<td>E</td>
<td>32.1 (7.1)</td>
<td>33.4 (6.8)</td>
</tr>
<tr>
<td>O</td>
<td>35.4 (6.1)</td>
<td>36.3 (5.5)</td>
</tr>
<tr>
<td>A*</td>
<td>32.8 (6.6)</td>
<td>39.4 (4.5)</td>
</tr>
<tr>
<td>C</td>
<td>31.3 (6.2)</td>
<td>34.9 (7.4)</td>
</tr>
<tr>
<td><strong>TEMPS-A††</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT*</td>
<td>2.4 (2.1)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td>CT*</td>
<td>6.8 (2.5)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td>HT</td>
<td>3.2 (2.4)</td>
<td>2.3 (1.8)</td>
</tr>
<tr>
<td>IT*</td>
<td>2.2 (1.7)</td>
<td>0.6 (0.6)</td>
</tr>
<tr>
<td>AT*</td>
<td>1.4 (1.0)</td>
<td>0.4 (0.7)</td>
</tr>
</tbody>
</table>

*Note. API = Australian Personality Inventory, TEMPS-A = Temperaments Autoquestionnaire.

n = 36 for both groups

† unequal variances for comparisons on A; df adjusted accordingly

†† unequal variances for comparisons on DT, CT, IT, and AT; df adjusted accordingly

* p < .001 (Bonferroni-adjusted for multiple comparisons).

Table 13 presents mean scores for each group on the cognitive style scales – schemas (YSQ) and attitudes (DAS-24). Significant differences were apparent between the two groups on the YSQ (t(70) = 6.66, p < .001, d = 1.58) and the DAS-24 (t(70) = 6.44, p < .001, d = 1.52). The High-GBI group reported higher mean scores on both scales, indicating greater prevalence of maladaptive schemas and dysfunctional attitudes in this group. Mean scores for individual subscales of the YSQ and the DAS-24 are available in Appendix D.
Table 13

*Distribution of Scores on the YSQ and DAS-24 Scales for the High GBI and Low GBI Groups*

<table>
<thead>
<tr>
<th></th>
<th>High GBI</th>
<th>Low GBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Schemas (YSQ) Total score*</td>
<td>3.0 (0.8)</td>
<td>1.9 (0.5)</td>
</tr>
<tr>
<td>Attitudes (DAS-24) Total score*</td>
<td>107.6 (20.3)</td>
<td>80.7 (14.6)</td>
</tr>
</tbody>
</table>

*Note. YSQ = Young Schema Questionnaire – short form (score is presented as average score per item), DAS-24 = Dysfunctional Attitudes Scale, 24-item version.

n = 36 for both groups

† unequal variances for comparisons on this scale; df adjusted accordingly

* p < .001.

5.8.2 Circadian rhythm instability

Average scores on the three outcome variables of circadian rhythm instability were compared across the two groups of High GBI and Low GBI participants. Correlations between the three outcome variables were also computed, and ranged from low for the relationship between IS and IV (r = -.17, ns) to high for the relationship between IS and RA (r = .63, p < .01). The relationship between IV and RA was low-moderate in strength (r = -.30, p < .05). Mean scores on the IS, IV, and RA variables for the High GBI and Low GBI groups are presented in Table 14. RA of the 24-hour activity rhythm is significantly lower in the High GBI group than the Low GBI group, t (68) = 3.27, p < .01. The size of the effect is medium-high (d = 0.70). IS was lower, and IV was higher in the High GBI group compared to the Low GBI group, both differences emerging in the expected direction. However, these differences on IS and IV were not statistically significant.
Table 14

Means and Standard Deviations for the High GBI and Low GBI Groups on the Circadian Rhythm Instability Variables

<table>
<thead>
<tr>
<th></th>
<th>High GBI M (SD)</th>
<th>Low GBI M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS</td>
<td>.49 (.11)</td>
<td>.53 (.12)</td>
</tr>
<tr>
<td>IV</td>
<td>.86 (.29)</td>
<td>.77 (.23)</td>
</tr>
<tr>
<td>RA†*</td>
<td>.84 (.10)</td>
<td>.90 (.07)</td>
</tr>
</tbody>
</table>

Note. IS = interdaily stability, IV = intradaily variability, RA = relative amplitude. 

$n = 35$ for both groups 

† unequal variances for comparisons on this variable; $df$ adjusted accordingly 

* $p < .017$ (Bonferroni-adjusted for three comparisons)

History of MDEs, self-reported via the CIDI-Auto diagnostic process, permitted post hoc analyses of the relationship between MDE history and RA, the only circadian rhythm instability variable to show significant between-group differences. Four groups were created in order of presumed vulnerability to BD: i) High GBI group, positive MDE history ($n = 16$), ii) High GBI group, negative MDE history ($n = 19$), iii) Low GBI group, positive MDE history ($n = 2$), iv) Low GBI group, negative MDE history ($n = 33$). Mean RA was computed for each group and this data is presented in Figure 9. Group 1 (High GBI with positive MDE history, and the highest presumed vulnerability to BD) had the lowest mean RA, while Group 4 (Low GBI with negative MDE history, and the lowest presumed vulnerability to BD) had the highest mean RA. Using ANOVA, a significant linear trend was evident ($contrast estimate = .084, p < .005$) indicating that RA decreased with increasing vulnerability to BD.
Figure 9. Mean RA for the four groups presented in order of presumed vulnerability to BD.

A post hoc investigation of correlations between GBI scores and the RA variable was also conducted. The full range of dimensional scores on the GBI are represented in a correlational analysis, and exploit the sensitivity of the measure to a wide range of affective intensities. A correlational analysis may provide greater detail regarding the relationship between RA and vulnerability to BD. The strongest relationship was found between RA and GBI Hypomania ($r = -.36, p < .01$). Significant relationships were also found between RA, and GBI Total score and GBI Depression score ($r = -.31, p < .01$ and $r = -.28, p < .05$, respectively). Thus, for the RA variable, the negative relationship was stronger with the GBI Hypomania scale than the GBI Depression scale. The difference in strength of this relationship was not significant however, according to a
comparison of dependent correlation coefficients (Cohen & Cohen, 1983); \( t (67) = -0.45, \text{ns.} \)

### 5.8.3 Sleep

Average scores on the TST, SE, and WASO sleep variables were compared across the two groups of High GBI and Low GBI participants. Table 15 presents means and standard deviations for the High GBI and Low GBI groups on these sleep variables. Between group differences were not significant for any of the variables. Therefore, there was no relationship between trait vulnerability to BD and sleep characteristics in this sample.

Table 15

**Means and Standard Deviations for the High GBI and Low GBI groups on the Sleep Variables**

<table>
<thead>
<tr>
<th></th>
<th>High GBI</th>
<th>Low GBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M (SD) )</td>
<td>( M (SD) )</td>
</tr>
<tr>
<td>TST</td>
<td>495.83 (78.41)</td>
<td>514.39 (75.12)</td>
</tr>
<tr>
<td>SE</td>
<td>77.79 (5.82)</td>
<td>77.54 (6.40)</td>
</tr>
<tr>
<td>WASO</td>
<td>59.55 (22.23)</td>
<td>61.95 (22.13)</td>
</tr>
</tbody>
</table>

*Note.* TST = total sleep time in minutes, SE = sleep efficiency, WASO = wake after sleep onset.

\( n = 35 \) for both groups

### 5.8.4 Total daytime activity

Average scores on the M10 Total Daytime Activity variable were also compared across the two groups of High GBI (\( M = 404.96, SD = 125.14 \)) and Low GBI (\( M = 415.86, SD = 110.88 \)) participants. The difference in mean scores between the two
groups was not significant. Therefore, there was no relationship between trait vulnerability to BD and Total Daytime Activity in this sample.

5.9 Discussion for Study 2

The aim of Study 2 was to investigate biological rhythm function amongst a group of well individuals separated into criterion groups of high and low vulnerability to BD. It was predicted that the higher vulnerability group, selected because they had higher scores on a measure of hypo/manic and depressive temperaments (High GBI), would exhibit reduced circadian rhythm stability than a lower vulnerability group (Low GBI). Group differences in sleep variables were also expected. Predicted outcomes, primarily based on data from clinical groups, were that the High GBI group would exhibit decreased sleep efficiency, and increased wake after sleep onset, compared to the Low GBI group. The total amount of sleep time was not expected to differ between the groups. Finally, daytime activity level was investigated as a potential correlate of vulnerability to BD, however there were no specific predictions regarding between-group differences for this variable in the current study.

Prior to discussing the key findings relating to hypothesis testing in Study 2, a brief diversion is made to discuss the findings relating to cognitive style and other correlates of vulnerability to BD. These constructs were investigated with the intention of developing further understanding of the trait vulnerability concept in BD. As such, the findings provide important background information on trait vulnerability to BD, even though the data was not part of hypothesis testing in Study 2.
5.9.1 Cognitive style and other correlates of trait vulnerability to Bipolar Disorder

The self-reported cognitive styles of participants in the current study were consistent with expectations. The High GBI group reported greater levels of dysfunctional thought patterns and maladaptive cognitive schemas than the Low GBI group. The group differences were apparent for total scores on the two cognitive style instruments, as well as their subscales (see Appendix D). Trait vulnerability to BD therefore appears to include an element of dysfunctional cognitive style that has much in common with the cognitive styles in those who have been diagnosed with the disorder. These findings provide further evidence in support of a continuum of vulnerability to BD, as discussed extensively in Study 1.

Consistency amongst the between-group findings of Study 2 and the correlational findings of Study 1 for the personality and temperament variables was also apparent. In particular, Neuroticism was found to be significantly higher, and Agreeableness significantly lower, in the High GBI group of the current study, supporting the correlations found in Study 1. Levels of Extraversion for the High GBI group in Study 2 were not significantly higher than those for the Low GBI group, as might have been expected from the correlational findings in Study 1. Significant group differences for the Cyclothymic, Dysthymic, Irritable, and Anxious temperaments were found in Study 2, supporting the correlations found in Study 1. Also supporting the correlations from Study 1 was the lack of significant group differences on the Hyperthymic temperament variable in Study 2. This outcome would appear to be consistent with a key finding of Study 1 – that the hyperthymic temperament may not be adequately captured by the GBI.
5.9.2 Circadian rhythm instability

Three variables were used to test the prediction that circadian rhythm instability would be associated with vulnerability to BD. The relative amplitude (RA) of the 24-hour activity rhythm was the only variable to show group differences, with the High GBI group having a significantly lower relative amplitude than the Low GBI group. A lower amplitude may indicate reduced stability in the circadian component of the 24-hour activity rhythm. A higher amplitude equates to greater differentiation in activity levels between day (M10) and night (L5), thus indicating stronger adherence to a stable 24-hour pattern of sleep and wake and, by implication, stronger association with the 24-hour light/dark schedule.

There were no between-group differences on the alternative measures of activity rhythm instability – interdaily stability (IS) and intradaily variability (IV). Although mean differences between the High GBI and Low GBI groups emerged in the expected direction, hypothesis testing of the group differences was not statistically significant. This part of the hypothesis for relationships between circadian rhythm instability and trait vulnerability to BD was therefore not supported.

There appears to be something specific to the RA variable that allows differences in activity rhythm stability between groups at higher and lower levels of trait vulnerability to BD to become apparent. The RA variable is calculated as the ratio between M10 and L5. Given that there were no differences in M10 between the two groups, but a trend towards group differences on the L5 variable (High GBI group higher; $t(68) = 2.58, p = .03$, $\alpha$ adjusted for multiple comparisons), it is proposed that the primary source of variation in the relative amplitude of the 24-hour activity rhythm is L5. As such, higher activity levels during the least active part of the day (presumed to be at night-time and occurring during the sleep period) reduce the average amplitude for the High GBI group. Vulnerability to BD therefore, may be associated with a shift in a proportion of activity from the day to the night, and this becomes significant when it is observed in the RA variable. The IS and IV variables, which do not incorporate L5 into their computation, are unable to reflect this ‘shifting’ of activity level data.
A post hoc analysis of mean RA amongst four independent groups of study participants arranged in descending order of presumed vulnerability to BD showed a significant linear trend (see Figure 9). RA appeared therefore to decrease with increasing vulnerability to BD in a linear fashion, supporting the circadian instability hypothesis in the current sample.

Although the design of Study 2 is unique amongst the relevant literature, the findings appear to be broadly consistent with those of a previous study that most closely resembles this study’s naturalistic design. Jones et al. (2005) reported significant differences in the stability (IS) and variability (IV) of the 24-hour activity rhythm between a group of outpatients with BD and a comparison group of age- and gender-matched non-psychiatric controls. The outpatient group exhibited a less stable pattern of 24-hour activity across days, and a more variable within-day activity pattern than their control group counterparts. There were no significant between-group differences however, in the relative amplitude of the 24-hour activity rhythm in their study. The findings of Jones et al. therefore, are somewhat different to those of Study 2 in which amplitude was the only 24-hour activity rhythm variable to show significant between-group differences. Nevertheless, it would appear that there is accumulating evidence of trait differences in 24-hour activity rhythm stability between ‘high BD risk’ groups and ‘low BD risk’ groups, regardless of between study variations in the locus of specific differences.20 The linear relationship observed between increasing levels of vulnerability to BD and attenuation of 24-hour activity rhythm amplitude shown in Study 2 provided particularly strong support for this potentially important relationship.

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20 The findings of a more recent study investigating relationships between the stability of the 24-hour activity rhythm and trait vulnerability to BD were more consistent with those of Study 2. Ankers and Jones (2009) found significantly reduced RA in their group of students at behavioural high-risk of hypomania, compared to a group of low-risk participants. Refer to the general discussion section of the current thesis for a more detailed discussion of their findings.
5.9.3 Sleep

Predicted associations between the sleep variables and vulnerability to BD were not found. Specifically, there were no group differences on measures of sleep efficiency (SE) and minutes of wake after sleep onset (WASO). Significant group differences were also not found for total sleep time (TST), although no predictions were made regarding this variable. The data therefore do not support the general sleep disturbances often observed in clinical BD populations across all phases of the illness, including euthymia, and in those deemed to be ‘at risk’ of BD. The data however is consistent with that of Jones et al. (2005) who found no significant between-group differences in sleep for their sample of outpatients with BD and matched controls. Two further studies have also shown no differences on sleep variables between outpatients with BD and healthy controls. Harvey et al. (2005) showed that objectively-measured sleep (specifically, sleep onset latency and wake after sleep onset) was not significantly different between groups of BD outpatients, insomnia patients (poor sleepers), and a control group of healthy good sleepers. Millar et al. (2004) showed that wake after sleep onset, sleep efficiency, and sleep onset latency were not significantly different between a group of BD outpatients and a comparison group of age- and gender-matched controls. There is evidence therefore, that sleep monitored using actigraphy (as used in the current study as well as in the studies of Harvey et al., 2005; Jones et al., 2005; Millar et al., 2004) is not significantly different between groups at varying risk of BD. Interestingly, Ankers and Jones (2009) demonstrated greater variability in sleep duration, fragmentation, and efficiency in their sample of high-risk participants compared to their low-risk group. The implications of these mixed findings for the monitoring of sleep using actigraphy are considered in further detail in Section 5.9.5.

In both the Harvey et al. (2005) and Millar et al. (2004) studies, stronger group differences in subjective sleep estimates were reported. Self-reported sleep quality was lower in the BD groups of both studies, contradicting the null findings reported for the sleep variables recorded using actigraphy. Self-reports of sleep quality were not obtained from participants in the current study, so the relationship between vulnerability
to BD and subjective evaluations of sleep quality could not be addressed. Future studies should include a subjective measure of sleep quality in their design. The findings of Harvey et al. and Millar et al. indicate that there may be a deficit in the cognitive representation of sleep amongst some BD outpatients. Cognitive behaviour therapy for insomnia and other sleep difficulties may therefore be potentially effective adjunct therapies to usual psychological treatment for BD (see Harvey et al., in press).

5.9.4 Total daytime activity

There were no differences in daytime activity level between the High GBI and Low GBI groups in the current study. Group differences at the trait level of vulnerability to BD were investigated based on the BAS dysregulation model of the disorder. The null findings of the current study do not support this model at the trait level. BAS activation appears more likely to be a feature of hypo/manic and depressive states in BD rather than a trait-based feature of vulnerability to BD. This conclusion however, is not consistent with the BAS dysregulation model of BD described by Urosevic et al. (2008), who report trait differences in BAS activation across a range of populations at varying levels of vulnerability to BD (see also Alloy, Bender et al., 2009). The actigraphic instrument used to measure BAS activation in the current study may explain some of the difference in findings with previous investigations. This issue will be discussed further in Section 5.9.5.

5.9.5 Limitations

Study 2 had a number of limitations. First, a larger sample at the screening phase would have permitted the creation of more extreme criterion groups and hence greater power to detect predicted effects. At the lower end of scores in the High GBI group, participants were reporting total GBI scores of around 75 to 80, placing them in the bottom 40th percentile of total possible GBI score. To create a greater level of
specificity in determining high risk for BD, perhaps a cut-off score on the GBI should be set for inclusion in the high vulnerability group. When data were scored in a casewise manner and graphed on a scatterplot (see Figure 4), 12 participants scoring below the cut-off scores for affective disorder identified by Depue and Klein (1988) were classified as ‘high vulnerability’ in the present study. They recommend that a cut-off score of 13 on the hypomania/biphasia scale and 22 on the depression scale represents a statistically valid and reliable differentiation between noncase and affective participants. In the current study there were not enough participants scoring above these cut-offs to create a sample of sufficient size for meaningful group comparisons. Nevertheless, a cut-off range of scores similar to that recommended by Depue and Klein (1988) could be applied in future studies for the purpose of identifying those with greater vulnerability to BD.

Second, limitations of actigraphy should also be noted. Scoring of the raw activity data from actigraphy involves some subjective judgements. In some circumstances, it can be difficult to determine precisely when the Actiwatch is removed. Periods of zero-activity are scored as sleep by Actiware. Extended periods of zero-activity may be valid data (e.g., a state of passive wakefulness) and therefore deserve to be retained. However, these extended periods may also be due to removal of the Actiwatch. Unless exact details of when the device was removed and when it was returned to the wrist are provided by participants, it is difficult to know how to handle these extended periods of zero-activity. Based on recommendations by Van Someren et al. (1999), periods greater than 60 minutes of continuous zero-activity were excluded from the analysis, as one hour of no movement is unlikely to occur naturally, even during sleep. On days where this was the case the entire 24-hour period was excluded, potentially limiting the amount of data available for analysis. While there are numerous techniques for replacing missing activity data (e.g., Catellier et al., 2005; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001), a conservative approach was adopted in the current study, especially as there were limited instances of missing data. The missing data periods in the current study were also of such considerable length that accuracy of replacement values chosen to represent the missing data was indefensible.
A related issue concerns actigraphic validity in capturing the essence of sleep difficulties as subjectively experienced by the person with BD. Subjective evaluations of sleep often do not correlate with actigraphic estimates in this population (e.g., Harvey et al., 2005; Millar et al., 2004). The two data gathering techniques target ostensibly similar sleep characteristics, and should correlate at a much higher level than is commonly observed. Although previous studies have provided evidence that actigraphy is an accurate measure of sleep/wake status (Pollak et al., 2001; Reid & Dawson, 1999; Sadeh, Sharkey, & Carskadon, 1994) the technology does not permit the collection of information regarding sleep architecture. As described in Sections 2.2 and 2.3, this information is crucial to understanding the sleep process. It has also been reported that sleep/wake identification using actigraphy becomes less reliable as sleep becomes more fragmented (Ancoli-Israel et al., 2003). Therefore, the more disordered the sleep is, the lower the chances of an accurate representation of sleep behaviour. For those with sleep disorders (and those with disorders that may involve significant sleep disturbance, such as BD), different sleep scoring algorithms may be required that account for this potential deficiency of actigraphy. These limitations conceivably extend to the assessment of sleep in those deemed to be vulnerable to BD.

Finally, as discussed in Section 3.1, 24-hour activity rhythm data derived from actigraphy represents the complex endpoint of several biological processes, including circadian, homeostatic, social, and motivational determinants (see Figure 4). It is therefore a rather gross measure of the variables of interest that is unable to be parsed into its constituent components. Actigraphy is a useful measurement tool for longitudinal, naturalistic study designs of circadian and related processes, but the data derived must be considered in the context of the limitations associated with the actigraphic technique (see also Dijk & Franken, 2005; Mistlberger et al., 2000).

5.9.6 Conclusions and future directions

Based on the findings of Study 2 it would seem that reduced amplitude of the 24-hour activity rhythm may be a useful biomarker of increased vulnerability to BD. In
contrast, total daytime activity levels and features of the sleep period do not appear to
differentiate between healthy people at high- versus low-risk for BD. The findings allow
us to advance the possibility that reduced amplitude of the 24-hour activity rhythm is an
dendophenotype for BD. Instability of the circadian signal has already been demonstrated
in clinical BD populations (Salvatore et al., 2008; Souetre et al., 1989; Souetre et al.,
1988). It has also been demonstrated in populations at increased risk for the disorder
under constant routine conditions (Murray et al., 2002). The findings of Study 2 add
incrementally to this body of research by supporting the circadian instability hypothesis
in a sample at increased vulnerability to BD, assessed under naturalistic conditions.

Within the context of the limitations presented, the findings of Study 2 also
demonstrated the feasibility of 24-hour activity rhythm monitoring via actigraphy. The
standardised amplitude of the rhythm would appear to be the most useful actigraphic
outcome variable for such monitoring in populations vulnerable to BD. Actigraphic
estimates of sleep and total daytime activity may not be useful variables for monitoring
in these populations, at least at the level of stable traits. Nevertheless, the information
drawn from Study 2 provides impetus for the investigation in finer detail of the
prospective relationships between features of the 24-hour activity rhythms and mood in
a clinical population. The nature of this relationship is of particular interest in the
clinical context where disordered mood states are often preceded by disruptions to the
sleep/wake cycle (see Section 3.3). If prospective relationships between mood and
features of the 24-hour activity rhythm can also be established, advancement towards
strategies for early intervention may be possible.

5.10 Summary of Chapter 5

Actigraphic correlates of vulnerability to BD were investigated as potentially useful
biomarkers of the disorder. Vulnerability to BD was quantified using the GBI, a
psychometrically reliable instrument that provides an interpretable measure of the
continuous BD phenotype. High and low vulnerability groups were selected on the basis
of total GBI score to maximise power to detect predicted effects. The two groups were different in important ways, further advancing understanding of the trait vulnerability concept in BD. Differences in history of MDEs, personality, temperament, and cognitive style were found.

Hypothesis testing found that one of three nonparametric variables measuring circadian activity rhythm instability (i.e., RA) was significantly different between the high and low vulnerability groups. Post hoc investigations that included history of MDE corroborated the potential importance of RA as a between-subject biomarker of vulnerability to BD. In contrast, none of the three objective sleep variables derived from actigraphy differed between the groups. Similarly, total daytime activity did not differentiate between the groups. It is concluded that a nonparametric measure of circadian activity rhythm amplitude (RA) derived from actigraphy warrants further investigation as a biomarker of the circadian endophenotype often proposed in BD. As it was not assumed that between-subject biomarkers of vulnerability to BD would be the same as within-subject biomarkers of disorder states, predictions in Study 3 were not limited to RA.
Chapter 6

Study 3: Actigraph-derived Measures of Circadian Instability, Sleep, and Daytime Activity, and their Prospective Relationships with Mood Deterioration in Bipolar Disorder

In the ultimate study of the project, a within-person version of the circadian vulnerability hypothesis for BD was investigated. Specifically, the three predictor variables of Study 2 (actigraphic measurement of circadian instability, sleep, and total daytime activity) were investigated prospectively as potential predictors of mood state in a sample of outpatients diagnosed with BD. As argued above, the ability to automatically and nonintrusively monitor a biomarker that predicts mood state in BD would have profound clinical implications.

Chapter 6 begins with a review of previous related research (6.1). Given the novel design of Study 3, several measurement decisions were confronted in the operationalisation of both predictor and outcome variables. Section 6.2 considers the issues surrounding the operationalisation of mood and concludes with the two outcome variables of daily mood state that were chosen for the purposes required in Study 3. As many of the issues surrounding the measurement of biological rhythm function were dealt with in the previous chapter, they are covered only briefly in Section 6.3. Sleep self-reports were added to the methodology of the current investigation and are also described in this section. Finally, the operationalisation of prospective associations between predictor and outcome variables is considered in Section 6.5, and a suitable strategy for capturing these relationships is presented. Hypotheses and research questions regarding circadian instability, sleep, and total daytime activity, and their prospective associations with daily mood are presented in Section 6.6. Findings from Study 2 and previous investigations were used for justification of predicted outcomes.
The unique exploratory design of Study 3, including description of the outpatient sample, the tools required for subjective and objective measurement of predictor and outcome variables, and the time-series statistical techniques required for data analysis are presented in Section 6.7. The results (6.8) showed that actigraph-derived measures of circadian instability and sleep were poor predictors of daily mood state in the current sample. Alternatively, actigraphic measurement of total daytime activity was a highly significant predictor of daily mood state. A case study of manic relapse is also described in the results section. Potential implications for clinical monitoring and prodrome identification in outpatients with BD, derived from both statistical analysis of the data and case study findings, are discussed in Section 6.9.

6.1 Prospective relationships between mood, circadian activity rhythms, sleep, and daytime activity in Bipolar Disorder

The exploratory design of Study 3 is unique. No published studies have investigated prospective associations between biological rhythms and mood variation in BD. Similarly, none have investigated the prospective association between daytime activity levels and mood in this population. Given that monitoring of symptoms is a prominent feature of many psychosocial interventions for BD (see Section 1.6), the lack of research is somewhat surprising. The data that is available relies predominantly on self-report measures of sleep and activity.

In a study of the prospective relationship between self-report sleep length and daily mood in 59 outpatients with BD, Bauer, Grof, Rasgon, Bschor et al. (2006) reported significant inverse relationships between bedrest and mood change the following day in 41% of participants. For this subgroup therefore, increased time in bed, both awake and asleep, was associated with lower moods the following day. Similar findings were apparent in a replication study by the same group using a larger BD outpatient sample (Bauer, Glenn et al., 2008). Such relationships would appear to be consistent with
clinical observations of increased sleep during depression and reduced sleep during mania (e.g., Mitchell et al., 2008)

In a non-psychiatric sample of community-dwelling older adults, McCrae et al. (2008) investigated daily associations between sleep and affect. The data supported prospective relationships between poor subjective sleep quality and lower positive affect. By investigating relationships in a non-clinical sample, this study was a step removed from those involving clinical samples. Although it has been demonstrated that low and high positive affect are associated with the states of depression and mania, respectively, in people vulnerable to BD (e.g., Lovejoy & Steuerwald, 1995; Watson, Clark, & Carey, 1988), the relevance to relationships between biological rhythms and clinical states in BD is unclear. The findings of McCrae et al. (2008) nevertheless inform clinical research, and represent an important and necessary step towards greater sophistication in understanding of these potentially related processes.

Mendlowicz et al. (1999) investigated the relationship between biological rhythms and mood in a non-psychiatric population, using actigraphy as an objective measure of the activity levels and sleep. The objective measurement strategy used by Mendlowicz et al. (1999) represents a methodological advance over the studies of Bauer, Grof, Rasgon, Bschor et al. (2006) and McCrae et al. (2008), in that relationships were investigated free of the potential complications associated with self-report (e.g., poor patient insight). Mendlowicz et al. (1999) reported that reduced daytime activity level was the strongest predictor of depressed mood in their sample. Total sleep time and time in bed were also significant predictors of depressed mood. Actigraph-derived measures of activity level and sleep therefore, were related to depressed mood in the direction expected by observations of clinical states of depression. The conclusions were limited somewhat by the small non-clinical sample. Nevertheless, the finding that objective measures of sleep and activity levels demonstrate similar relationships with mood as that found in the self-report data of Bauer, Grof, Rasgon, Bschor et al. and McCrae et al., and that derived from clinical observation (e.g., Mitchell et al., 2008) provides further impetus for the investigation of these potentially useful relationships.

21 Patient awareness of behaviour can be impaired in people with BD, particularly during the manic phase of the illness (Dell'Osso et al., 2002; Yen et al., 2007).
6.2 Operationalisation of mood state in Study 3

A fundamental decision for Study 3 design was the optimal operationalisation of mood state. The measurement of mood state across time in BD is inconsistent across studies (e.g., Leverich et al., 2001; Sachs et al., 2003). A definition of mood was required here that was consistent with theoretical models of mood states in BD, and which suited the long-term, naturalistic, and prospective design of Study 3.

It was firstly decided to operationalise mood state within a 24-hour context. The decision to use daily mood state as the outcome variable, as opposed to weekly or monthly durations, was based on a number of considerations. Firstly, the 24-hour (circadian) period was central to the investigative themes of the entire project. Secondly, it is standard practice to monitor mood in BD on a daily basis for the purposes of relapse prevention in the clinical setting (Basco & Rush, 2007; Sachs, Printz, Kahn, Carpenter, & Docherty, 2000; Yatham et al., 2009). The 24-hour timeframe therefore was generalisable clinically. Thirdly, previous studies of prospective relationships between sleep and mood use daily monitoring as the time-frame for investigation (e.g., Bauer, Grof, Rasgon, Bschor et al., 2006). Finally, the choice of a 24-hour timeframe permitted the use of a validated existing computer-based data collection interface – the ChronoRecord software package.

6.2.1 ChronoRecord

The ChronoRecord software package (Bauer et al., 2004) was chosen as the self-report mood recording methodology in the current study. ChronoRecord is a computerised version of the established pen-and-paper Chronosheet (Bauer et al., 1991), and contains a retrospective log of 24-hour mood level, sleep, life events, and medications, with data entered daily into a computer by the user. The mood recording component has a user-friendly interface and a defendable theoretical structure. Mood level is recorded daily on a 100-unit VAS with user-defined extremes of mania and
depression anchoring each end point (see Appendix E). User-defined extremes of mood are identified by the participant reporting the ‘most depressed’ (1 on the VAS scale) and ‘most manic’ (100 on the VAS scale) they had ever felt. A score of 50 in the middle of the VAS is used to indicate ‘usual mood’. ChronoRecord therefore provides a measure of daily mood state that reflects daily variation in mood amongst BD populations.

Mood recording with the ChronoRecord interface requires participants to move an indicator up or down the 100-point VAS, according to their subjective average mood for the preceding 24-hour period. When rating their mood, participants are instructed to carefully review the entire 24-hour period, to not allow the previous day’s rating influence how the current day is rated, to calibrate the rating to the extreme anchor points defined during software set-up, and to enter data at the same time each day. Bauer et al. (2004) describe ratings in the 0-19 range as indicative of moderate to severe depression, and ratings in the 20-39 range as mild depression. Euthymic states are indicated by ratings in the range of 40-60, while ratings above 60 are considered manic mood (61-80 mild, 81-100 moderate to severe).

ChronoRecord has been tested against established measures of depression and mania (Bauer et al., 2004). A sample of 80 BD outpatients recorded daily mood using ChronoRecord for 3 months. The results demonstrated concurrent validity between ChronoRecord reports and the clinician-rated Hamilton Depression Scale (HAM-D; Hamilton, 1967) and the self-report Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) as measured at four times over the 3 month period. In contrast, association between ChronoRecord mood ratings and the clinician-rated Young Mania Rating Scale (YMRS; Young, Briggs, & Meyer, 1978) was unsatisfactory, with low correlations between the two measures and poor fit of a linear regression model. The authors proposed that this may have been due to the low number of days rated in the ‘manic’ range. A more recent validation study using a cohort of inpatients with mania found stronger support for concurrent validity with the YMRS (Bauer, Wilson et al., 2008).

ChronoRecord has a number of design characteristics that make it suitable to the aims and methodology of Study 3. Firstly, ChronoRecord automatically date stamps all data entries. A major weakness of paper-and-pencil self-report mood instruments is the
tendency for some participants to complete many entries in one sitting, a practice that is usually undetectable and introduces elements of error and recall bias (Kobak, Greist, Jefferson, Katzelnick, & Mundt, 2001). Although this problem may still occur with ChronoRecord (the software allows retrospective mood reporting for periods greater than 24 hours), it can be identified at the data processing stage. Secondly, the ChronoRecord interface is accessible and easy to navigate. It has proven to be user friendly amongst samples of BD patients (Bauer et al., 2004; Bauer et al., 2005). To avoid high attrition rates and ensure consistent data recording, ease of use is critical in long-term prospective studies (Bolger, Davis, & Rafaeli, 2003). Thirdly, bypassing the transcription process from paper to computer by facilitating emailing of daily data to the experimenter eliminates data input errors. Finally, the single dimension response format in ChronoRecord implies theoretical consistency with the neurobehavioural BAS model of approach motivation and reward sensitivity in vulnerability to BD (see Section 2.5.3). Variation in mood above 50 (towards hypo/mania) in ChronoRecord is consistent with the hypersensitivity to reward and increased environmental engagement associated with heightened BAS activation. Variation in mood below 50 (towards depression) is consistent with hyposensitivity to reward and reduced environmental engagement associated with decreased BAS activation.

### 6.2.2 Deterioration in daily mood state: a paradox

As described above, the response format in ChronoRecord ranges from 0 to 100. This simple score is used by Bauer and colleagues (e.g., Bauer, Grof, Rasgon, Bschor et al., 2006) to represent mood state in BD on a daily basis. This score however, can be conceptualised in other ways. Two separate variables were derived from the ChronoRecord score to represent daily mood state in Study 3.

The first variable, labeled Mood Level, was operationally defined as the raw mood score as entered into ChronoRecord. This is the usual operational definition of daily mood in studies using ChronoRecord. It has been used successfully in ChronoRecord-based investigations that have a design generally consistent with that of Study 3 (e.g.,
Bauer, Grof, Rasgon, Bschor et al., 2006). This usual definition of daily mood state however, masks some interpretive complexities associated with defining mood deterioration in BD. In particular, the interpretation of relationships between daily mood state and features of the circadian activity rhythm are problematic.

In BD, pathological mood occurs in both lowered and elevated forms. That is, mood deterioration can appear as shifts towards either depression or mania. In Study 3 predictions are relevant to both manifestations of pathological mood. Reduced amplitude in the 24-hour activity rhythm has been associated with both manic (Salvatore et al., 2008) and depressed states (Lemke, Puhl, & Broderick, 1999; Raoux, 1994; Winkler, Pjrek, Praschak-Rieder et al., 2005). Thus, increased stability should be associated with higher mood. This linear relationship would be interrupted however, at the ChronoRecord-defined intersection between ‘healthy’ mood improvements (i.e., mood ratings between 50 and 60), and pathological ‘worsening’ mood (i.e., mood ratings above 60). The simple variable of Mood Level does not capture this complexity. An alternative operationalisation of daily mood state is therefore required to model the relationship between predictor (circadian instability) and outcome (daily mood state) variables.

Deviation from usual mood was used to measure mood deterioration in Study 3. The term Mood Deviation was used here to refer to absolute deviation both above and below usual mood (raw score of 50 in ChronoRecord). Higher scores, according to this operational definition, represent greater mood deterioration irrespective of the direction of the mood change. Two variables derived from ChronoRecord’s 0-100 scale (raw score, labeled Mood Level, and deviation from neutral, labeled Mood Deviation) were therefore potential outcome variables of interest. Both were investigated in the analysis of Study 3.  

22 A categorical operationalization of mood deterioration allowing for the negative impact of extreme mood states, was also considered in Study 3. To reflect the negative connotation of extreme ‘up’ states, mood scores were categorized into dichotomous pairs of depressed vs. not depressed, manic vs. not manic, and euthymic vs. unwell. Preliminary analyses of relationships with the predictor variables showed that the two former categorical descriptors produced correlations with the predictor variables that were essentially similar to the Mood Level outcome variable. This was most likely due to the relatively low number of manic scores in the daily mood ratings of participants. Similarly, the latter dichotomous mood variable was found to produce similar relationships with the predictor variables as those found with Mood.
6.3 Operationalisation of biological rhythm function in Study 3

The clinical goal of the current project was to assess the feasibility of several variables derived from actigraphy for the purposes of behavioural monitoring in BD. Three predictor variables were inferred from actigraphic measurement of the 24-hour activity rhythm – circadian rhythm instability, sleep, and total daytime activity (see Figure 4). In Study 3 these variables were operationalised in the same way as in Study 2. Self-reports of sleep, incorporated as part of the ChronoRecord program, were also investigated in Study 3.

6.3.1 Circadian rhythm instability

In Study 2, circadian rhythm instability was operationalised using three variables. Two of these operational definitions, RA and IV, were adopted for the current study. The third operationalisation of activity rhythm stability used in Study 2, IS, was not used in the current study. The focus of the current study on daily associations between the 24-hour activity rhythm and mood meant that the IS variable, which is computed using activity patterns over several days (see Section 5.3.1), was not an appropriate operationalisation of activity rhythm stability.

RA, defined as the amplitude of the 24-hour rhythm in activity and standardised according to mean activity level, was used as a measure of circadian rhythm instability in Study 3. Study 2 demonstrated that RA was significantly reduced in a group of well students with higher vulnerability to BD than a group of well students with lower vulnerability. This variable may therefore be a useful operationalisation of circadian instability and a primary target for monitoring. It is theoretically possible that severely

Deviation. The amount of deviation from usual mood, either up or down, was therefore deemed to be an adequate approximation of wellness vs. unwellness in the current study. In order to limit redundancy in the analytic design of the current study the three categorical descriptors of mood were not analysed further.
deviant changes in state levels of vulnerability traits can be used to predict episodic exacerbations (see Section 1.3).

IV, a variable describing the daily frequency of rest/activity transitions, was also used in Study 3 to measure circadian rhythm instability. Although this variable did not emerge as a significantly different outcome between the two groups in Study 2, increases at the trait level in samples with higher vulnerability to BD have been demonstrated in previous research (e.g., Jones et al., 2005). Again, it is conceivable that greater variability of the 24-hour activity rhythm may act to predict episodes of mania or depression.

### 6.3.2 Sleep

Sleep was measured objectively via actigraph and also subjectively using ChronoRecord. Actigraph-derived indices of sleep were identical to those used in Study 2. Total sleep time (TST), sleep efficiency (SE), and wake after sleep onset (WASO) were computed using the Actiware-derived algorithms described in Chapter 5. As described in Chapter 2, arguments for an association between sleep and mood variation are compelling.

The ChronoRecord software package provided the opportunity to collect self-report sleep variables for Study 3. As discussed above, numerous studies demonstrate divergence between subjective and objective measures of sleep phenomena (Ancoli-Israel et al., 2003). Self-reports of sleep are also a widely used clinical monitoring device in psychotherapy for BD (Frank et al., 2000; Sachs, 1993), and thus suit the clinical goals of the project. Two sleep variables were derived from the self-reports: Sleep Length and Total Bedrest. The first variable was used to represent the amount of time spent in bed asleep per day, and the latter variable represented the total amount of time spent in bed per day, either awake or asleep. Both operationalisations of self-reported sleep have been demonstrated to have significant associations with mood change on a daily basis (Bauer, Grof, Rasgon, Bschor et al., 2006).
6.3.3 Total daytime activity

Total daytime activity was also calculated from the actigraph data. As reviewed in Section 2.5.3, activity levels are strongly associated with mood change in BD. As in Study 2, total daytime activity was operationalised as the average level of activity during the most active 10-hour period of the day (M10).

6.4 Summary of operationalised variables in Study 3

Figure 10 presents a schematic representation of the predictor (circadian rhythm instability, sleep, total daytime activity) and outcome (daily mood state) variables in Study 3 and how they were operationally defined (cf. Figure 7 in Chapter 5). Variables with a single asterisk were self-report (i.e., recorded using ChronoRecord) and variables with a double asterisk were derived from actigraph data. The IS variable, excluded from Study 3, is semi-obscured in Figure 10, but serves as a reminder of where this variable was situated in the context of the predictor variables. Hypotheses and research questions regarding the predicted relationships between the operationalised variables in Figure 10 are articulated in Section 6.6.
Figure 10. Schematic representation of relationships between predictor and outcome variables in Study 3.
6.5 Associations between predictors and outcomes: synchronous and predictive relationships

The prospective within-subject design provided the opportunity for time-series analysis. A number of consequences of this analytic approach should be noted. First, hypotheses were formed in terms of zero-lag (synchronous) and -1 lag (predictive) relationships. Both types of relationship are of clinical interest. If changes in actigraphically derived variables precede mood changes they can function as early warning information. Synchronous relationships may also translate to a useful clinical application, given that automatic, objective measurement may be more effective than reliance on self-report as a measure of clinical state.

Results presented below refer only to predictive associations between variables for up to a maximum lag of -1 day. This decision was based on three considerations. First, a predictive relationship of 1 day between predictor and outcome variables was considered to be sufficient to capture a potentially useful association. The effect size of relationships between predictor and outcome variables was expected to be small given the array of potentially confounding physiological (e.g., food, drugs) and psychological (e.g., stress, relationships) variables. Any significant effect was considered unlikely to extend beyond 1 day. Second, Bauer, Grof, Rasgon, Bschor et al. (2006) found significant negative correlations between mood and sleep either the night before or the night of mood change in 41% of their BD sample, with correlations “uniformly low for all other time shifts” (p. 162). Finally, relationships between predictor and outcome variables for lags of up to 7 days were explored in the current data using the cross-correlation function and ARIMA filtering. No consistent effects beyond a lag of -1 day were found. If predictive relationships between activity, sleep, and mood were to be found in the clinical sample of Study 3, it was expected that they would be found at a maximum lag of -1 day.

ChronoRecord self-reports were made at 8pm and referred to mood that day and sleep the preceding night. Actigraphic data was recorded continuously. For the purposes of defining synchronous and predictive relationships between predictor and outcome
variables, the 24-hour window for actigraph data commenced at 8am and was deemed to
be aligned synchronously with the daily mood report made at 8pm that evening.

6.6 Research questions and hypotheses for Study 3

The overarching aim of Study 3 was to investigate circadian rhythm instability,
sleep, and total daytime activity, respectively, as predictors of daily mood state in BD
using a prospective design. Given the exploratory nature of Study 3, a large number of
potential associations were tested. To focus the investigation, where warranted,
hypotheses ($n = 10$) and research questions ($n = 5$) were framed. Table 16 presents an
overview of the relationships investigated, and indicates those where specific outcomes
were hypothesised. More specific justification for expected outcomes are provided in the
proceeding sections.

Table 16

Overview of Relationships to be Investigated in Study 3 and their Expected Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Synchronous (zero lag)</th>
<th>Predictive (-1 lag)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mood Level</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>Circadian Rhythm</td>
<td>RA</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>+</td>
</tr>
<tr>
<td>TST</td>
<td>-</td>
<td>$^+_{(q)}$</td>
</tr>
<tr>
<td>WASO</td>
<td>$?$</td>
<td>$?$</td>
</tr>
<tr>
<td>SE</td>
<td>$?$</td>
<td>$?$</td>
</tr>
<tr>
<td>Sleep</td>
<td>-</td>
<td>$^+_{(q)}$</td>
</tr>
<tr>
<td>Length</td>
<td>-</td>
<td>$^+_{(q)}$</td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>-</td>
<td>$^+_{(q)}$</td>
</tr>
<tr>
<td>Daytime Activity</td>
<td>M10</td>
<td>+</td>
</tr>
</tbody>
</table>

Note. ‘-’ = negative relationship, ‘+’ = positive relationship, ‘?’ = research question, $^+_{(q)}$ = quadratic
function. Blank quadrants indicate that no prediction was made or research question investigated (within-
subject parameter estimates were computed for these relationships and can be found in Appendix G).
Three general expectations guided decision-making for setting hypotheses, as outlined in Table 16. First, circadian instability was expected to be associated with mood deterioration. Second, increased daytime activity was expected to be associated with increased mood level. Third, sleep was expected to interact with mood deterioration in complex ways.

### 6.6.1 Circadian rhythm instability and mood deterioration

Reduced stability of the 24-hour activity rhythm (lower RA) was expected to be associated with greater mood deterioration (greater Mood Deviation) at zero lag (Hypothesis 1). The predictive (-1 lag) association between RA and Mood Deviation was expected to emerge in the same negative direction (Hypothesis 2). These hypotheses were based on the significant association found in Study 2 between lower RA and greater vulnerability to BD at the trait level. Similar findings at the trait level of vulnerability to BD have emerged in previous studies (Jones et al., 2005) and were also used as justification for expected outcomes.

No hypotheses or research questions were set regarding the association between RA and Mood Level at either zero or -1 lags. This was due to the interpretive difficulties associated with the relationship between mood ‘improvements’ and increased stability in the 24-hour activity rhythm (see Section 6.2.2). Hypotheses 1 and 2, investigating the relationships between stability of the activity rhythm and Mood Deviation, were intended to capture the nature of the relationship between circadian rhythm instability and mood deterioration in this population.

Increased intradaily variability of the 24-hour activity rhythm (higher IV) was expected to be positively associated with greater mood deterioration (greater Mood Deviation) at zero lag (Hypothesis 3). The predictive (-1 lag) association between IV and Mood Deviation was expected to emerge in the same positive direction (Hypothesis 4). Although IV was not associated with trait vulnerability to BD in Study 2, previous research has demonstrated higher IV amongst groups with greater vulnerability to BD (Jones et al., 2005). No hypotheses or research questions were set regarding the
association between IV and Mood Level at either zero or -1 lags, again due to the interpretive difficulties associated with such relationships.

6.6.2 Sleep and mood deterioration

Negative associations between the two self-report sleep estimates – Sleep Length (Hypothesis 5) and Total Bedrest (Hypothesis 6) – and Mood Level were hypothesised. A negative association between the objective measure of sleep length (TST) and Mood Level was also expected (Hypothesis 7). While no significant trait differences were found between the two vulnerability groups on any of the index sleep variables in Study 2, at the state level of vulnerability to BD, patterns of sleep/wake have consistently been shown by previous studies in BD populations to be significantly disturbed at around the time of a manic or depressive event (Jackson et al., 2003). Reduction in the amount of sleep is a particularly robust predictor of manic onset in vulnerable people (Wehr et al., 1987). Hypersomnia (increased sleep) has also been associated with the depressive phase in BD (Mitchell et al., 2008). In addition to these clinical observations, Bauer, Grof, Rasgon, Bschor et al. (2006) demonstrated negative cross-correlations between the amount of self-reported sleep and self-rated mood the next day in a proportion of outpatients with BD. In the same study, Bauer, Grof, Rasgon, Bschor et al. demonstrated a similar relationship between self-reported time spent in bed (awake or asleep) and self-rated mood.

Novel predictions regarding the relationship between the subjective (Sleep Length and Total Bedrest) and objective (TST) measures of sleep and Mood Deviation were also proposed. As both increases and decreases in Sleep Length, Total Bedrest, and TST were expected to be associated with greater levels of mood deterioration (greater Mood Deviation), a quadratic function was used to model this relationship. That is, a positive quadratic function was expected to characterise the nature of the relationship between the three sleep variables (Sleep Length, Total Bedrest, TST) and Mood Deviation (Hypotheses 8, 9, and 10, respectively).
Figure 11. Graphical representation of the expected positive quadratic relationship between Sleep and Mood Deviation

Figure 11 demonstrates the general form of the quadratic function expected to describe the relationship between sleep variables and Mood Deviation. The nonlinear nature of the relationship shows that greater mood deterioration (greater Mood Deviation) was expected to be associated with both increases and decreases in the amount of sleep and/or bedrest.

Hypothesised relationships between the sleep variables and the mood variables were expected to be shown at the synchronous (zero lag) level only. The recording of sleep, both by self-report and objective means, was timed to relate to the recording of mood the following day (see Section 6.5). Thus, the predictive element of the relationship between sleep and mood was automatically incorporated in to the recording of these variables at zero lag. The investigation of relationships at -1 lag were not conducted in this context as they referred to relationships between Mood Level and sleep from two nights prior to the evening mood report. As described in Section 6.5, relationships between variables were not expected to extend beyond lags of -1day.
There were no predictions regarding the direction or magnitude of relationships between the objective sleep variables of sleep efficiency (SE) and the amount of wake after sleep onset (WASO), and the two mood variables. Prospective relationships between these actigraph-derived sleep variables and mood in BD have yet to be empirically demonstrated. These relationships were investigated as research questions only. Research Questions 1 and 2 investigated the zero lag relationships between SE and Mood Level, and between SE and Mood Deviation, respectively. Research Questions 3 and 4 investigated the zero lag relationships between WASO and Mood Level, and between WASO and Mood Deviation, respectively.

6.6.3 Total daytime activity and mood deterioration

Total daytime activity (M10) was expected to be positively associated with Mood Level at a lag of zero (Hypothesis 11). The BAS dysregulation model of BD associates increases and decreases in goal-directed activity with the states of mania and depression, respectively (see Section 2.5.3). This association was hypothesised to persist at the level of non-clinical mood variation in Study 3.

Predictive (-1 lag) associations between M10 and Mood Level were also investigated. Although there is no previous research to support an association, the potential clinical importance of a predictive relationship between these variables necessitates such an analysis. This relationship was investigated as Research Question 5.

Associations between M10 and Mood Deviation were not assessed. There is no theoretical justification for investigating such associations. The BAS dysregulation model of vulnerability to BD describes directional relationships between daytime activity and mood. The lack of directional information contained in the Mood Deviation operationalisation of mood means that this variable is unsuitable for making predictions regarding associations with M10.
6.6.4 Individual differences in the relationship between predictor and outcome variables

The longitudinal course of manic and depressive symptoms and their associated features is highly idiosyncratic (Sierra et al., 2007). It was expected therefore that significant variation in the predicted relationships between variables would be demonstrated across participants in Study 3. That is, the predicted relationships were expected to vary in strength between participants, and may not exist at all for some participants even if an average group association was found to be significant. The analytic approach adopted here, Multilevel Linear Modelling (MLM), permitted the quantification of this between-subject effect (see Section 6.7.5.4 below). No hypotheses were set regarding individual differences in predicted relationships, but all analyses were conducted with individual differences properly modeled.

6.7 Method for Study 3

6.7.1 Participants

Fifteen participants (8 females, 7 males; age $M = 47.6$ years) were recruited through the Bendigo Health Care Group (BHCG), a public area health service in regional Victoria. Initial approaches were made through the participants’ case manager who distributed study information to their clients. Inclusion criteria for the study were a primary diagnosis of BD-I with no significant comorbidity, not working shiftwork, absence of a physical disability that may interfere with recording of ambulatory wrist movement, and a currently stable clinical state. Significant comorbidity was defined as the presence of a full-blown Axis-II disorder, or a psychotic or substance use disorder that had warranted intervention in the preceding 12 months. Shiftwork was an exclusion criterion because of its confounding impact on the sleep/wake cycle. Finally, co-existing physical disabilities, particularly those affecting arm movement, were an exclusion
criterion because of their impact on actigraph data. To ensure informed consent was adequately obtained participants were also required to be clinically stable at the commencement of the study. Relevant diagnostic and medication information for each participant is provided in Table 17.

Table 17

<table>
<thead>
<tr>
<th>Participant</th>
<th>Comorbid Diagnoses</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Panic Disorder</td>
<td>Epilim (500mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manerix (150mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abilify (30mg)</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
<td>Quilonum (450mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abilify (30mg)</td>
</tr>
<tr>
<td>D</td>
<td>Social Phobia</td>
<td>Lithium (250mg)</td>
</tr>
<tr>
<td>E</td>
<td>Panic Disorder</td>
<td>Epilim (200mg)</td>
</tr>
<tr>
<td>F</td>
<td>Dysthymic Disorder</td>
<td>Effexor (150mg)</td>
</tr>
<tr>
<td></td>
<td>Panic Disorder</td>
<td>Solian (100mg)</td>
</tr>
<tr>
<td></td>
<td>Social Phobia</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Panic Disorder</td>
<td>Lithium (250mg)</td>
</tr>
<tr>
<td></td>
<td>Social Phobia</td>
<td>Seroquel (200mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aropax (20mg)</td>
</tr>
<tr>
<td>H</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>I</td>
<td>None</td>
<td>Epilim (500mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoloft (100mg)</td>
</tr>
<tr>
<td>J</td>
<td>Panic Disorder</td>
<td>Valpro (500mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seroquel (100mg)</td>
</tr>
<tr>
<td>K</td>
<td>None</td>
<td>Valpro (500mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lovan (20mg)</td>
</tr>
<tr>
<td>Participant</td>
<td>Comorbid Diagnoses</td>
<td>Medications</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>L</td>
<td>None</td>
<td>Valium (5mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zyprexa (10mg)</td>
</tr>
<tr>
<td>M</td>
<td>Schizophrenia</td>
<td>Valpro (500mg)</td>
</tr>
<tr>
<td></td>
<td>Dysthymic Disorder</td>
<td>Epilim (200mg)</td>
</tr>
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<td></td>
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<td>Effexor (75mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stelazine (1mg)</td>
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<tr>
<td>N</td>
<td>Dysthymic Disorder</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Panic Disorder</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Dysthymic Disorder</td>
<td>Quinolum (450mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lexapro (10mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zyprexa (5mg)</td>
</tr>
</tbody>
</table>

*Note: Medication types are presented using their Australian commercial name.*

Four participants provided data of either insufficient quality or quantity and were excluded from hypothesis testing. Participant B was hospitalised for a manic episode recurrence four months after starting the data collection period and consequently withdrawn from the study. No mood data was available at the time of withdrawal from the study, however actigraph data was available up until this time. At a debriefing interview Participant B confirmed that they did not want to continue with the study, but declined the offer of withdrawing the data that had already been generated. This data is discussed on a single-case basis in the Results section, but was not used for hypothesis testing. A review of ChronoRecord mood reports for Participant D revealed no variation in self-reported mood for the duration of his involvement in data collection. Specifically, a score of 50 (the default score in ChronoRecord) was entered for every day of the data collection period. The invariant pattern of mood data for Participant D rendered any analysis of hypothesised relationships with sleep and activity meaningless. Participants H and N did not provide any self-report mood or sleep data for the duration of their brief

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23 Possible reasons for this pattern of mood recording are discussed in Appendix H.
involvement in data collection. Thus, time series data from 11 participants remained for the purposes of hypothesis testing.

Missing observations were found in the self-report mood and sleep time series’ data for seven out of the 11 participants available for hypothesis testing. The percentage of missing self-report mood and sleep observations for the whole sample was low, with 3.7% of total possible data points not recorded. Table 18 presents the total number of days of self-report mood and sleep data and the number of missing observations for each participant.

Table 18

*Total Number of Daily ChronoRecord Mood and Sleep Observations Available for Hypothesis Testing*

<table>
<thead>
<tr>
<th>Participant</th>
<th>Sleep</th>
<th>Mood</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>31</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>210</td>
<td>210</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>110</td>
<td>110</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>231</td>
<td>231</td>
<td>3</td>
</tr>
<tr>
<td>G</td>
<td>160</td>
<td>160</td>
<td>8</td>
</tr>
<tr>
<td>I</td>
<td>222</td>
<td>222</td>
<td>1</td>
</tr>
<tr>
<td>J</td>
<td>139</td>
<td>139</td>
<td>3</td>
</tr>
<tr>
<td>K</td>
<td>183</td>
<td>183</td>
<td>5</td>
</tr>
<tr>
<td>L</td>
<td>14</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>99</td>
<td>99</td>
<td>33</td>
</tr>
<tr>
<td>O</td>
<td>30</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>1429</td>
<td>1429</td>
<td>54</td>
</tr>
</tbody>
</table>
6.7.2 Materials

6.7.2.1 Screening

The CIDI-Auto (Robins et al., 1988), a computerised diagnostic interview based on DSM-IV and ICD-10 criteria, was used to confirm the primary diagnosis that had been recorded in case files and checked by a BHCG psychiatrist. In all circumstances the primary diagnosis was confirmed in the CIDI-Auto. The psychometric properties of the CIDI-Auto have been described in Chapter 4 above.

6.7.2.2 Baseline self-report instruments

Participants completed a baseline questionnaire that consisted of the GBI (Depue et al., 1989), TEMPS-A (Akiskal, Mendlowicz et al., 2005), and NEO-FFI (Costa & McCrae, 1992). Descriptions of these instruments as well as their psychometric properties can be found in Chapter 4. These instruments were used to confirm that the clinical sample in Study 3 was not substantially different from a typical BD-I sample. Demographic information was also obtained (e.g., date of birth, gender, contact details). Data processing of baseline questionnaire data was conducted in SPSS 17.0 for Windows (SPSS, Inc., Chicago, Illinois).

6.7.2.3 Daily self-report mood recording

The outcome variables of Mood Level and Mood Deviation were measured using ChronoRecord (Bauer et al., 2004). The mood recoding procedure in ChronoRecord is described above in Section 6.2.1.
6.7.2.4 Daily self-report sleep recording

Participants recorded the amount and quality of their sleep each night using ChronoRecord. A sleep graphic interface in ChronoRecord is divided into 24 boxes, each representing one hour, covering the period from 12pm the previous day to 12pm of the current day (see Appendix F). The boxes are toggled between three options – Awake, In Bed Asleep, and In Bed Awake. Participants select the option that best represents their degree of ‘wakefulness’ for each hour in the 24-hour period. The sleep module of ChronoRecord has yet to be externally validated, however similar methods of sleep/wake self-reporting (e.g., sleep diaries) have proven to be valid in various populations (Manber et al., 2005; Wilson, Watson, & Currie, 1998), including a BD outpatient sample (Millar et al., 2004). Significant life events (if any) and medications (if any) are also recorded for each 24-hour period, but this data was not analysed here. The software was configured to suit Australian medication practices and relevant brand names.

6.7.2.5 24-hour activity rhythm monitoring

As in Study 2, all predictor variables derived from the 24-hour activity rhythm were assessed using actigraphy. The Respironics/Mini-Mitter Actiwatch-L (Respironics, Inc., Bend, Oregon) models used in Study 3 were identical to those used in Study 2 (see Chapter 5). Participants were instructed to wear the device on their non-dominant wrist and to avoid removing it. Activity data was recorded in 1-minute epochs for 11 participants and 2-minute epochs for four participants. The difference in epoch length was necessary to ensure there was sufficient memory storage for the four participants who were using an older model Actiwatch. For the purposes of activity-based sleep/wake identification the wake threshold was set at Medium for all participants, as in Study 2. Actiwatch data was downloaded fortnightly using the ActiReader into the
associated Actiware 5.0 software program, where it was screened and prepared for analysis.

6.7.3 Procedure

Investigators approached case managers through case conferences to promote the study and to assist in disseminating study information to their clients. Case managed clients who were interested in participating contacted the investigators and a mutually agreed time was arranged to start the screening process. At the initial meeting, potential participants completed the CIDI-Auto as well as the requisite consent forms if they consented to participate. Participants also gave consent at this stage for their confidential medical records and case manager notes to be made available to the researchers for review. The external review of participants’ case files was conducted by a BHCG psychiatrist.

When suitability of a participant was confirmed and consent obtained, they were inducted into the study and trained in the use of ChronoRecord, email, and care of the Actiwatch. At this time participants also completed the baseline questionnaire. Participants received a computer package that included all the equipment (e.g., modem) and software (ChronoRecord and an appropriate email package) necessary to complete and submit mood and sleep reports. Dial-up internet access was also provided to facilitate electronic sending and receiving of mood reports and summary charts. Providing a computer package for all participants limited the possibility of sampling bias by not restricting study involvement to only those with compatible existing computer systems. Only four of the 15 participants recruited into the study proper owned a personal computer at the commencement of the study and would otherwise have been excluded from participation. Computers became the property of the participant once data recording began and were theirs to keep even if they decided to withdraw from the study. Internet access was only provided for the duration of their participation in the study. Investigators visited participants every two weeks throughout the data collection period to download Actiwatch data into a central Actiware database.
Participants were asked to commit to the study for a maximum period of 12 months. They were paid $20 for participation in the screening phase and a further $20 upon completion of the baseline questionnaire if they were accepted into the study proper. Ethical approval for the study was gained through both the Swinburne University of Technology Human Research Ethics Committee and the BHCG Human Research Ethics Committee.

6.7.4 Ethical considerations

As with all research involving clinical groups, duty-of-care and other ethical considerations are of paramount importance. Such considerations are particularly important for research involving relapsing and remitting conditions like BD, as was the case in the current study. All participants in Study 3 were clinically stable at the commencement of the study so relapse into hypo/mania and depression was unlikely. However, given the cyclical nature of BD symptomatology, and the longitudinal design of Study 3, there was a chance that episodes could occur during the course of participant involvement in data collection. As described in Section 1.6, long-term relapse into mania or depression occurs in up to 73% of BD cases (Gitlin et al., 1995). It was necessary therefore, to be mindful of the possibility of relapse.

All participants were informed that they could withdraw from the study at any time. This included circumstances where their condition deteriorated, or they simply did not want to continue with the study. It was made clear to participants that there was no penalty for withdrawing from the study. They were able to keep the computer, including the pre-installed software, although internet access was discontinued upon their withdrawal. If participants felt that the demands of data collection outweighed the benefits of the self-monitoring process (refer Sections 1.6 and 3.3) and they wished to discontinue data collection, they were free to do so.

A deliberate consideration of the study design was to minimise the impact of data collection on participants’ usual routine. Indeed, such considerations were prominent throughout the decision-making process in designing key aspects of the study. A key
part of the methodology therefore was to encourage participants to maintain a treatment-as-usual approach to their ongoing therapy. Treatment-as-usual varied between participants, although medication and regular appointments with case managers were common elements across the sample. The minimal interference approach adopted by the current study also ensured that if relapse did occur the usual procedures were in place to ensure the fastest and most appropriate course of action.

6.7.5 Data preparation and analytic strategy

This section presents the data processing strategies and techniques for dealing with missing data for the three major types of data: baseline self-report instruments, daily self-report mood and sleep data, and activity data.

6.7.5.1 Baseline self-report data

Scoring procedures for the GBI, TEMPS-A, and NEO-FFI were as described above for Study 1 and Study 2. Scores on these instruments were then screened for out-of-range and missing values. Two missing values, one each for two participants, on the GBI Hypomania scale were replaced with the within-subject series mean of this subscale. There was no missing data on the TEMPS-A or the NEO-FFI. The distribution of scores on most baseline questionnaire measures was normal or near normal. The exceptions were the E subscale of the NEO-FFI (negative skew), and the DT (positive skew), IT (positive skew), and CT (negative skew) subscales of the TEMPS-A. An appropriate transformation was applied to the skewed distributions of the TEMPS-A subscales before these variables were entered into group comparisons with the High GBI and Low GBI groups from Study 2. Transformation of the E subscale of the NEO-FFI was not necessary as it was not used for statistical comparisons.
6.7.5.2 Daily self-report mood and sleep data

Self-report mood and sleep data were recorded daily in ChronoRecord. Daily mood state was the outcome variable of interest and was operationalised using the Mood Level and Mood Deviation variables. Mood Level was defined as the raw mood score and had a theoretical range of 0-100. Mood Deviation was defined as the absolute deviation from the mid-point of 50 on the ChronoRecord mood rating scale and so ranged from 0-50. A raw mood score of 54 for example, would generate a Mood Deviation score of 4, as would a raw mood score of 46. Under the Mood Deviation operationalisation therefore, the magnitude of deviation is important and not the direction.

Self-report Sleep Length was a predictor variable and was operationalised as the raw number of hours scored as ‘In bed asleep’ by participants. Total Bedrest was an additional predictor variable computed using self-report sleep data. Total Bedrest was calculated as the sum of the number of hours scored as ‘In bed asleep’ and the number of hours scored as ‘In bed awake’.

Eligible self-report data entries were required to be date-stamped as entered on or soon after the reference date. A lag-time of up to 14 days between the reference date and when data was entered was allowed, as long as evidence was shown that a manual record of mood and sleep had been maintained throughout the period where data was not entered. Participant E, who spent extended periods of time staying with relatives during the data collection phase and did not have access to a computer, often used this alternative method of data recording. Two other participants (C and G) also kept manual records of their mood and sleep when they went on holiday during the data collection period and entered it into ChronoRecord on their return. Participant A entered 37 consecutive days of mood and sleep data in one sitting and, as there was no manual record of daily monitoring evident, the risk of recall error over this period was deemed to be too great and this sequence of data was excluded from the analysis.
6.7.5.3 Activity data

Activity data were initially viewed in the form of actograms in the Actiware 5.0 software (see Appendix I for an example actogram). The date and approximate time of ‘gaps’ (periods of zero activity) in the actograms were tagged as possible instances of missing data and investigated as such in raw data format in Microsoft Excel (Microsoft Corporation, Redmond, Washington). Missing activity data is typically due to either removal or malfunction of the Actiwatch.

Van Someren et al. (1999) recommends that continuous periods of zero activity greater than 1 hour should be treated as missing data and excluded from analysis (see Section 5.4.4.2). However, in the context of Study 3 this was seen as an overly conservative approach, particularly since some participants may have been taking medications that were intended to help them sleep. For example, it has been shown that sedatives can affect actigraphic recording by increasing the proportion of zero activity counts (Denise & Bocca, 2003; Kiang, Daskalakis, Christensen, Remington, & Kapur, 2003).

For the BD population in Study 3, a less conservative approach to missing data than that proposed by Van Someren et al. (1999) was used. The general rule for dealing with ‘gaps’ in the actigraph record was that extended periods of zero activity near the base of the 24-hour activity curve (i.e., periods of sleep and/or rest) were replaced via linear interpolation of adjacent points. Three participants (C, E, and I) in Study 3 each had one period greater than 1 hour, but less than 3 hours, of zero activity replaced with linear interpolation. Periods of zero activity near the peak of the curve (i.e., daytime activity) were more problematic. The linear interpolation technique was deemed unsuitable in this circumstance because replacement values were likely to be poor estimates of such a variable period in the data sequence. Thus, where there was unexplained missing data near the peak of the activity curve, the entire 24-hour period was removed from the analysis.

Table 19 presents the number of days of activity data contributed by each participant in Study 3, as well as the number of missing observations per participant. A
total of 16 days of activity data were removed from the actigraph record for five participants due to extended periods of zero activity at or near the peak of the daily activity curve. Days of data removed from participants’ activity records due to unexplainable gaps were not replaced using missing data estimation techniques.

Table 19

**Total Number of Actigraph-derived Activity and Sleep Observations Available for Hypothesis Testing**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Days</th>
<th>Excluded due to missing data</th>
<th>Total for analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>35</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>C</td>
<td>217</td>
<td>-</td>
<td>217</td>
</tr>
<tr>
<td>E</td>
<td>120</td>
<td>-</td>
<td>120</td>
</tr>
<tr>
<td>F</td>
<td>231</td>
<td>1</td>
<td>230</td>
</tr>
<tr>
<td>G</td>
<td>175</td>
<td>5</td>
<td>170</td>
</tr>
<tr>
<td>I</td>
<td>229</td>
<td>-</td>
<td>229</td>
</tr>
<tr>
<td>J</td>
<td>139</td>
<td>2</td>
<td>137</td>
</tr>
<tr>
<td>K</td>
<td>183</td>
<td>6</td>
<td>177</td>
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<tr>
<td>L</td>
<td>14</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>M</td>
<td>99</td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>O</td>
<td>30</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>1472</strong></td>
<td><strong>16</strong></td>
<td><strong>1456</strong></td>
</tr>
</tbody>
</table>

Three activity variables were derived from the activity data. Stability of the 24-hour activity rhythm was operationalised using RA and IV. Computational algorithms for these variables have been presented in Study 2 (see also Appendix C). Total daytime activity was operationalised using the M10 variable. Again, this variable was calculated as described in Study 2.
Three sleep variables were also derived from the raw activity data. TST, SE, and WASO were used to operationalise daily sleep patterns. They were computed using the same Actiware-derived algorithms as used in Study 2.

6.7.5.4 Hypothesis testing

Multilevel Linear Modelling (MLM) was used to assess hypothesised within-subject relationships between predictor and outcome variables. The MLM technique also allows intercepts (means) and slopes (relationships between predictor and outcome variables) to vary between individuals and groups, thus allowing the individual differences in relationships between variables to be assessed (i.e., between-subject effects; Bickel, 2007). Between-subject effects were evaluated using an unstructured covariance algorithm. Unlike general linear models, MLM does not require independent observations, making the technique particularly suitable for time-dependent designs (e.g., McCrae et al., 2008). MLM can also accommodate unequal data series’ lengths between participants and discontinuous data sequences due to missing data. Unlike more common time series analysis techniques (e.g., ARIMA) the MLM technique is robust with regards to unequal sample sizes and missing data.

A brief diversion is necessary here to address issues relating to MLM terminology. The SPSS MIXED (SPSS, Inc., Chicago, Illinois) procedure used in Study 3 uses the terms Fixed and Random to refer to effects that occur at the level of the individual and effects that occur at the level of the group, respectively. The commonly used Hierarchical Linear and Nonlinear Modeling program (HLM; Scientific Software International, Inc., Lincolnwood, Illinois) uses the terms Level I and Level II to refer to the same effects. In the current study, for the sake of consistency, the terms ‘within-subject’ and ‘between-subject’ will be used to refer to Fixed/Level I effects and Random/Level II effects, respectively. Thus, within-subject effects are those that describe the magnitude and direction of the relationship between variables for each individual in the sample, while between-subject effects indicate the amount of inter-individual variability in the magnitude of the within-subject effects (Bickel, 2007).
Significant between-subject effects indicate that there are individual differences in the relationship between predictor and outcome variables. In Study 3, the within-subject effect was assessed as the time-dependent relationship between predictor (activity, sleep) and outcome (mood) variables. The between-subject effect referred to nested between-person differences in the relationships between these variables. The strength of the model was determined by comparing the error variance between predictor models and an unconditional linear growth model which simply assesses relationships between variables regardless of inter-individual variation. A reduction in error variance from unconditional linear growth to predictor model was used as an indicator of goodness-of-fit, and demonstrates the degree of predictability in the latter (McCrae et al., 2008).

For the analyses in Study 3, eleven separate multilevel regression equations were constructed for the purposes of hypothesis testing, each relating to the hypotheses stated in Section 6.6. Hypotheses 1, 2, 3, 4, 5, 6, 7, and 11 required linear equations, while Hypotheses 8, 9, and 10 required quadratic equations. The variables used for each equation are shown in Table 22. Multilevel regression equations were also constructed for the five Research Questions stated in Section 6.6. All Research Questions required linear equations. The variables used in each of these equations are also shown in Table 20.

Quadratic within-subject effect relationships were investigated separately for the association between the Mood Deviation outcome variable, and the Sleep Length, Total Bedrest, and TST predictor variables. Some multilevel relationships may be considered bi-directional, in that mood changes may be associated with both positive and negative changes in the level of the predictor variable. The addition of a quadratic term to models with linear predictors best captures the nature of this relationship. Within-subject effects for a quadratic function have a different meaning to those described by a linear function. The magnitude and, especially, the direction (positive/negative) of relationships between variables described by a quadratic function for example will vary depending on the magnitude of the predictor variable. In a linear relationship, the magnitude and direction of the relationship remains the same regardless of the magnitude of the predictor variable. A significant improvement in model fit (reduced error variance) using a
quadratic function indicated bi-directional effects in the nature of the relationship between predictor and outcome variables and supported the use of a quadratic function.

Table 20

*Predictor and Outcome Variables used for Hypothesis Testing and Investigation of Research Questions in Study 3*

<table>
<thead>
<tr>
<th></th>
<th>Hypotheses</th>
<th>Research Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predictor Variable</td>
<td>Outcome Variable</td>
</tr>
<tr>
<td>1</td>
<td>RA</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>2</td>
<td>RA(_{-1})</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>4</td>
<td>IV(_{-1})</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>5</td>
<td>Sleep Length</td>
<td>Mood Level</td>
</tr>
<tr>
<td>6</td>
<td>Total Bedrest</td>
<td>Mood Level</td>
</tr>
<tr>
<td>7</td>
<td>TST</td>
<td>Mood Level</td>
</tr>
<tr>
<td>8</td>
<td>Sleep Length</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>9</td>
<td>Total Bedrest</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>10</td>
<td>TST</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td>11</td>
<td>M10</td>
<td>Mood Level</td>
</tr>
</tbody>
</table>

*Note.* \(_{-1}\) subscript = predictive (lag -1) relationship.

Distributional assumptions associated with the MLM technique were assessed prior to analysis. The presence of univariate outliers in the predictor variables was investigated in the first instance, as outliers can adversely affect the regression solution.
Extreme values (scores greater than three times outside the interquartile range of the standard boxplot) were removed from the series’ and replaced with values computed using the EM algorithm (Dempster, Laird, & Rubin, 1977; see also Velicer & Colby, 2005). Univariate outliers in the two mood variables (Mood Level and Mood Deviation) were also investigated. The distribution of scores on these variables was narrow and many extreme outliers existed. Removal and/or replacement of all these values was deemed too detrimental to the natural distribution of scores. Consequently, all scores were retained in the data series’ for these variables. Multivariate outliers between the outcome variables and each of the predictor variables were also investigated, although as most of the extreme variance had been reduced through the removal of extreme univariate values in the predictor series’, only a small number were identified. Those that were identified were evaluated on a case-by-case basis, and were generally retained in the data series’ to be used for MLM. Three multivariate outliers were deleted, pairwise, for three separate MLM equations even though they were not expected to affect the solution.

After the replacement of outliers, the distribution of scores on each of the predictor variables was investigated. Normal distribution of scores on the predictor and outcome variables is an important assumption associated with the MLM technique as it enhances linearity of the relationship between variables (Tabachnick & Fidell, 2007). The distribution of scores on most of the predictor variables was normal or near normal. Therefore, unless transformation was beneficial in substantially reducing the influence of any remaining outliers, all distributions were retained in their raw format. The M10 variable displayed a positively skewed distribution that was made normal after applying a square root transformation. The transformed data was used for hypothesis testing. The distribution of scores on the Mood Level variable was highly leptokurtic, with many scores around the mid-point of 50 on the 100-point VAS. Similarly, the distribution of scores on the Mood Deviation variable was highly positively skewed, with many scores around zero. Inverse transformation did not improve the univariate distribution of data for Mood Level or Mood Deviation, so the raw data was retained for hypothesis testing.
Centering of predictor variables is a necessary preliminary data manipulation in MLM analysis that improves numerical performance of the modelling algorithm (Kreft, de Leeuw, & Aiken, 1995). It can also limit the possibility of multicollinearity in the solution. Singer and Willett (2003) recommend the use of a centering constant with substantive meaning for the population and parameter being investigated (e.g., 100 is a meaningful centering constant for the investigation of IQ in the general population). However, given that natural variation in each of the predictor variables was expected, and that there are no ‘typical’ values for each of the variables, the sample mean was considered the most useful centering constant. Thus, all predictor variables were grand-mean centered prior to MLM.

6.8 Results for Study 3

The Results section is presented in three parts. Descriptive findings are presented first and include data from the baseline questionnaire and mean data for the activity, sleep, and mood variables (6.8.1). Group comparisons with those from the High and Low GBI groups in Study 2 on these mean variables are also presented in this section. The second part of the Results section focuses on investigation of autocorrelation patterns in the two outcome variables, and relationships between the various measures of activity and sleep (6.8.2). Hypothesis testing of the relationships between predictor and outcome variables using MLM is presented next (6.8.3). Finally, exploratory analysis of a case study of manic relapse is presented (6.8.4).

6.8.1 Descriptive findings

6.8.1.1 Baseline data

Means and standard deviations for all self-report scales used in the baseline questionnaire are presented in Table 21.
Table 21

Means and Standard Deviations for the GBI, TEMPS-A, and NEO-FFI Temperament and Personality Scales

<table>
<thead>
<tr>
<th></th>
<th>GBI</th>
<th></th>
<th>TEMPS-A</th>
<th></th>
<th>NEO-FFI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyp</td>
<td>Dep</td>
<td>Total</td>
<td>DT</td>
<td>CT</td>
</tr>
<tr>
<td>Mean</td>
<td>42.5</td>
<td>70.2</td>
<td>113.0</td>
<td>1.3</td>
<td>6.8</td>
</tr>
<tr>
<td>SD</td>
<td>19.6</td>
<td>35.5</td>
<td>52.9</td>
<td>1.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Note. GBI = General Behavior Inventory, Hyp = Hypomania subscale score, Dep = Depression subscale score, Total = GBI Total scale score, TEMPS-A = Temperaments Autoquestionnaire, DT = Dysthymic temperament, CT = Cyclothymic temperament, HT = Hyperthymic temperament, IT = Irritable temperament, AT = Anxious temperament, NEO-FFI = NEO-Five Factor Inventory, N = Neuroticism, E = Extraversion, O = Openness to experience, A = Agreeableness, C = Conscientiousness.

N = 15.
Table 21 shows that scores on all subscales of the TEMPS-A, except CT, are similar to the normative data means reported for a group of clinically recovered BD outpatients (1.05, 3.48, 1.61, 0.80, for the DT, HT, IT, and AT subscales, respectively; Mendlowicz et al., 2005). The mean score on the CT subscale in the Study 3 sample was substantially higher than that described in Mendlowicz et al. \( M = 3.66 \). Scores on the N and O subscales of the NEO-FFI in the sample were substantially higher than those reported in a normative adult sample (17.60 and 27.09 for the N and O subscales, respectively; Costa & McCrae, 1992). Scores on the E, A, and C subscales in the sample were not substantially different from the means from the same normative sample (27.22, 31.93, 34.10, for the E, A, and C subscales, respectively). There are no normative data for Likert-scored GBI with which to compare GBI scores in the Study 3 sample. Mean Likert-scores in a well student sample \( N = 176 \) were reported by Murray et al. (2007). The mean total GBI score for the BD sample in Study 3 was well above that reported by Murray et al. for their student sample \( M = 44.7 \).

Mean scores on the GBI and TEMPS-A for the BD group in Study 3 were compared to scores for the High GBI and Low GBI groups in Study 2. There was an overall effect of group on the CT \( F(2,84) = 60.23, p < .001, \text{partial } \eta^2 = .59 \), DT \( F(2,84) = 13.31, p < .001, \text{partial } \eta^2 = .24 \), IT \( F(2,84) = 11.76, p < .001, \text{partial } \eta^2 = .22 \), and AT \( F(2,84) = 8.95, p < .001, \text{partial } \eta^2 = .18 \) subscales of the TEMPS-A. Post hoc comparisons revealed that the BD group scored significantly lower than the High GBI group on the DT subscale. Both the High GBI group and the BD group scored significantly higher on the CT subscale than the Low GBI group. There was no significant difference on the IT and AT subscales between the High GBI group and the BD group. Scores on the Hypomania and Depression scales of the GBI in the BD group were not significantly different from scores on these scales in the High GBI group \( t(49) = 0.76, ns \), \( t(49) = 0.07, ns \), and \( t(49) = 0.33, ns \), for the Hypomania, Depression, and Total scale scores of the GBI, respectively. Mean differences in scores on the GBI between the BD group and the Low GBI group were not evaluated.

In summary, investigation of personality and temperament showed that the sample of BD outpatients in Study 3 reported very similar temperament characteristics to
previous samples of BD outpatients. CT was an exception, with substantially higher scores in the current sample compared to previous samples. There were no differences in CT score between the BD sample in Study 3 and the High GBI group from Study 2, but both were significantly higher in CT than the Low GBI group. Personality characteristics in the current sample were similar to normative data, except for the N and O dimensions, which were substantially higher. As reviewed in Study 1, these are not unusual findings. There was no difference on mean GBI score between the BD group in Study 3 and the High GBI group from Study 2, supportive of the dimensional trait hypothesis of vulnerability to BD.

6.8.1.2 Longitudinal data

Means and standard deviations for the 24-hour activity rhythm variables are presented in Table 22. They are intended to serve as a brief representation of participants’ scores in the context of comparable data from other sources.

Table 22

<table>
<thead>
<tr>
<th></th>
<th>Daytime Activity M10</th>
<th>Circadian Rhythm Stability IV</th>
<th>RA</th>
<th>Objective Sleep TST</th>
<th>SE</th>
<th>WASO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>318.41</td>
<td>.85</td>
<td>.88</td>
<td>447.45</td>
<td>78.80</td>
<td>66.42</td>
</tr>
<tr>
<td>SD</td>
<td>138.03</td>
<td>.26</td>
<td>.05</td>
<td>98.35</td>
<td>7.52</td>
<td>25.63</td>
</tr>
</tbody>
</table>

Note. M10 = average activity during the most active 10-hour period of the day, IV = intradaily variability, RA = relative amplitude, TST = total sleep time (minutes), SE = sleep efficiency (%), WASO = wake after sleep onset (minutes).

N = 15
Mean circadian rhythm stability in the clinical group of Study 3 was lower than that reported by Jones et al. (2005) in their sample of BD-I outpatients. However, differences were not substantial. Jones et al. reported mean IV of 0.81 (SD = 0.25) and mean RA of 0.90 (SD = 0.07) for their BD group. Mean M10 scores for the purposes of comparison are not available from their study. Mean SE was lower, and mean WASO higher, in the Study 3 sample compared to the data of Jones et al. (M = 84.22, SD = 6.46; M = 57.86, SD = 30.60, for the SE and WASO variables, respectively), potentially indicating poorer quality sleep in the current group. There was no substantial difference in TST between BD groups (M = 450.76, SD = 65.86 for the Jones et al. group). The Study 3 group slept less and woke more often during sleep compared to the BD-I group of Harvey et al. (2005). Mean TST in the Harvey et al. BD group was 524 minutes (SD = 78) and mean WASO was 37.50 minutes (SD = 30.20).

In comparison with the well student groups from Study 2 on the variables derived from the 24-hour activity rhythm, a multivariate ANOVA with participants’ age as a covariate revealed an overall effect of group with a moderate effect size, F(8,158) = 2.63, p < .05, partial η² = .12. Using a Bonferroni-adjusted significance level of .01 for five comparisons, between-group differences were significant for the RA variable only, F(2,81) = 5.66, p < .01, partial η² = .12. After adjustments for age, the High GBI group exhibited the lowest mean RA (M = .84, SE = .02), followed by the BD group (M = .86, SE = .04), and the Low GBI group (M = .91, SE = .02). Between group comparisons on the objective sleep variables were not significant according to a multivariate ANOVA using age as a statistical covariate, F(6,160) = 1.32, ns.

Descriptive data for the mood and sleep self-reports using ChronoRecord are also provided, again, primarily for the purposes of comparisons with comparable data from other sources. Table 23 presents means and standard deviations for the two self-report mood variables (Mood Level and Mood Deviation) and the two self-report sleep variables (Sleep Length and Total Bedrest).
Table 23

*Means and Standard Deviations for the Mood and Sleep Self-reports from ChronoRecord*

<table>
<thead>
<tr>
<th></th>
<th>Self-reported Mood</th>
<th></th>
<th>Self-reported Sleep</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mood Level</td>
<td>Mood Deviation</td>
<td>Sleep Length</td>
<td>Total Bedrest</td>
</tr>
<tr>
<td>Mean</td>
<td>48.84</td>
<td>7.23</td>
<td>482.44</td>
<td>533.68</td>
</tr>
<tr>
<td>SD</td>
<td>12.03</td>
<td>9.68</td>
<td>198.50</td>
<td>193.07</td>
</tr>
</tbody>
</table>

*Note.* Four participants did not provide self-report mood and sleep data of sufficient length or quality and are thus not included in these descriptive statistics (see Section 6.7.1).

* N = 11

There is minimal published ChronoRecord data with which to directly compare the mean Mood Level of the Study 3 sample. Glenn et al. (2006) reported a mean mood of 47.8 (SD = 4.7) in a sample of BD-I outpatients in the 60 days prior to a euthymic period. In the same study, mean mood was reported to be lower in the 60 days prior to the onset of depression (M = 42.7, SD = 7.1) or mania (M = 44.4, SD = 11.5). These average findings would appear to be consistent with those of Study 3 in finding a sub-50 mean mood rating.

As Mood Deviation is a variable that is unique to Study 3, there are no published data with which to compare the clinical group. However, studies with which to compare the percentage of time spent euthymic, depressed, or hypo/manic based on ChronoRecord ratings are available. In a sample of 79 outpatients with BD-I, Adli et al. (2005) reported that 69.4% of days were rated in the euthymic range, 22.9% of days were rated in the depressed range, and 7.7% of days were rated in the hypo/manic range. A smaller BD outpatient sample consisting of only female participants reported 34% of days depressed, 57% euthymic, and 10% hypo/manic over a 3 month period (Rasgon, Bauer, Glenn, Elman, & Whybrow, 2003). In Study 3, 77.0% of days were rated as euthymic, 14.3% of days were rated as depressed, and 8.7% of days were rated as hypo/manic. The percentage of depressed days was therefore lower, and percentage of
euthymic days higher, in the Study 3 sample compared to previous samples of BD-I outpatients.

No studies reporting mean ChronoRecord sleep hours are available with which to compare the self-report sleep data in Study 3. There are however studies that have reported mean self-reported sleep hours using different methods, such as sleep diaries. Harvey et al. (2005) reported a mean subjective total sleep time estimate of 426 minutes ($SD = 96$) in their sample of BD-I outpatients. Millar et al. (2004) reported an average subjective sleep duration estimate of 473.5 minutes ($SD = 112.9$) in their BD-I sample. The mean self-reported sleep duration in the clinical sample of Study 3 was somewhat higher than both of these average values. No data is available with which to compare mean values on the Total Bedrest variable.

**6.8.2 Preliminary analysis of within-subject relationships**

Prior to hypothesis testing, autocorrelation structures in the mood outcome variables were investigated for evidence of linear trends (6.8.2.1). Strong autocorrelation structures amongst variables can affect the interpretation of outcomes in time series designs (Box, Jenkins, & Reinsel, 1994). Interdependent associations between predictor variables were also investigated for the purposes of evaluating potentially informative relationships between predictors (6.8.2.2).

**6.8.2.1 Autocorrelation structures within mood variables**

Investigation of interdaily patterns in the Mood Level variable revealed a significant positive autocorrelation on successive days ($r = .41$, $p < .001$). Autocorrelations at lags of 2 and 3 days were also positive and significant ($r = .37$ and $r = .30$, for days 2 and 3, respectively; $p < .001$ for both), although the magnitude of the associations was greatly reduced after the influence of the strong correlation at lag 1 had been partialled out.
(partial $r = .24$ and partial $r = .12$, for days 2 and 3, respectively). Thus, the autocorrelation for the sample was positive and strong, particularly at a lag of 1 day.

To investigate the influence of between-subject differences in this relationship, an MLM equation was constructed with Mood Level differenced by 1 day predicting the Mood Level variable. The between-subject effects model failed to converge, indicating that there was no significant between-subject variation in the average relationship between Mood Level and Mood Level -1 day. The within-subject effect for this model was positive and significant (parameter estimate = 0.78, approx $df = 1284$, $p < .05$), and the addition of a quadratic term did not significantly improve model fit (-2logl statistic = 10,005.60 and 10,004.00, for the linear and quadratic equations, respectively; $\chi^2$ diff = 1.60, ns). Therefore, the best model of the relationship between Mood Level and Mood Level -1 day was positive and linear, with no between-subject moderation of the within-subject effect.

A significant positive autocorrelation was also found for the Mood Deviation variable. The autocorrelation parameter at a lag of 1 day was $r = .52$, $p < .001$. Strong autocorrelations were also apparent at lags of up to 7 days. However, the partial correlation was substantially reduced beyond lags of 2 and 3 days (partial $r = .28$ and partial $r = .17$, respectively). Between-subject differences in the relationship between Mood Deviation and Mood Deviation -1 day were also investigated. The within-subject effect for this model was positive and significant (parameter estimate = 0.07, approx $df = 1311$, $p < .05$). The addition of a between-subject effect term improved model fit significantly ($\chi^2$ diff = 9.74, $p < .005$, 1 $df$) indicating significant between-subject variation in the average relationship between Mood Deviation and Mood Deviation -1 day.

It would appear that linear trends characterise the longitudinal within-parameter relationship for both mood variables. It is necessary to model these trends to remove their influence on the relationship between predictor and outcome variables in MLM analysis. Thus, linear trends were modeled using ARMA(1,1) for all MLM equations.
6.8.2.2 Relationships between circadian rhythm instability and total daytime activity

Zero lag correlations between the two measures of circadian rhythm instability (RA and IV) and total daytime activity (M10) were investigated for potentially informative relationships. RA and IV are proposed to measure different components of the 24-hour activity rhythm (Van Someren et al., 1999; see also Section 5.3.1), and M10 is intended to measure a separate activity-based process. Table 24 presents the bivariate, zero lag correlations between RA, IV, and M10.

Table 24

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>IV</th>
<th>M10</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>-</td>
<td>-.32*</td>
<td>.25*</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>-</td>
<td>-.54*</td>
</tr>
<tr>
<td>M10</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

Note. M10 = average activity during the most active 10-hour period of the day, IV = intradaily variability, RA = relative amplitude.

* p < .001

Correlations revealed weak-moderate associations between all variables, as expected. The separability of these variables was therefore supported, and all were retained for hypothesis testing.
6.8.2.3 Relationships between objective and subjective measures of sleep

The average amount of time spent sleeping, as self-reported by participants in ChronoRecord (Sleep Length; $M = 482.44$ minutes per day), was substantially greater than the amount of sleep time recorded objectively using actigraphy (TST; $M = 447.45$ minutes per day). Consistent with previous studies, the synchronous correlation between the objective and subjective measures of sleep was $r = .13$, indicating only weak agreement between these two measures (see Section 3.2).

6.8.3 Hypothesis testing

The predictor variables for MLM analyses were M10, IV, RA, TST, SE, WASO, Sleep Length, and Total Bedrest. The outcome variables were Mood Level and Mood Deviation. Within-subject associations were assessed for all hypothesised relationships. Between-subject differences in these relationships were also assessed.

6.8.3.1 Circadian rhythm instability and mood deterioration

Table 25 presents the results of MLM analyses investigating within-subject associations between activity rhythm stability estimates and Mood Deviation, for both zero and -1 lag relationships between variables. It can be seen that there were no significant linear relationships between RA and the Mood Deviation variable at either zero (Hypothesis 1) or -1 lags (Hypothesis 2). Similarly, there were no significant associations between IV and Mood Deviation at either zero (Hypothesis 3) or -1 lags (Hypothesis 4).
Table 25

Within-Subject Parameter Estimates for Zero and -1 Lag Relationships Between Circadian Rhythm Instability and Mood Deviation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Zero lag</td>
<td>0.17</td>
<td>0.23</td>
<td>0.74</td>
<td>1318</td>
</tr>
<tr>
<td></td>
<td>-1 lag</td>
<td>-0.27</td>
<td>0.23</td>
<td>-1.19</td>
<td>1317</td>
</tr>
<tr>
<td>IV</td>
<td>Zero lag</td>
<td>0.08</td>
<td>0.23</td>
<td>0.35</td>
<td>1261</td>
</tr>
<tr>
<td></td>
<td>-1 lag</td>
<td>-0.45</td>
<td>0.23</td>
<td>-0.60</td>
<td>1246</td>
</tr>
</tbody>
</table>

Note. IV = intradaily variability, RA = relative amplitude.

Between-subject effects in the relationships between the Mood Deviation outcome variable and the RA and IV predictor variables were not found. Between-subject effect models failed to converge for all MLM equations, indicating redundancy in the parameter estimates for these models. Thus, the nonsignificant within-subject associations between variables in this part of the analysis did not vary between participants.

In sum, there was no evidence that measures of circadian rhythm instability were prospectively associated with mood deterioration.

6.8.3.2 Sleep and mood deterioration

Table 26 presents the results of MLM analyses investigating within-subject associations between sleep measures (self-report and actigraph-derived), and Mood Level. Parameter estimates are presented for zero lag relationships between variables only, as per the stated hypotheses.
Table 26

*Within-Subject Parameter Estimates for Zero Lag Relationships Between Sleep Variables and Mood Level*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Length</td>
<td>0.04</td>
<td>0.42</td>
<td>0.10</td>
<td>882</td>
<td>.92</td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>-0.73</td>
<td>0.50</td>
<td>-1.46</td>
<td>596</td>
<td>.14</td>
</tr>
<tr>
<td>TST</td>
<td>-0.53</td>
<td>0.30</td>
<td>-1.76</td>
<td>1192</td>
<td>.08</td>
</tr>
<tr>
<td>SE</td>
<td>-0.68</td>
<td>0.37</td>
<td>-1.85</td>
<td>1080</td>
<td>.07</td>
</tr>
<tr>
<td>WASO</td>
<td>0.20</td>
<td>0.35</td>
<td>0.56</td>
<td>1233</td>
<td>.58</td>
</tr>
</tbody>
</table>

*Note.* TST = total sleep time, SE = sleep efficiency, WASO = wake after sleep onset.

Linear associations between the self-report measures of sleep (Sleep Length, Total Bedrest) and Mood Level were not found. Hypotheses 5 and 6 were therefore not supported. A linear association between the objective measure of sleep length (TST) and Mood Level was also not found. Hypothesis 7 was therefore also not supported. A nonsignificant trend towards a negative linear association was apparent in the relationship between TST and Mood Level, indicating that increases in Mood Level may be associated with reduced TST and, vice versa, decreases in Mood Level may be associated with increased TST.

Linear associations between Mood Level and both SE (Research Question 1) and WASO (Research Question 3) were not found. Again however, a nonsignificant trend for a negative linear association between SE and Mood Level was apparent.

Between-subject effects in the synchronous associations between the sleep predictor variables and the Mood Level outcome variable were not found. Between-subject effect models failed to converge for all MLM equations, indicating redundancy in the
parameter estimates for these models. Thus, the nonsignificant within-subject associations between variables in this analysis did not vary between participants.

Table 27 presents the results of MLM analyses investigating within-subject associations between sleep estimates (self-report and actigraph-derived), and Mood Deviation. Quadratic effects are presented for the relationships between the Sleep Length and Total Bedrest predictor variables. The improvement in fit diagnostics between linear and quadratic models was significant according to the \(-2\log l\) statistics (\(\chi^2\) diff = 15.91 and 16.89 for the Sleep Length and Total Bedrest predictors, respectively; \(p < .001\) for both). Quadratic within-subject effects are not presented for the TST variable because there was no significant improvement in the \(-2\log l\) statistic for this model (\(\chi^2\) diff = 0.24). Parameter estimates are presented for zero lag relationships between variables only.

Table 27

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>(p) (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Length(_q)</td>
<td>0.44</td>
<td>0.26</td>
<td>1.72</td>
<td>900</td>
<td>.09</td>
</tr>
<tr>
<td>Total Bedrest(_q)</td>
<td>1.07</td>
<td>0.31</td>
<td>3.43</td>
<td>53</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>TST</td>
<td>0.31</td>
<td>0.22</td>
<td>1.42</td>
<td>1248</td>
<td>.16</td>
</tr>
<tr>
<td>SE</td>
<td>0.45</td>
<td>0.27</td>
<td>1.65</td>
<td>1280</td>
<td>.10</td>
</tr>
<tr>
<td>WASO</td>
<td>-0.29</td>
<td>0.26</td>
<td>-1.12</td>
<td>1316</td>
<td>.26</td>
</tr>
</tbody>
</table>

*Note.* TST = total sleep time, SE = sleep efficiency, WASO = wake after sleep onset.

\((q)\) subscript = quadratic function used to estimate within-subject parameter estimate.
A significant quadratic within-subject association was apparent for the relationship between the self-report Total Bedrest variable and Mood Deviation, supporting Hypothesis 9. The relationship was positive, indicating a standard U-shaped distribution for this association. In real terms, this means that both increases and decreases in the amount of Total Bedrest on the night immediately preceding the index mood rating was associated with increasing Mood Deviation. The quadratic relationship between Sleep Length and Mood Deviation was not significant. Hypothesis 8 was therefore not supported. The lack of improved fit diagnostics from linear to quadratic models for the association between TST and Mood Deviation indicate that Hypothesis 10 was not supported. The linear association between these variables was not significant. Linear associations between the SE and WASO predictor variables, and the Mood Deviation outcome variable (Research Questions 2 and 4, respectively) were also not significant.

Significant improvement in model fit occurred with the addition of a between-subjects factor to the relationships between Sleep Length and Mood Deviation, and between Total Bedrest and Mood Deviation ($\chi^2$ difference = 31.26, $p < .001$ for 3 df; and $\chi^2$ difference = 5.48, $p < .05$ for 2 df, respectively). Parameter estimates and model statistics are shown in Table 28 for both between-subject effect models.

Table 28

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>Wald Z</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Length</td>
<td>10.27</td>
<td>5.79</td>
<td>1.77</td>
<td>.08</td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>1.77</td>
<td>1.81</td>
<td>0.98</td>
<td>.33</td>
</tr>
</tbody>
</table>

The significant improvement in model fit with the addition of a between-subjects factor did not translate into significant between-subject parameter estimates for either
model. The significant within-subject association between Total Bedrest and Mood Deviation therefore, would appear to be consistent for the whole sample. Similarly, the nonsignificant within-subject association between Sleep Length and Mood Deviation would appear to be consistent across the sample, although a possible trend towards significant between-subject variation was apparent for this latter association.

Between-subject effects were not found for the relationships between the Mood Deviation outcome variable, and the TST, SE, and WASO predictor variables, respectively. Between-subject effect models failed to converge for these equations, indicating redundancy in the parameter estimates for these models.

In sum, one sleep variable was significantly associated with mood in Study 3. The self-report estimate of Total Bedrest, incorporating both time spent in bed asleep and time spent in bed awake, was found to be positively associated with Mood Deviation using a quadratic function. Thus, both increases and decreases in the amount of Total Bedrest was associated with increasing Mood Deviation the next day. No between-subject differences were apparent in this relationship. For the remaining sleep predictor variables, significant associations with either operationalisation of mood were not apparent. However, possible trends towards negative linear relationships between both the TST and SE predictor variables and the Mood Level outcome variable were observed.

6.8.3.3 Total daytime activity and mood deterioration

Table 29 presents the results of MLM analyses investigating linear associations between Activity Level and Mood Level. Within-subject parameter estimates are presented for both zero lag and -1 lag relationships between variables.
Table 29

*Within-Subject Parameter Estimates for Zero and -1 Lag Relationships Between Total Daytime Activity and Mood Level*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>M10 Zero lag</td>
<td>1.86</td>
<td>0.46</td>
<td>4.04</td>
<td>705</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>-1 lag</td>
<td>0.79</td>
<td>0.46</td>
<td>1.70</td>
<td>719</td>
<td>.09</td>
</tr>
</tbody>
</table>

*Note.* M10 = average activity during the most active 10-hour period of the day

A significant linear effect was apparent for the within-subject relationship between M10 and Mood Level, supporting Hypothesis 11. The positive sign of the parameter estimate describes a relationship whereby both predictor and outcome variables increase (or decrease) in magnitude in the same direction. Increases in activity were associated with increases in mood. There was no significant association between M10 and Mood Level at -1 lag.

Between-subject effects were not apparent for the relationships between M10 and Mood Level at either zero or -1 lag. Between-subject effect models failed to converge for these equations, indicating redundancy in the parameter estimates for these models. Thus, the significant zero lag association between M10 and Mood Level would appear to be consistent across all participants.

In sum, the average amount of activity during the 10 most active hours of the day was associated with mood on the same day. This linear relationship was positive, indicating that increases in daytime activity were associated with higher moods, and decreases in daytime activity were associated with lower moods. There was no significant association between daytime activity and mood the following day.
6.8.3.4 Hypothesis testing summary

As shown in Table 30, investigations of numerous predicted and exploratory relationships led to negative findings in all cases, bar two. A significant association was found at the zero lag between Total Bedrest and Mood Deviation (Hypothesis 9). The positive quadratic association between these variables indicated that the amount of Mood Deviation increased the further Total Bedrest deviated from usual, both when more or less than the normal amount of Total Bedrest was achieved the night before. A significant linear relationship was found between M10 and Mood Level, indicating that Total Daytime Activity and Mood Level were positively associated on the same day (Hypothesis 11). There was no between-subject variation in any of the relationships investigated in Study 3.

Table 30

<table>
<thead>
<tr>
<th></th>
<th>Synchronous (zero lag)</th>
<th>Predictive (-1 lag)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mood Level</td>
<td>Mood Deviation</td>
</tr>
<tr>
<td><strong>Circadian Rhythm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>WASO</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Sleep Length</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Daytime Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M10</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Note. ✓ = significant relationship; hypothesis supported; x = no significant relationship
6.8.4 Case study of manic relapse

Manic and depressive episodes were not anticipated in the medicated, clinically stable sample employed in Study 3. However, one participant (Participant B) was withdrawn from the early stages of the study due to hospitalisation for a manic episode, providing the opportunity for a potentially illuminating post hoc analysis. Before the episode, the participant contributed approximately 100 days of actigraph data, but no ChronoRecord mood or self-report sleep data. The raw data actogram for this participant for the period leading up to manic onset is shown in Figure 12.24 The figure shows that little to no sleep occurred for three nights leading up to manic onset and subsequent removal of the Actiwatch. The gradual increase in activity during the sleepless nights is conspicuous. A possible phase delay in sleep onset is also apparent in the days leading up to the removal of the Actiwatch.

24 Dates have been removed to ensure participant anonymity.
Figure 12. Raw data actogram for Participant B in the 14 days prior to manic onset.

A limited set of activity (M10, IV, RA) and sleep variables (TST) were computed for the period leading up to hospitalisation for Participant B, for the purposes of exploring relationships between predictor variables and onset of the mood episode. The relationships were assessed via visual inspection of the smoothed data sequences. A compound data smoother (T4253H in SPSS 17.0 for Windows; SPSS, Inc., Chicago,
Illinois) was applied to predictor variable data to reduce the visual frequency of transitions in the data series and facilitate identification of simple patterns and trends. The onset of the manic episode was estimated at Day 98 of Participant B’s involvement in the study according to the dates noted in the participant’s case file. There is no data beyond Day 103 as this was when the Actiwatch was removed by the participant. Hospitalisation occurred soon after the Actiwatch was removed. Figure 13 presents the smoothed M10 data sequence for Participant B leading up to onset of mania.

Figure 13. Smoothed M10 data sequence as a function of time for Participant B

There does not appear to be any obvious patterns of maximum activity around the time of the manic episode, apart from a conspicuous peak approximately 10-15 days before the manic event. Activity levels then decreased in the days prior to episode onset. Increases in activity are a central feature of mania (Serretti & Olgiati, 2005), and would be expected to be demonstrated here. The relatively high mean level of M10 for
Participant B ($M = 469.99$) compared to the mean level of M10 for the rest of the sample ($M = 338.60$) may partially explain why there was no increase in activity at manic onset.

The pattern of 24-hour activity rhythm stability (IV) around the time of manic onset is shown in Figure 14.

![Figure 14. Smoothed IV data sequence as a function of time for Participant B](image)

A conspicuous pattern of changes in the intradaily variability of the 24-hour activity rhythm emerges at around the time of manic onset. Firstly, the level of intradaily variability reaches a peak on the day the episode is estimated to have commenced. The peak is immediately preceded by a sharp increase and, from a visual perspective at least, presents evidence of an ‘event’ occurring at around this time. Secondly, and perhaps more interesting, is the approximately linear decrease in IV in the months leading up to the manic event, starting at Day 35 and reaching its nadir 10 days before manic onset.

Similar changes in RA can be seen in Figure 15 below on the day the manic episode is estimated to have commenced. For this variable however, there does not appear to be
any obvious change in the longitudinal course of RA prior to the onset of the manic episode. All major changes in the longitudinal course of RA occur after manic onset.

Figure 15. Smoothed RA data sequence as a function of time for Participant B

Self-report Sleep Length and Total Bedrest data was not available for Participant B, as this participant withdrew from the study before the ChronoRecord program could be installed. Actigraph-derived sleep data (TST) was available however, and the longitudinal course of this data leading up to the onset of mania is presented in Figure 16.
Figure 16. Smoothed TST data sequence as a function of time for Participant B

An associated decrease in the amount of total sleep per day can be seen in Figure 16 at around the time of manic onset. This pattern of sleep is not unusual in the pre-episodic period of patients with BD (Wehr et al., 1987). For Participant B, this would certainly appear to be the case with little or no sleep occurring on Days 72, 88, 98, 100, and 102 according to the raw activity data (Figure 13 shows the last 3 nights of sleep loss prior to manic onset). In this case therefore, a pattern of increasingly regular nights of sleep loss begins to occur up to one month before the onset of the manic event.

For the only person to experience an externally validated, clinically-relevant, manic or depressive event therefore, a pattern can be seen in actigraph-derived variables around the time of a manic episode. The dramatic change in activity at this time appears to be limited to the two measures of 24-hour activity rhythm stability. In addition, for the IV variable, a systematic trend of decreasing stability in the 24-hour activity rhythm appeared to characterise the months leading up to the manic event. Similarly, an increase in the number of nights with little or no sleep was observed in the month leading up to
manic onset. No change was apparent in the level of activity during the most active part
of the day (M10), either before or after the onset of mania.

6.9 Discussion for Study 3

The aim of Study 3 was to investigate prospective relationships between the
Circadian Rhythm Instability, Sleep, and Total Daytime Activity predictor variables, and
two mood outcome variables (Mood Level and Mood Deviation) in a sample of case
managed, community-dwelling patients with BD-I. Hypothesis testing consisted of a
series of MLM equations. The findings from Study 3 are presented below according to
the order in which hypotheses were presented; viz., Circadian Rhythm Instability
predicting mood deterioration (6.9.1), Sleep predicting mood deterioration (6.9.2), and
Total Daytime Activity predicting mood deterioration (6.9.3). The findings from
investigation of between-subject analyses of predictor/outcome variable relationships
are presented in Section 6.9.4. The implications of both within- and between-subject
findings for clinical practice are presented next (6.9.5), followed by a review of the
exploratory findings from the case study investigation of manic onset (6.9.6). Finally,
methodological limitations of Study 3 (6.9.7) and future directions for research of this
kind are presented (6.9.8).

6.9.1 Circadian rhythm instability and mood deterioration

MLM analysis was expected to reveal a significant linear association between a
weaker circadian activity rhythm (operationalised as reduced amplitude, RA, and
increased intradaily variability, IV, of the 24-hour activity rhythm) and mood
deterioration (operationalised as the amount of deviation from usual mood, Mood
Deviation) on the same day (Hypotheses 1 and 3, respectively). These hypotheses were
not supported. Daily changes in the amplitude and variability of the 24-hour activity rhythm were not significantly associated with deterioration in daily mood.

Relationships between the two measures of circadian activity rhythm stability and the level mood deterioration the next day were also investigated (Hypotheses 2 and 4, respectively). The associations between both RA and IV, and Mood Deviation at -1 lag were investigated because they may have important implications for the identification and management of episode prodromes. Analyses revealed no significant associations between these variables. The level of mood deterioration was not predictable from changes in the stability of the circadian activity rhythm the previous day.

Some previous studies have found cross-sectional differences in the stability of the 24-hour activity rhythm between BD populations and groups of non-BD controls (e.g., Jones et al., 2005). Salvatore et al. (2008) also found significant differences in the stability of the activity rhythm between a group of BD patients experiencing manic or mixed episodes and non-BD controls. These associations were not supported by the findings of Study 3. The effects of circadian rhythm instability on daily mood deterioration thus appear to be different to those at the trait level (as found by Jones et al., 2005) and those at the level of clinical mood deviation (as found by Salvatore et al., 2008), and add a further level of sophistication to our understanding of the complex relationships between circadian rhythm instability and mood change in this specific population. Possible implications of these findings are discussed in Chapter 7.

Based on the findings of Study 3, it would appear that stability of the 24-hour activity rhythm is not a state marker of daily mood variation in people with BD. As a consequence of these findings, the amplitude of the activity rhythm can not be regarded as a mediating vulnerability factor in BD (see Section 1.3). The potential role played by activity rhythm stability in vulnerability to BD, particularly at the level of trait vulnerability to the disorder, will be considered in more detail in Chapter 7. For the moment however, it is sufficient to conclude that this particular feature of the 24-hour activity rhythm is not a state marker of vulnerability to BD.

25 Stability of the activity rhythm in the Salvatore et al. study was represented by the amplitude of the 1 cycle-per-day cosinor curve fitted to the activity data.
6.9.2 Sleep and mood deterioration

6.9.2.1 Self-report measures of sleep

Self-report measures of sleep time (Sleep Length; Hypothesis 5) and the amount of time spent in bed both awake and asleep (Total Bedrest; Hypothesis 6) were expected to be negatively and linearly associated with Mood Level the next day (following Bauer, Grof, Rasgon, Bschor et al., 2006). Neither of these predictions were supported by the data. The total amount of self-reported sleep time was not significantly correlated with self-reported mood the following day. Similarly, the total amount of self-reported time spent in bed was not significantly correlated with self-reported mood the following day. These were unexpected findings, particularly as the experimental procedures used in the current study were very similar to those used by Bauer, Grof, Rasgon, Bschor et al.. It is possible that, given the comparatively small sample in the current study, and the fact that only 41% of participants in the Bauer, Grof, Rasgon, Bschor et al. study were found to exhibit a significant association between sleep and mood, differences in sample composition may explain much of the variation in findings. For example, the 11 participants in the current study may have more in common with the majority of participants in the Bauer, Grof, Rasgon, Bschor et al. study who did not exhibit significant associations between sleep and mood. The source of variation in relationships between self-reported sleep and self-reported mood the following day however, is not confirmed at this stage.

Self-reports of Sleep Length and Total Bedrest were expected to be positively associated with Mood Deviation the next day, using a quadratic function (Hypotheses 8 and 9, respectively). In constructing these quadratic analyses, it was considered possible that mood may deviate more from usual for both under- and over-sleeping, hence the need for a quadratic function to model the relationship.

Hypothesis 8 was not supported. Self-reported sleep time was not significantly associated with mood deterioration the following day, using a quadratic function. The relationship emerged in the expected positive direction, and a trend towards a significant
association was found \((p = .09)\). Nevertheless, the nonsignificant findings limit the veracity of conclusions that can be drawn from this data, particularly as the volume of data available for analysis was large.

Hypothesis 9 was supported. The total amount of self-reported time spent in bed, both awake and asleep, was positively and significantly associated with mood deterioration the following day, using a quadratic function. Therefore, both greater and lesser amounts of bedrest, when compared to the usual amount of time spent in bed, were associated with an increase in the amount of deviation from usual mood the next day in the current BD sample. These data support the findings of Bauer, Grof, Rasgon, Bschor et al. (2006) but only if it is assumed that decreases in Total Bedrest were associated with mood deterioration towards hypo/mania, and increases in Total Bedrest were associated with mood deterioration towards depression. The nonsignificant zero lag relationship between Total Bedrest and Mood Level do not support this assumption. Also, given the relatively small number of ‘manic’ days reported as a proportion of total mood ratings in the current sample (see Section 6.8.1.2), the suggestion that manic mood may be associated with a reduced amount of time spent in bed can not be explicitly supported by the data in Study 3. Nevertheless, the significant positive quadratic association between Total Bedrest and Mood Deviation adds to current data by showing that sleep changes, regardless of direction (less or more than usual), may have adverse consequences for the longitudinal course of mood in people with BD.

Consistent with the findings of Bauer, Grof, Rasgon, Bschor et al. (2006), the total amount of time spent in bed, and not just the amount of time spent in bed asleep, had the closest relationship with mood in BD. Study 3 showed that Sleep Length alone was not significantly associated with Mood Deviation, while Total Bedrest was significantly associated with Mood Deviation. This can be seen to support the idea that the phenomenon captured in the data from Study 3 explains the relationship between the self-reported sleep variables and lower moods, but not higher moods. Sleep time, whether less or more than usual, was not significantly associated with mood deterioration the next day in the current data. Alternatively, time spent in bed lying awake was significantly associated with mood deterioration the next day. The anhedonic
manifestation of depression describes a state of low motivation, and may explain why many depressed patients, particularly those with BD (Mitchell et al., 2008), experience difficulty getting out of bed. Patients in a manic state on the other hand, given their increased level of goal-directedness (Johnson et al., 2008), are likely to experience little trouble getting out of bed. It is therefore a reasonable assumption that much of the Mood Deviation captured in the clinical sample of Study 3 is on the depressive side, given its significant association with the total amount of time spent in bed, and not just the amount of time spent asleep.

6.9.2.2 Objective measures of sleep

Objective measures of sleep were investigated for zero lag relationships with both operationalisations of mood. Consistent with previous studies (e.g., Harvey et al., 2005; Lockley et al., 1999), the objective measures of sleep in Study 3 were weakly correlated with their subjective counterparts. Nevertheless, it was expected that TST would be associated with mood deterioration in the same way that self-report measures of sleep (Sleep Length and Total Bedrest) were expected to be associated with mood deterioration (Hypotheses 7 and 10). Neither hypothesis was supported.

No predictions were made regarding the direction of potential relationships between the SE and WASO predictor variables, and mood deterioration. Nevertheless, relationships between these objective sleep variables and mood deterioration were investigated (Research Questions 1, 2, 3, and 4) due to the potentially important role that disrupted sleep can play in BD psychopathology (Jackson et al., 2003).

Significant linear relationships between the Mood Level outcome variable, and each of the TST, SE, and WASO predictor variables (Research Questions 4, 6, and 8, respectively) were not found. Nonsignificant trends were apparent for Mood Level relationships with TST ($p = .08$) and SE ($p = .07$), with both relationships emerging in the negative direction. However, there would appear to be enough power in the design of the study (given the large volume of data available) to identify a significant
relationship if one indeed exists. This was not the case, and so these questions remain open.

Significant relationships between the Mood Deviation outcome variable, and each of the TST, SE, and WASO predictor variables (Research Questions 5, 7, and 9, respectively) were also not found. The relationship between Mood Deviation and TST was investigated using a quadratic function. The significant quadratic association between self-reported Total Bedrest and Mood Deviation the next day was therefore not supported when an objective measure of total sleep time was used.

### 6.9.3 Total daytime activity and mood deterioration

Total Daytime Activity (operationalised as the average level of activity during the most active 10-hour period of each day, M10) was expected to be positively and linearly associated with Mood Level on the same day (Hypothesis 11). This hypothesis was supported by the data. Activity levels during the 10 most active hours of the day were increased on days with higher moods, and decreased on days with lower moods. In people with BD this linear association between activity levels and mood, including states of mood disorder such as hypo/mania and depression, has been reported numerous times (e.g., Klein et al., 1992; Mendlowicz et al., 1999; Serretti & Olgiati, 2005; Teicher, 1995). Indeed, changes in activity levels form essential components of the signs and symptoms of both mania and depression as described in DSM-IV (APA, 2000). The data in the current study is consistent with previously identified associations at the level of clinical mood change. This is the first time that changes in activity level have been demonstrated to be associated with changes in sub-clinical mood states in a BD population.

The relationship between Total Daytime Activity and Mood Level was also investigated at -1 lag (Research Question 5). Such predictive relationships may present opportunities for potential applications in the clinical setting, particularly in circumstances where changes in mood can be predicted by changes in activity the previous day. The data in Study 3 did not support relationships between activity and
mood at -1 lag. It does not appear therefore, that sub-clinical mood can be prospectively predicted by changes in activity from the previous day.

### 6.9.4 Between-subject effects in the relationships between predictor and outcome variables

Between-subject effects, indicative of variations in predictor/outcome variable relationships between participants, were also evaluated using the MLM technique. No formal predictions were made regarding these between-subject differences. Nevertheless, it was suspected that some within-subject relationships may be characterised by significant variations across people. No significant between-subject effects were identified. Therefore, in the current sample, there was little variation between people in the average relationship between predictor and outcome variables.

The lack of variation across people in the predictor/outcome variable relationships was surprising. One of the key justifications for choosing the MLM statistical technique for analysing data in Study 3 was to allow quantification of the expected variation between people in these relationships. The low level of variation between people in these relationships does not correspond with what many mental health professionals describe in day-to-day interactions with BD patients (e.g., Sierra et al., 2007) and indeed what has been shown in previous studies of a similar aim and purpose (e.g., Bauer, Grof, Rasgon, Bschor et al., 2006). In many ways, the lack of variation is an encouraging finding. It means that found associations between variables are more likely to generalise to a broader population. Nevertheless, from a clinical perspective, the lack of between-subject variation was unexpected.

Two explanations can be offered for why variations between participants were not demonstrated in the current study. Firstly, while there were a large number of observations collected from each participant, the number of participants ($N = 11$) in this study was small. This was a commendable effort from each participant, one that allowed important average effects to be demonstrated. However, for significant variation
between people to be demonstrated, if indeed variation does exist, it would appear that a much larger sample may be required.

The second explanation for a lack of significant variation across people in predictor/outcome variable relationships may relate to the structure and disposition of the sample itself, regardless of its size. Strict controls for the eligibility of participation in Study 3 were designed to simplify interpretation of findings. Inclusion of BD-subtypes (e.g., BD-II and BDNOS) and those with significant comorbid conditions (e.g., Axis II and substance-use disorders) may interfere with the precise characterisation of relationships, as each subtype may be subject to different disorder etiologies (Akiskal, Kilzieh et al., 2006) and longitudinal courses (Judd, Akiskal, Schettler, Coryell, Maser et al., 2003). The risk was however that restricting eligibility could result in an atypical BD sample, especially as it is apparent that significant comorbidities are the norm amongst this population (McElroy et al., 2001). It is possible therefore, that the relative similarity of the participants’ BD-related features in Study 3 may have been antithetic to the chances of demonstrating individual variation in many of the predicted relationships. These and other sampling issues will be discussed in further detail in the limitations section.

6.9.5 Implications for prodrome identification in Bipolar Disorder

The data in Study 3 may have important implications for the longitudinal monitoring of mood symptoms and sleep in patients with BD. The self-report measure of Total Bedrest was significantly associated with deterioration in mood (greater Mood Deviation) the following day. Self-reporting of the total time spent in bed, both asleep and awake, may therefore be an important monitoring variable that patients can use to keep track of their moods. Instances of excessive deterioration in mood, including excursions into hypo/mania and depression, may be circumvented through considered evaluation of daily bedrest patterns coupled with targeted interventions. Indeed, it may be possible to construct a ‘profile’ of an individual’s bedrest/mood relationship using ChronoRecord which can be used for this purpose.
While significant correlations characterised the prospective relationship between subjective reports of bedrest and mood, an objective measure of sleep (TST), recorded using actigraphy, was not prospectively correlated with mood in the current study. The difference in findings between subjective and objective measures of sleep-related phenomena, and their relationship with mood change is perhaps not surprising (see 6.9.2.2 above). Nevertheless, the variation in findings between data recording methods may have important consequences for their use in BD prodrome identification. Firstly, the potential for shared, or common, method variance (Doty & Glick, 1998; Spector, 2006) in the recording of self-report sleep and mood data can not be ruled out. Mood and sleep hours from the previous night were recorded in ChronoRecord at the same time (see Section 6.5), raising the possibility that reporting of one may be contaminated by simultaneous recording of the other. This limitation of the ChronoRecord self-reporting methodology is addressed in further detail below (Section 6.9.7). Secondly, actigraphy may have limitations in the accurate representation of sleep phenomena, especially in populations experiencing significant sleep disturbance (Ancoli-Israel et al., 2003), potentially limiting its usefulness as a monitoring tool for prodrome identification in BD. This limitation in actigraphic recording of sleep is also addressed in further detail below (Section 6.9.7).

Activity level monitoring using actigraphy may also have important implications for prodrome identification in patients with BD. Changes in daytime activity were significantly correlated with changes mood on the same day in Study 3. The positive linear relationship observed between Total Daytime Activity and Mood Level suggests that improvements in mood were associated with increases in activity. Excessively high or low levels of daytime activity, when compared to baseline levels, may be an independent and objective indicator of hypo/manic or depressive onset. The most obvious application of actigraphy for this purpose involves the ability to automatically monitor increases in activity, bypassing the need to rely on potentially unreliable subjective reports of changes in activity (see Section 3.3.). Current actigraphic technology however, does not permit real-time monitoring of activity, somewhat
limiting its use for this purpose. This and other limitations of actigraphy are discussed in further detail in Section 6.9.7.

It must be reiterated at this point that the mood data collected in Study 3 was limited to observations of sub-clinical mood changes, and not specifically episodes of mania and depression. It has yet to be fully understood how these sub-clinical mood changes are related to episodes of mania and depression. A minimum length criterion is required by DSM-IV for diagnosis of BD, however there are few evaluative requirements regarding the quality of the mood experience. Mania is an intense state of euphoria (high mood) for some people with BD, while others deal with anxiety, irritability, and delusions during this phase of the illness (Swann et al., 2001). A cut-point has been set by the authors of ChronoRecord to demarcate pleasurable moods from pathological hypomania, however the validity of this distinction has not been demonstrated.

It is also worth noting here that effect sizes for the significant fixed effect relationships found in Study 3 were both small, and any implications for applying such relationships in clinical practice must take this into account.

6.9.6 Case study review

Assessment of the prospective activity and sleep correlates of a clinically-defined manic episode provided an alternative picture of the relationship between the predictor variables and mood in BD. Distinctive patterns in the longitudinal course of objectively measured sleep time (TST) and the stability of the 24-hour activity rhythm (RA and IV) at the time of the manic episode were observed. Specifically, sleep duration decreased gradually over an extended period, and nights of significant sleep loss increased in frequency from about a month prior to manic onset. Three nights of no sleep in the final five days prior to hospitalisation could be observed in the actogram (Figure 12). This pattern appeared to be consistent with the 48-hour sleep/wake cycles often observed clinically in the days preceding manic onset (Wehr et al., 1987).

A noteworthy feature of the data shown for Participant B was the pattern of instability in the circadian activity rhythm observed immediately prior to manic onset.
The mean level of both variables describing the stability of the activity rhythm (IV and RA) shifted dramatically at this time (Figure 14 and Figure 15, respectively). IV increased, and RA decreased, indicating greater instability of the circadian activity rhythm. These patterns provided an interesting counterpoint to the nonsignificant findings for the relationship between activity rhythm instability and sub-clinical mood as tested in the planned hypotheses. The findings suggest that instability of the circadian activity rhythm may be a feature of vulnerability to full-blown relapse but not daily variations in sub-clinical mood. The post hoc and single-observation nature of these findings limit the inferences that may be drawn. Nevertheless, the longitudinal representation of these relationships is striking and warrants further investigation.

The pattern of average activity during the most active part of the day (M10) did not show a similar change at the time of manic onset for Participant B (Figure 13). Increased psychomotor activation and goal-driven activity are core physiological features of the hypo/manic state (Serretti & Olgiati, 2005; Urosevic et al., 2008) and both would be expected to appear as sharp spikes in the pattern of activity data for this participant. Such an increase was not observed, although this may have been due to the already elevated activity levels for this participant compared to the rest of the sample. Nevertheless, reduced stability in the circadian activity rhythm, in the absence of associated increases in mean day-time activity levels, is suggestive of a possible diathesis at the level of the circadian system, a suggestion that has been made in previous investigations (e.g., Jones et al., 2005). Again, however, further investigation is warranted to see if this finding can be demonstrated in inferential analyses in a sample which includes multiple relapses into full-blown episodes.

6.9.7 Limitations

Study 3 had a number of limitations. The use of ChronoRecord to measure mood variation in BD may be problematic. Mood is just one, albeit central, component of the syndrome of physiological and behavioural distress associated with depressive and hypo/manic states. Indicators associated with some of the cognitive (flight of ideas,
rumination, indecisiveness) and behavioural (irritability, hyperverbosity, hyperphagia) features of these states are necessary for a full appreciation of their internal and external manifestations. In Study 3, this may have affected the ability to find significant associations between variables, if indeed they do exist. Shared method variance in the simultaneous recording of sleep and mood, even if cognitive associations between the two occur at the subconscious level, is another limiting factor of the ChronoRecord methodology. Encouraging people with BD to be aware of the strong association between sleep and mood is a common element of many psychosocial therapies (Suto et al., 2010). This constant message may conflate the relationship between the two phenomena and amplify the level of correlation found.

Actigraphy also has some limitations. Firstly, the nature of the interaction between the circadian activity rhythm and sleep homeostat processes remains unresolved (see Dijk & Franken, 2005 and Chapter 3). In the context of Study 3, this means that there is much shared variance between the variables inferred from the 24-hour activity rhythm which cannot be parsed. Shared variance may affect how relationships between these inferred variables and mood are interpreted. Actigraphy has also demonstrated reduced validity in differentiating sleep from wake amongst sleep-disturbed populations (Ancoli-Israel et al., 2003). This may have implications for the validity of objective sleep outcome variables in Study 3 as many of the participants would be expected to experience disturbed sleeping patterns as part of the BD illness process. On a related point, computation of the sleep variables in Actiware 5.0 (Respironics, Inc., Bend, Oregon) requires user input for estimation of sleep onset. This can be achieved by asking participants to record their ‘lights out’ time, either by self-report or by pressing an event marker on the Actiwatch at the time of ‘lights out’. As these options were not available for all participants at all times no request was made of them to record ‘lights out’ time. Thus, this time was estimated in a post hoc manner at the data analysis stage. The accuracy of the actigraph-derived sleep variables must therefore be regarded with a degree of caution.

Some general limitations regarding study design are also noteworthy. While the volume of data collected on each person was sufficient to demonstrate some key within-
subject relationships between predictor and outcome variables, there were insufficient participants to investigate between-subject differences in these relationships. The small sample enrolled in Study 3 highlights the difficulties in recruiting and retaining participants, especially those with BD, in longitudinal investigations of this kind (see Hennen, 2003).

A non-BD control group would also have been a welcome addition to the methodology of Study 3. It is possible that the relationships found in Study 3 between sleep, daytime activity, and mood are not specific to BD populations. This possibility cannot be discounted without the inclusion of an age- and gender-matched comparison group.

Life events and other interventions were not controlled in the current study. The design was deliberately naturalistic for the purposes of informing monitoring procedures in clinical practice. Disrupting life events conceivably could explain a proportion of the variance in predictor/outcome variable relationships. The considerable range of life events that may cause disruption precludes consideration of them all. Nevertheless, a select few that have proven to be episode-triggering events in the patients’ history may be worthy of consideration as factors to control in future investigations.

All investigations of the neurobiology of BD must acknowledge the confounding effects of medication. Some medications may substantially limit the strength of associations between the three key variables of interest. The primary action of the prescribed medications in this sample was to, literally, stabilise mood patterns. Medications that restrict mood excursions into hypo/mania and depression may therefore affect the strength of associations with other variables. A secondary action of many medications for BD (e.g., lithium, valproate) is to stabilise circadian rhythms (McClung, 2007) and this may extend to stabilisation of the 24-hour activity rhythm. Many of the participants in Study 3 were on a regular course of at least one of these common mood stabilisers (see Table 17). Mood stabilisers and anti-psychotic medications can also have side-effects that may influence the natural sleep/wake cycle (e.g., by increased sedation; Abad & Guilleminault, 2005; Bowden et al., 2000) and possibly increase the natural amount of total bed rest for some people. Some participants
were also taking irregular doses of sedative-hypnotic medications to help them sleep which may have also affected the natural course of sleeping patterns and, consequently, relationships with mood. It has been shown that some medications can mediate this relationship (e.g., benzodiazepines; Bauer, Grof, Rasgon, Bschor et al., 2006).

Finally, the potential for cumulative effects on mood due to successive days of sleep and activity changes was not assessed in the Study 3. It is possible that one day of disturbed sleep or instability of the circadian activity rhythm is insufficient to trigger significant mood deterioration. Multiple days may be necessary before the level of allostatic overload is sufficient to cause mood deterioration. However, the specific focus on single day predictive relationships was a strategic decision, given the probable small effect sizes being investigated, and the expectation based on a previous investigation with similar methodology (Bauer, Grof, Rasgon, Bschor et al., 2006) that significant relationships between variables were unlikely to extend beyond one day (see Section 6.5 above).

**6.9.8 Conclusions and future directions**

Circadian rhythm instability and sleep phenomena derived from actigraphic measurement of the 24-hour activity rhythm are not useable predictors of daily mood deterioration in BD. There were no significant prospective correlations between any of the circadian activity rhythm and sleep predictor variables, and either of the mood outcome variables in Study 3. A third variable, measuring daytime activity levels and also inferred from actigraphic measurement of the 24-hour activity rhythm, may be a useable predictor of daily mood deterioration. A positive relationship between daytime activity and mood levels on the same day was found in Study 3. Increased daytime activity therefore appears to be significantly associated with higher moods. Actigraphy provides a valid and reliable measure of daytime activity levels and has the advantage of being an independent predictor of mood change in BD populations.

Self-reports of total time spent in bed was another significant, albeit subjective, predictor of mood deterioration in Study 3. Self-reports of total time spent in bed may
therefore be a useable predictor of daily mood deterioration the next day in BD populations. Similar findings have previously been presented (e.g., Bauer, Grof, Rasgon, Bschor et al., 2006), but the data from Study 3 adds to current knowledge by demonstrating that any deviation from the usual amount of sleep (both more and less than usual) can have adverse affects on mood for people with BD.

The ultimate success of this and similar studies is measured in how they inform clinical practice. The demonstration in Study 3 of significant associations between an objective measure of daytime activity and a subjective measure of time spent in bed, and changes in mood at the sub-clinical level is an important step in the necessary direction. However, until associations can be supported at the clinical level, like those reported by Salvatore et al. (2008), the associations found in Study 3 are unlikely to have a significant impact on clinical practice.

The occurrence of a manic episode requiring hospitalisation for one participant in Study 3 permitted a tentative contribution to the discussion surrounding clinical applications of 24-hour activity rhythm variables. Distinctive changes in the stability of the circadian activity rhythm and the length of the sleep/wake cycle for this participant were noticeable at the time of, or just prior to, manic onset. Perhaps the greatest contribution that this data can make to outpatient care is the ability to objectively identify the increasing frequency of sleepless nights leading up to the manic episode. If this data can be made available in real time, substantial efforts can be made towards early intervention and relapse prevention. Privacy issues concerning who has access to the data and whether people with BD want their activity patterns constantly monitored are impediments to progress in this area. Technological limitations too currently impede progress. The addition of remote communication capabilities (e.g., Bluetooth™) to ActiWatches may be a worthwhile target of future research that would facilitate the timely delivery of data. These current limitations may be overcome if more data supportive of that found in Study 3 can be demonstrated.
6.10 Summary of Chapter 6

The aim of Study 3, a novel naturalistic prospective monitoring study, was to test whether actigraph-derived variables could predict deterioration in daily mood state in a small sample of outpatients diagnosed with BD. As in Study 2, predictor variables fell into three groups; circadian rhythm instability, sleep, and total daytime activity. Operationalisation of these three were RA, IS (circadian rhythm instability), TST, WASO, SE (sleep), and M10 (total daytime activity). Beyond these actigraph-derived variables, subjective sleep was added as a predictor variable as operationalised in the ChronoRecord software interface. ChronoRecord was also used as the source of daily self-report mood data, from which two dependent variables were derived. As discussed above, a fundamental paradox of in BD is that deterioration in mood can appear as shifts towards mood elevation or depression. As also noted above however, empirically the most common manifestation of deterioration in mood is movement towards depression. In the absence of comparable studies, in Study 3 both operationalisations were investigated. Mood Deviation referred to absolute deviation from a neutral score of 50 on the 0-100 ChronoRecord scale. Mood Level referred to a raw score from the ChronoRecord scale, where 0 represents most depressed, and 100 represents most manic ever. Prediction of deterioration in daily self-reported mood was investigated in two forms of time-series relationship, namely zero lag and -1 lag (prediction of DV’s by IV’s on the previous day). With eight predictor variables, and four dependent variables, a large number of analyses were conducted in this exploratory investigation. Further, by using MLM the possibility of between-subject differences in the within-subject relationships could be quantified.

It was found that none of the circadian activity rhythm or sleep variables derived from actigraphy had significant associations with the mood outcome variables. A significant positive association was found however, between total daytime activity and mood on the same day. A significant positive association was also found between self-reported time spent in bed and mood deterioration. Both increases and decreases in total time spent in bed were associated with greater mood deterioration the next day. A post
hoc case study of the actigraphic correlates of manic onset in one participant showed striking visual evidence of changes in circadian rhythm instability and sleep, but not in total daytime activity, at the time of manic onset.
Chapter 7

General Discussion

A large amount of theory and data was covered across the three studies that supported the aims of the current project. In Chapter 7, the key findings and conclusions from each study are therefore reviewed (7.1). Theoretical implications of the findings are also presented (7.2). The implications are divided into separate sections dedicated firstly, to the description of BD (7.2.1), and secondly, possible roles for the circadian activity rhythm (7.2.2), sleep (7.2.3), and daytime activity (7.2.4) in evaluations of state/trait vulnerability to BD. Potential applications of actigraphy (7.3.1) and daily self-report (7.3.3) for relapse prevention in the clinical setting, as well as the limitations of each method (7.3.2 and 7.3.4, respectively) are also presented. Limitations of the project design (7.4) and conclusions regarding the investigation of the 24-hour activity rhythm in state/trait vulnerability to BD (7.5) end the chapter.

7.1 Review of findings from Studies 1, 2, and 3

Study 1 investigated the psychometric properties of two self-report instruments designed to measure temperamental vulnerability to BD – the GBI (Depue et al., 1989) and the TEMPS-A (Akiskal, Akiskal et al., 2005). Both instruments were psychometrically sound, and their factor structure in the Study 1 sample was consistent with the theory underpinning each instrument. The factor structure of the GBI, incorporating two separable and highly correlated dimensions of depression and hypo/mania, was particularly strong. The external correlates of both the GBI and the TEMPS-A, measured using the NEO-FFI (Costa & McCrae, 1992), MDQ (Hirschfeld et al., 2000), and the ups and downs item (Angst, Gamma, & Endrass, 2003), were also consistent with theory and previous research. Exploratory investigation of the factor
structure underpinning the combined GBI and TEMPS-A revealed two dominant factors, labeled hypo/mania and depression, supporting the two-dimensional theory of trait vulnerability to BD. Items from the GBI were prominent in both factors. The emergence of smaller third and fourth factors, consisting of TEMPS-A items describing traits of irritability and hyperthymia, indicated potential limitations of the GBI in providing a comprehensive self-report measure of trait vulnerability to BD. Nevertheless, it was concluded that the GBI provided the most psychometrically reliable, interpretable, and parsimonious self-report measure of trait-like vulnerability to BD.

Study 2 investigated three variables derived from the 24-hour activity rhythm as potential correlates of trait-like vulnerability to BD. Circadian rhythm instability, sleep, and total daytime activity were measured using actigraphy across 7 days in two groups of participants. The group with higher vulnerability to BD (higher scores on the GBI) exhibited lower stability in the circadian activity rhythm than the lower vulnerability group (lower scores on the GBI). Reduced stability in the circadian activity rhythm was interpreted as an indication of a weakened circadian signal. This finding was therefore consistent with the circadian instability hypothesis of vulnerability to BD. No between-group differences were apparent for the sleep and daytime activity variables. It was concluded in Study 2 that reduced amplitude of the circadian activity rhythm is a potential biomarker of trait-like vulnerability to BD.

Study 3 investigated a within-subject version of the circadian instability hypothesis of vulnerability to BD. Changes in the stability of the circadian activity rhythm, sleep, and total daytime activity were monitored for daily associations with mood deterioration in a sample of clinically stable outpatients with BD. It was found that self-reported bed rest was positively associated with greater mood deterioration the following day when a quadratic function was used. That is, greater mood deterioration occurred both when there was increased bed rest, and when there was decreased bed rest. Notably, the linear association between mood and the amount of bed rest from the night before was not significant, contradicting previous research. Total daytime activity was found to be positively correlated with mood level on the same day. It was concluded in Study 3 that these specific features of sleep and daytime activity may be useful in predicting daily
mood deterioration in samples of outpatients with BD. Monitoring of these features may therefore be useful for prodrome identification in BD populations. A post hoc case study provided tentative support for the utility of objectively monitoring sleep time and stability of the circadian activity rhythm in predicting manic onset.

7.2 Theoretical implications of the project

7.2.1 Description of Bipolar Disorder

The outcomes from the current project would appear to be supportive of reconceptualising the description of BD. Two sources of support are particularly prominent. In the first instance, the concept of vulnerability to BD associated with variation along a series of dimensional traits receives tentative support from the data in Study 1 and Study 2. In Study 1, putative BD vulnerability traits correlated as expected with dimensional traits of normal personality. Vulnerability to BD was strongly and positively correlated with the trait dimension of N, and moderately and negatively correlated with trait dimensions of E, A, and C. These relationships between dimensions were broadly consistent with previous research in both well student samples (e.g., Murray et al., 2007) and clinical samples (e.g., Akiskal, Kilzieh et al., 2006; Quilty, Sellbom, Tackett, & Bagby, 2009). The data from Study 1 was most consistent with relationships found between normal personality traits and BD-II, but not BD-I.

The trait vulnerability construct for BD received further support from Study 2. Separate groups of high- and low-vulnerability to BD reported significantly different rates of MDE, ‘ups and downs’, and maladaptive cognitive schema. Personality dimensions and affective temperaments also differed between the two groups. Specifically, the higher vulnerability group in Study 2 reported greater incidence of MDE, which is consistent with expectations of people with greater vulnerability to BD (Judd & Akiskal, 2003). The higher vulnerability group also reported significantly
greater levels of dimensional traits associated with BD-II (i.e., ‘ups and downs’, N, DT, CT). These findings were also consistent with expectations based on previous research (Akiskal, Kilzieh et al., 2006; Bagby et al., 1997; Benazzi, 2004; Murray et al., 2007). Finally, the higher rate of maladaptive cognitive schema and dysfunctional attitudes amongst the higher vulnerability group was consistent with expectations based on previous research of these constructs amongst clinical BD populations (Lam et al., 2004; Scott & Pope, 2003) and healthy populations at higher putative risk of BD (Carver & Johnson, 2009; Knowles et al., 2005).

Trait-like vulnerability to BD is a relatively modern concept in the description and classification of the disorder. It has received strong support from numerous sources, including the outcomes from the current project. Indeed, proposals that trait dimensions should form the basis of diagnostic strategies in future revisions of the DSM taxonomy are increasingly prominent (e.g., Maser et al., 2009; Vieta & Phillips, 2007; Widiger & Samuel, 2005).

It has been argued that reconceptualising BD to incorporate dimensional traits of vulnerability instead of the categorical descriptors contained in DSM-IV and ICD-10 is not a practical option at this stage (Phelps et al., 2008). Those dissatisfied with the DSM-IV categorical approach (Akiskal being the most notable), have yet to construct a widely accepted, consensual model of spectrum and/or dimensional phenomena in BD. DSM-V, currently under development and due for release in 2013, will most likely retain the categorical nosology of its predecessors. The addition of dimensional assessments, and the formalisation of prodromal and subthreshold conditions are a potentially fruitful, but as yet unclear, proposition. How BD will be conceptualised in the new system remains to be seen, and there appears to be ample scope for debate from both sides of the categorical/dimensional divide.

The most useful application of the vulnerability concept has been wider recognition of the subtle indicators of underlying bipolarity amongst patients who present with depression ("soft bipolarity"; Akiskal, 2005; p. 282). The increasing assignment of BDNOS diagnoses in the clinical setting represents evidence for improved clinical awareness of these indicators (see also Berk et al., 2006; Ozcan et al., 2003). The
The importance of accurate BD diagnosis upon first clinical presentation cannot be understated, particularly as incorrect treatment choice in the early stages can negatively affect long-term outcomes (Awad et al., 2007; Leverich et al., 2006). The identification of temperamental indicators of latent bipolarity is a significant advance in this regard.

The concept of trait-like vulnerability to BD is a useful one for the purposes of clinical research. In particular, the investigation of endophenotypes amongst those at risk of BD is a key area that can benefit from the vulnerability concept. The benefits are twofold; correlates of BD can be investigated free of the complications associated with temperamental scarring (Akiskal et al., 1983), and description of the disorder at the molecular level may be enhanced by the investigation of smaller genetic ‘chunks’ rather than the broad polygenic configurations that characterise genetic predisposition to the disorder (Bearden & Freimer, 2006). The valid and reliable quantification of individual risk for BD is a worthy short-term research goal.

The second outcome from the current project that supports the reconceptualisation of BD concerns the number and nature of the dimensions that are proposed to underlie the construct. In Study 1, two dimensions provided the best representation of the latent structure of trait vulnerability to BD. Vulnerability to BD was characterised by separate dimensions of depressive- and manic-like tendencies. This finding was consistent with many previous studies of vulnerability to BD (Cuellar, Johnson, & Winters, 2005; Joffe, Young, & MacQueen, 1999; Lara et al., 2006; McGuffin et al., 2003; Murray et al., 2007). Notably, the separate dimensions were highly correlated in Study 1, and this is also consistent with previous research. The two-factor solution was shown to capture information contained in Akiskal’s multi-dimensional model adequately, although not completely.

Perhaps most importantly, no traits describing mood lability emerged strongly in the Study 1 factor analysis. Under the two-dimension model of vulnerability to BD, mood lability indicates the presence of both depressive and manic traits. Clinical presentations that include mood lability may therefore be a useful indicator of latent bipolarity, particularly as it pertains to BD-II (Akiskal, Kilzieh et al., 2006). Again, this is a useful
conceptualisation of the vulnerability construct, as identification of latent bipolarity in depressive presentations is a critical clinical decision.

The two-dimension conceptualisation of trait vulnerability to BD may also be useful for the description of vulnerability to BD states. Most popular models of mania and depression describe a unidimensional model of vulnerability (e.g., Bauer et al., 2004; Depue & Iacono, 1989; Watson et al., 1999). Under these models, high and low PA or BAS activation is assumed to underlie the states of mania and depression, respectively. Such models have proven useful in characterising the mood changes associated with mania and depression, and the relevant data would appear to be generally supportive (Alloy, Bender et al., 2009; Clark et al., 1994; Urosevic et al., 2008). In the representation of mixed episodes however, the unidimensional framework of vulnerability to BD states may be deficient. This deficiency in the PA and BAS dysregulation theories and how they relate to mixed states has yet to be adequately addressed in the relevant literature.

Mixed episodes in the course of BD are characterised by rapidly alternating states of mania and depression (APA, 2000). They are common within BD pathology, affecting approximately 28% of this clinical group (Goodwin & Jamison, 2007; p. 79). The existence of mixed episodes within BD phenomenology pose serious concerns for the validity of unidimensional BAS models of manic and depressive states. It is not possible under these models for example, to be both manic and depressed at the same time. Patients with BD often describe their most manic episode in terms that are qualitatively consistent with a mixed episode (Bauer et al., 2004). This ad hoc rationalisation goes some way towards fitting mixed states within the unidimensional framework. Indeed, it is perhaps not surprising that a person who has previously experienced a mixed episode would describe their most manic experience in the context of a mixed state, given that the mixed state experience can be remembered as the most “dreadful” and “psychotically manic” they have ever felt (Jamison, 1996; p. 82). While this information is beneficial for theoretical justification of the unidimensional model of mood in BD, the fact remains that people with BD can experience both pure manic and mixed manic states at different times throughout the course of their lifetime. From a
phenomenological perspective too, they appear to be different states (Cassidy, Murry, Forest, & Carroll, 1998; Harvey, Endicott, & Loebel, 2008; Sato, Bottlender, Kleindienst, & Moller, 2002), and may be subjectively experienced as such in a self-rating situation. Thus, from a theoretical perspective it is difficult to fully justify the equality of the two states for the sake of parsimony in self-report measurement.

Using separate dimensions of mania and depression to describe BD states may provide a method by which mixed episodes can be accommodated in the self-reporting of mood. Conceptualising mood in this manner would not only allow the more accurate representation of mixed states, it would also align state and trait theories of vulnerability to BD as both would be characterised by separable, but correlated dimensions of mania and depression. The description of manic and depressive states in this manner may enhance understanding of BD phenomenology. The burden on those reporting their mood is doubled (two separate ratings as opposed to the one that is used in ChronoRecord, for example), and this may decrease compliance (T. Glenn, personal communication, 2005). Nevertheless, from a theoretical perspective, the description of BD would benefit from such a reconceptualisation.

7.2.2 Circadian rhythm instability and state/trait vulnerability to Bipolar Disorder

Instability of the circadian activity rhythm was found to be a trait (between-person), but not state (within-person), biomarker of vulnerability to BD. This particular feature of the 24-hour activity rhythm does not appear to act therefore, as a mediating vulnerability factor in BD. Akiskal, Kilzieh et al. (2006) and others (e.g., Nuechterlein et al., 1992; Watson, Clark, & Tellegen, 1988) have described how some biological characteristics can act to both increase vulnerability to disorder and influence the course of the disorder. Instability of the circadian activity rhythm is a candidate for the former, but not the latter based on the findings of the current project. Ankers and Jones (2009) reported similar findings regarding between-subject effects, with the amplitude of the circadian
activity rhythm significantly reduced in their sample of students with high behavioural risk for BD compared to a sample of lower risk students. Reduced amplitude of the 24-hour activity rhythm may therefore be considered a potential endophenotype for vulnerability to BD, but not a state biomarker of subclinical mood deterioration.

A methodological issue concerning the RA variable may explain the null findings with respect to its role in predicting within-person mood variation in BD. The computation of this variable under the Van Someren approach is heavily influenced by the average amount of activity during the 5 least active hours of the 24-hour period (i.e., L5). Theoretically at least, this 5-hour period should occur at night when the participant is sleeping. Given the low range of activity at night, and the strong possibility of a ‘floor effect’ in this variable, limited day-to-day variation in the RA variable should perhaps not be unexpected. This variable may not therefore, be the best measure of 24-hour activity rhythm instability. The effects of RA may only be discernible when averaged data and the associated increases in between-day variability are used, as was the case in Study 2 and in the findings of Ankers and Jones (2009).

Operationalising circadian instability as reduced amplitude may not be appropriate when applied to 24-hour activity rhythm monitoring. While such operational definitions have served circadian research on other output mechanisms well (e.g., Aschoff & Wever, 1981), the amplitude of the activity rhythm may not be a useful application of this concept. In the chronobiological literature on depression, the amplitude of the output rhythm is used as a measure of the strength of the circadian signal (Czeisler, Kronauer, Mooney, Anderson, & Allan, 1987; Daimon, Yamada, Tsujimoto, & Takahashi, 1992; Souetre, Salvati, Candito, & Darcourt, 1991). A more robust rhythm is found in a greater difference between the acme and nadir of the fitted cosine curve of the rhythm. It is more difficult to argue that this is the case in the context of circadian activity rhythms which do not conform well to a cosine curve shape (Van Someren et al., 1999; Witting et al., 1990). The difference between the acme and the nadir of the square-like shape of the circadian activity rhythm does not necessarily reflect the strength of coupling between SCN processes and external zeitgebers. Interpreting
changes in the amplitude of the 24-hour activity rhythm as changes in the strength of the rhythm may therefore not be a useful conceptualisation.

The limitations associated with the RA variable do not apply to the IV variable, an alternative measure of 24-hour activity rhythm stability used in Studies 2 and 3. IV reflects the frequency and extent of transitions between rest and activity in each 24-hour period. A less stable rhythm is characterised by more frequent transitions between the two states. Greater variability (i.e., higher IV scores) hints at poor synchronisation between the circadian activity rhythm and external zeitgebers, perhaps providing a better indication of the strength of the rhythm. Intradaily variability may also provide an indication of the extent to which daytime napping occurs (Huang et al., 2002), a phenomenon that appears to be particularly relevant to the depressive phase in BD populations (Forty et al., 2008; Salvatore et al., 2008), and which may indicate weak entrainment to zeitgebers. In the current project, IV was neither a between- or within-person predictor of vulnerability to BD. Nevertheless, the calculations underpinning this variable may mean it is a more valid and reliable operationalisation of circadian rhythm instability.

A further issue to consider in the assessment of circadian rhythm instability in BD is the nature of their dynamic pattern. It was assumed throughout the current project that linear patterns characterised the longitudinal course of the circadian activity rhythm. It is possible however, that reduced variability of the circadian activity rhythm is part of the pathogenesis in BD in the same way that reduced heart rate variability is pathogenic for heart disease (see Chattipakorn, Incharoen, Kanlop, & Chattipakorn, 2007). Analysis of nonlinear dynamic patterns in the circadian activity rhythm may shed light on this hypothesis. Such patterns were not considered in the current project, but may be a future direction for analyses of this type. Some studies have already considered this approach to studying the nonlinear dynamics of biological process in BD (e.g., Glenn et al., 2006), including one based on a subset of data from the current project (Murray, Bullock, Indic, & Judd, 2010). Findings were encouraging in both studies, although clearly more research is required here.
Finally, levels of both IV and RA variables were observed to change dramatically at the point of manic onset in the case study reported in Study 3. A decrease in RA and an increase in IV, both consistent with expectations regarding the direction of change in these variables in the presence of mania, were observed in the period just prior to the onset of mania for one participant. Interpretation of this particular finding will be considered later in this chapter when clinical implications of the results from the current project are discussed.

7.2.3 Sleep and state/trait vulnerability to Bipolar Disorder

Changes in the amount of sleep per night was a state, but not trait, feature of vulnerability to BD. In particular, the total amount of self-reported time spent in bed was significantly associated with mood change the following day in Study 3. Self-reports of sleep and/or bed rest were not measured in Study 2. An objective measure of sleep time, recorded using actigraphy, was used in this study however, but did not emerge as a significant between-group factor differentiating high and low trait vulnerability to BD.\(^{26}\) This finding from Study 2 was inconsistent with recent data demonstrating group differences in objective measurements of sleep at the trait level in well populations at behavioural risk of BD when compared to those at low behavioural risk (Ankers & Jones, 2009). It is consistent however, with previous research that failed to demonstrate group differences in objective measurements of sleep at the trait level in euthymic BD populations (e.g., Jones et al., 2005; Millar et al., 2004). The inconsistent findings across studies is surprising, given that strong associations between the two features are often reported in clinical observations.

There does not appear to be a clear picture emerging regarding the relationship between actigraph-derived sleep characteristics and between-subject vulnerability to BD. Three potential explanations can be forwarded to describe the inconsistent findings.

\(^{26}\) Notably, the objective actigraphic recording of sleep was not a state predictor of mood change in Study 3. This was despite the finding that mood could be predicted by self-reports of bed rest in this study. Implications of these apparently contradictory findings are discussed later in this section.
First, aggregated effects may not be sufficient to explain the type of association that exists between sleep and vulnerability to BD. Longitudinal variation in sleep characteristics, a feature of disturbed sleep often reported in observations of people with BD (see Frank et al., 1997), may be lost in the computation of averaged data. Average within-subject variability across nights has been reported to be higher in some BD populations (e.g., Millar et al., 2004) and some populations at higher risk of BD (e.g., Ankers & Jones, 2009; Meyer & Maier, 2006). Measures of variability in sleep may provide a better indication of sleep differences at the trait level in populations at higher risk of BD. Average within-subject variability of sleep characteristics in BD populations may be a more useful predictor of trait vulnerability to BD than mean scores.

The second explanation for inconsistent findings in the relationship between sleep and trait vulnerability to BD concerns the potential for scarring to affect relationships. As described in Chapter 4, previous mood episodes may permanently alter, or ‘scar’, the neurobiology of people with BD, potentially affecting their sleep. Studying relationships between sleep and trait vulnerability to BD in people at higher risk of the disorder, but who have yet to manifest disorder pathology, may circumvent such issues. This research strategy was employed in Study 2 of the current project and by Ankers and Jones (2009) in their investigation of sleep characteristics amongst students at higher behavioural risk of BD. Despite the similarities in research methodology for these two studies, findings relating to objectively recorded sleep characteristics were still inconsistent. Indeed, the outcomes of Study 2 in the current project with regards to sleep had more in common with the outcomes of studies involving euthymic BD outpatients, who were potentially subject to neurobiological scarring from previous episodes (Jones et al., 2005; Millar et al., 2004). Clearly, more research is required here to determine the locus of sleep disturbances in people at increased risk of BD.

The third explanation for inconsistent findings in the relationship between sleep and trait vulnerability to BD may be a measurement issue. In studies of patients in the euthymic phase of BD, differences between subjective and objective sleep measurement is often reported (e.g., Harvey et al., 2005; Millar et al., 2004). In Study 3 of the current project, within-person cross-correlations of daily sleep self-reports and daily objective
estimates from actigraphy were small ($r = .13$), consistent with the poor agreement between these variables sometimes shown at the trait level. Either actigraphy is failing to capture the subjective element of sleep disturbance in BD populations, or people with BD are misinterpreting the signs of sleep disturbance. Both arguments are valid, although recent research suggests the latter has significant merit as a reason for poor agreement between subjective and objective estimates of sleep. Harvey et al. (2005), for example, reported that a group of patients in the euthymic phase of BD displayed a similar level of dysfunctional beliefs about sleep to a comparison group of people with insomnia. Ankers and Jones (2009) also reported cognitive self-appraisal differences in their group of behavioural high-risk participants, and suggested that this may adversely affect how individuals responded to circadian disturbance. Taken together, these findings suggest that cognitive distortion of sleep disturbance may be pervasive amongst people at risk of BD. The interaction between dysfunctional cognitions, circadian/sleep disturbance, and affective dysregulation in people with BD is a fruitful line of enquiry which may lead to improved management of the disorder (see Alloy, Abramson et al., 2009; Ankers & Jones, 2009; Benca et al., 2009; Harvey, 2008; Harvey et al., 2005; Jones, 2001).

In contrast to the inconsistent findings associated with sleep and trait vulnerability to BD, self-reports of sleep appear to be important predictors of state vulnerability to BD. In Study 3, the total amount of subjectively estimated time spent in bed each day was significantly associated with the degree of deviation from usual mood the following day. In contrast, self-reported sleep length (without bed rest) was not associated with the degree of deviation from usual mood the following day. Bauer, Grof, Rasgon, Bschor et al. (2006) also found that the total amount of subjectively estimated time spent in bed each day was a better predictor of mood change in people with BD than just the amount of sleep. Specifically, they showed that changes greater than 3 hours in the amount of time spent in bed per day were significantly associated with mood change either on the same day or the next day in a proportion of their BD sample. Thus, it would appear that the Total Bedrest variable constitutes important information about the relationship between self-report sleep-related features and mood the following day.
The addition of information regarding the quality of sleep would appear to be the main reason for differences found in the relationships between the Sleep Length and Total Bedrest predictor variables, and the Mood Deviation outcome variable. The two predictor variables are closely related, and indeed were shown to correlate highly at a lag of zero in Study 3 ($r = .89$). However, the two measures represent slightly different interpretations of sleep-related phenomena, especially as they relate to mania and depression. The Sleep Length measure provides a direct quantitative reflection of sleep time, and is a predictor variable that may be taken at face value. Alternatively, Total Bedrest, with the added input of time spent in bed awake, introduces an element of the subjective quality of sleep to the data. Thus, it is assumed that an increase in the amount of time spent in bed awake reflects poorer quality sleep, manifesting as either difficulties falling asleep, difficulties staying asleep, or difficulties arising from bed in the morning. It is noteworthy that each of these sleep-related problems are features associated with the depressive state in both MDD and BD (Mitchell et al., 2008).

Using a quadratic function to model the prospective relationship between the Total Bedrest predictor variable and the Mood Deviation outcome variable was a methodological advance on previous studies of similar relationships. Bauer, Grof, Rasgon, Bschor et al. (2006) demonstrated a negative linear relationship between the total amount of time spent in bed and levels of mood change the following day in their study of 59 outpatients with BD. This effect was apparent in only 41% of their sample, and only when effects were combined for the night before the mood change, and the night of the mood change. Thus, predictive relationships between the total amount of bed rest and mood the next day were only demonstrated for a limited proportion of their sample. In contrast to the findings of Bauer, Grof, Rasgon, Bschor et al., significant linear associations between the Total Bedrest and Mood Level variables were not found in Study 3. The quadratic association between the Total Bedrest and Mood Deviation variables was significant, however. In the Study 3 sample therefore, mood deterioration was greater when the total amount of bed rest deviated both above and below average levels. While a quadratic function was not expected to characterise the relationship between Total Bedrest and Mood Level, the methodological point still stands. Quadratic
functions should be considered when evaluating relationships between sleep and mood deterioration in BD populations, as negative mood outcomes can be expected from both increases and decreases in sleep.

A final methodological issue to consider in investigations of the relationships between sleep and state vulnerability to BD concerns the amount of between-person variability in such relationships. The limited proportion of the sample in the Bauer, Grof, Rasgon, Bschor et al. (2006) study to show significant cross-correlations between sleep and mood supports the high level of variability in symptomatology between BD participants. Sierra et al. (2007) has also reported that pronounced variation in symptom profiles tend to be the norm rather than the exception, not only in BD, but for many disorders of a psychological nature. Between-person differences in the relationship between predictor and outcome variables in Study 3 were not found, most likely due to the small sample size. Nevertheless, it is important to note that average effects may be difficult to find in studies with expected low effect sizes, and evaluation of between-person variation should be considered in such investigations.

In the case study of manic onset described in Study 3, objective monitoring of sleep revealed some distinctive sleep loss patterns in the period leading up to hospitalisation. The participant appeared to enter a 48-hour sleep/wake cycle in the six days prior to the onset of mania. This pattern of sleep loss is a common feature of the prodromal phase to mania (see Lam & Wong, 2005; Wehr et al., 1987), but to our knowledge, Study 3 provided the first prospective objectively measured description of this process. Objective monitoring using actigraphy may provide the basis of a mania ‘warning system’ in these circumstances. The case study in Study 3, and discussion of potential approaches to monitoring of behaviour for the purposes of relapse prevention in BD will be considered in more detail in the clinical implications section (Section 7.3).
7.2.4 Total daytime activity and state/trait vulnerability to Bipolar Disorder

Changes in daytime activity levels were found to be state, but not trait, features of vulnerability to BD. A positive linear relationship was found for the daily association between average activity during the most active part of the day (M10) and self-reported Mood Level on the same day in Study 3. In Study 2, there were no significant differences in M10 between the higher- and lower-risk groups of students. On the basis of these findings, it would appear that BD patients’ mood may be predicted by daytime activity levels. Risk for BD however, does not appear to be associated with higher or lower levels of daytime activity.

The finding that daytime activity was positively associated with mood on the same day is consistent with previous research in both normal and clinical populations. Watson (1988) and Mendlowicz et al. (1999) for example, demonstrated that increased activity was strongly associated with better moods, and reduced activity was associated with lower moods. The positive association applies equally in BD populations according to previous research, with the clinical states of mania and depression associated with raw activity increases and decreases, respectively (Mitchell et al., 2008; see also Urosevic et al., 2008; Watson et al., 1999). A robust relationship between activity levels and mood therefore appears to be established. Moreover, the relationship has been shown to occur at multiple levels of the mood spectrum, with associations demonstrated in healthy populations with normal mood deviations (Mendlowicz et al., 1999) and clinical populations with either mania (Mansell & Pedley, 2008; Urosevic et al., 2008) or depression (Mitchell et al., 2008), as well as the findings from Study 3 in a stable clinical population.

The association between daytime activity and mood can be understood at both the neurobiological and psychosocial level. At the neurobiological level, it has been shown that some monoamines with mood influencing qualities are also associated with the control of activity via psychomotor pathways. Serotonin, for example, has been implicated in both the regulation of mood and locomotor activity function (Sari, 2004).
In addition, the BAS system is proposed to control reward motivation and approach behaviour, as previously described (see Section 2.5.3). The states of mania and depression are associated with over- and underactivation, respectively, of the BAS, thus providing a framework in which to consider the associated roles of mood and activity in BD.

At the psychosocial level, higher moods are likely to be associated with a greater level of social activity. Watson (1988) for example, showed that socialising amongst university students was positively related to positive affect. Such increases in social activity can be reflected in higher daytime activity as captured by actigraphy. Conversely, lower moods (reduced PA), were associated with social withdrawal in the same study, and can be observed in reductions of activity output. The same relationships between social activity and mood can be found in BD populations. Indeed, Goodwin and Jamison (2007) have asserted that “fluctuations in levels of sociability almost define bipolar illness” (p. 339). A need for increased interpersonal contact and ‘people seeking’ for the purposes of stimulation are commonly reported features of the manic state (e.g., Lam et al., 1999) and also appear in clinical descriptions of the manic episode (APA, 2000). Social withdrawal and introverted self-absorption are commonly reported features of the depressive state (e.g., Lam et al., 1999; see also APA, 2000). Both data and theory therefore, support associations between activity and mood in BD.

Recording and analysis of raw activity data is not subject to the same issues of interpretation as the 24-hour activity rhythm and sleep. Activity level data can be taken at face value and there are few alternative options for recording this information, especially at the level of resolution afforded by actigraphy. Self-reports of activity, such as that recorded using the SRM (Monk et al., 1990), are clinically useful instruments. However, they are subject to the same limitations as any self-report instrument, viz., issues of ecological validity, accuracy verification, and socially desirable responding. Actigraphy is a face valid, objective, and non-intrusive measure of activity levels.

Defining the daytime activity variable in the Van Someren tradition as the average amount of activity during the 10 most active hours of the day is a logical and defendable operationalisation of the activity output concept. It is a particularly suitable operational
definition for a study investigating prospective relationships between activity and deterioration in daily mood, as both measures should reflect approximately the same period in the 24-hour day. That is, both variables reflect their respective constructs during the subjective daytime. In contrast, measures of total 24-hour activity include a period of low activity (i.e., sleep) in which mood is clearly not an appropriate outcome variable. The M10 variable is therefore strongly recommended for use in investigations of daily associations between activity and mood.

For the case study of manic onset described in Study 3, activity during the most active part of the day did not show any distinctive patterns leading into the manic period (Figure 13). This observation was somewhat surprising given the significant association between activity levels and mood in the prospective analysis of Study 3, and the prominent role activity is reported to play in the clinical presentation of mania (Urosevic et al., 2008). One explanation noted in Chapter 6 was the high level of activity already exhibited by this person prior to manic onset. A possible ceiling effect may therefore be apparent in this case, as higher activity levels than those observed may not be possible. It has also been shown that patients with BD who have higher baseline levels of daytime activity are at higher risk of relapse (Klein et al., 1992). The case study observations are supportive of this finding. The consequences of these findings for the management of relapse prevention in BD outpatients will be discussed in more detail in Section 7.3 addressing clinical implications of the current project.

7.3 Going further: Potential application of actigraphy for prodrome identification and relapse prevention in Bipolar Disorder

The clinical goal of the current project was to investigate the possibility of prodrome identification using non-intrusive methods to monitor biological rhythm function in people with BD. The findings from Study 3 addressed these questions most directly, and predominate the ensuing discussion of the potential clinical implications of
the current project. Issues surrounding the application of actigraphy to the monitoring of circadian rhythm instability, sleep, and daytime activity in BD is presented (7.3.1), followed by a discussion of the limitations of this monitoring technique in the clinical setting (7.3.2). Given the significant findings in Study 3 regarding the prospective association between subjective sleep reports and mood deterioration, the application of ChronoRecord in clinical settings is also briefly considered (7.3.3), again followed by a discussion of associated limitations (7.3.4).

7.3.1 Using actigraphy to monitor the longitudinal course of activity and sleep in Bipolar Disorder

A key aim of the current project was to evaluate the feasibility of monitoring the 24-hour activity rhythm in a BD population using actigraphy. No significant relationships were found in Study 3 between self-reported mood deterioration and actigraphic measures of circadian rhythm instability and sleep. Such findings offer little incentive for the introduction of actigraphy to the clinical setting. The average amount of activity during the most active 10-hour period of the day however, was a highly significant predictor of mood in Study 3. The relationship between predictor and outcome variables was in the positive direction. Although this relationship was found at the sub-clinical level of mood deterioration, it is consistent with expected outcomes in BD populations experiencing episodes of mania and depression. Psychomotor retardation during periods of low mood is a potential indicator of BD depression and can be used to differentiate this form of depression from that associated with MDD (Mitchell et al., 2008), an important clinical decision (Forty et al., 2008). Increased psychomotor activation is a cardinal sign of mania (Mansell & Pedley, 2008). Actigraphy may thus provide an objective measurement of vulnerability to these states in people with BD through the monitoring of daytime activity.

While the actigraphic measures of circadian rhythm instability and sleep were not significant predictors of daily mood deterioration in Study 3, the case study of manic
onset in this study appeared to offer a different perspective. Noticeable changes in the stability of the circadian activity rhythm and in the sleep/wake pattern of the participant who entered a manic phase during Study 3 were observed in the period immediately prior to manic onset. As sleep loss is such a common prodromal feature of the manic phase, the ability to identify these patterns early and non-intrusively may be crucial for relapse prevention. Changes in the stability of the circadian activity rhythm may also serve as early warning signs. The case study observations from Study 3 suggest that actigraphy may be a useful tool for identifying these features of the manic prodrome.

The case study also showed that activity data in its raw form may be useful for monitoring increases in psychomotor activity, as well as reductions in sleep that are signature prodromal features for many BD patients. Both of these features can be easily viewed from the raw Actogram produced by the Actiware software (see Figure 12 for an example). Instances of increased activity combined with a lack of sleep may be used to initiate contact with the outpatient, and could perhaps result in relapse prevention strategies being implemented. The single case study design of this part of the analysis limits the veracity of conclusions that can be drawn. Nevertheless, there is impetus for further study on the actigraphic correlates of manic onset, in particular, as well as depressive manifestations of BD.

In summary, actigraphy is an objective and non-intrusive monitor of activity levels that requires little input from users, thus limiting the possibility of missing or purposeful misrepresentation of data. Data derived from actigraphy is reliable and produces valid output variables shown to be germane to the relapsing course of the BD illness process. The ability to show nights of little or no sleep in BD outpatients is a particularly advantageous feature of actigraphic technology, as severe disruption to the sleep/wake cycle is a frequently observed antecedent to mania.
7.3.2 Limitations of actigraphic monitoring for collecting daily activity and sleep data in the clinical setting

The validity of actigraphy in measuring sleep duration is potentially compromised in populations that experience sleep difficulties (Ancoli-Israel et al., 2003; Kushida et al., 2001). The consequences for using actigraphy to monitor sleep in people with BD are obvious, given the central role that sleep disturbance plays in the BD illness process. There have been no published validation studies of actigraphy in BD populations, so the magnitude of measurement error is not known amongst this specific group. Caution in the interpretation of sleep-related data from actigraphy is therefore recommended, as is a validation study of actigraphy in a BD population. Specific sleep disturbances are common in BD patients (e.g., hypersomnolence, reduced bed rest, delayed sleep phase), and the continued investigation of BD using actigraphy would benefit from studies of actigraphic validity under these conditions. Such studies may also produce standardised norms against which data from future investigations could be evaluated, a recommendation that has been made previously (Morgenthaler et al., 2007).

Timely access to activity data is another limitation of actigraphy in the clinical setting. As the technology currently stands, data may only be retrieved through download from the Actiwatch using a reader attached to an appropriate computer with the relevant software. The watch must therefore be physically returned by the outpatient to a central data point for downloading. This defeats the purpose of using a remote monitor of activity patterns, as the outpatient must attend regular appointments to provide useable monitoring data. The data is also viewed in retrospect, by which time activity patterns relevant to manic onset may have passed. A useful addition to the current actigraphic technology in this regard would be a remote downloading capacity. This could be achieved by incorporating Bluetooth™-like capabilities into the Actiwatch hardware. Sleep and activity data could then be received by doctors or case managers in real-time, up to a maximum 48-hour delay. Data received in such a timely manner would allow informed judgements to be made regarding potentially unhealthy sleep and activity patterns, and thus facilitate the implementation of appropriate relapse
prevention strategies. Appropriate software algorithms, such as those used in Study 3 (viz., IV and RA), may be needed to facilitate immediate and accurate interpretation of raw activity data. Instances of total sleep loss are immediately apparent when viewing the raw activity actogram. Instances of increased activity are not immediately apparent however, and an algorithm may be necessary for judicious interpretation of raw data. Threshold and rate-of-change values may be appropriate variables for this purpose.

The use of actigraphy for monitoring of patients in clinical situations, especially if the data is received by doctors and case managers in real-time as proposed, also raises significant issues of autonomy. There is potential for patients to perceive automated remote monitoring as an obtrusive observation of their lives. A collaborative working relationship between clinician and patient would most likely circumvent such issues. A related psychological issue concerns the visibility of the Actiwatch. The stigma still attached to BD diagnoses means that attention drawn to the watch may be a source of discomfort. Such discomfort may be eased somewhat through the development of rote responses in consultation with the outpatient’s doctor or case manager.

As it currently stands, there are a number of significant hurdles for the successful application of actigraphy to the clinical situation. From a resources perspective, the set-up costs associated with actigraphic hardware are currently prohibitive. This is especially the case in large-scale environments such as hospitals where many Actiwatch devices would be required. Comprehensive training for judicious interpretation of actigraph data output by medical professionals would also be required before the technology can be applied in clinical settings in the manner indicated. Finally, although the current project provides some indication of the appropriate activity and sleep parameters that can be used in clinical applications, there is much work to be done on testing and refining said parameters to the point where they can provide the necessary levels of reliability for clinical prediction.
Self-report is commonly used for the collection of psychological data. Many researchers rely on the established validity of self-report instruments to provide a picture of the highly idiosyncratic internal make-up of individuals. Thus, it is important that the instruments are adequately tested for validity and reliability, and that their theoretical basis is sound.

Mood is a psychological construct that is almost exclusively assessed using self-report. As Watson (2000) explains, “self-ratings of experienced affect are the clearest and most proximal measures of mood that are available” (p. 20). While some aspects of mood can be inferred from behaviour, a full appreciation of mood states as experienced by the person requires an element of personal description or self-rating (Thayer, 1989), especially as external representations of behaviour may not always match what is being experienced internally (e.g., Watson & Clark, 1991). Thus, mood lends itself particularly well to assessment by self-report, although there is debate about the language that should be used (e.g., Larsen & Diener, 1992; Watson & Clark, 1997).

The use of daily mood self-reports in patients with BD is not new. Zealley and Aitken (1969) for example, used a 100-point VAS, anchored at each end by descriptors of ‘most depressed’ to ‘most happy’ with ‘normal’ at the mid-point, to record the self-rated mood of a small sample of BD inpatients. It would appear that a similar model of self-report mood was adopted by Bauer et al. (1991) to develop the Chronosheet, which later formed the basis for the ChronoRecord self-report software program as used in Study 3.

The ChronoRecord measure is explicitly anchored with extreme state descriptors of ‘manic’ and ‘depressed’ mood with ‘normal’ in the middle (see Appendix E). Such terms are presumably familiar to people diagnosed with BD. During training in the use of the software, patients are advised to think of the ‘manic’ end of the scale (i.e., a score of 100) as the ‘most manic state you have ever experienced’, and the ‘depressed’ end of the scale (i.e., a score of 0) as the ‘most depressed state you have ever experienced’.
Consequently, there are no absolute definitions of the relevant states, just those relevant
to each individual. The mid-point of the VAS is perhaps the most difficult to interpret,
with the descriptor ‘normal’ having different meanings for different people, especially
those with a mood disorder. Again however, some attempt is made to standardise the
meaning of this word by advising users during training that a score of 50 equals ‘usual
mood’.

A significant relationship between self-reported time spent in bed and mood the
following day was found in Study 3. This may be an important relationship for the long-
term monitoring of mood change and prodrome identification in outpatients with BD. At
the very least, this relationship can be used to educate those with BD on the importance
of regular sleeping patterns in managing moods. The data from Study 3 adds to current
knowledge by demonstrating that both increases and decreases in the amount of self-
reported time spent in bed can affect mood adversely. The relationship between irregular
sleep patterns and mood problems is familiar to most people with BD (Lam & Wong,
2005), and the data shown here reinforces the strength of this relationship using the
patients’ own self-ratings.

The data derived from Study 3 and the benefit of observing the ChronoRecord
program in operation amongst a BD population affords the opportunity for a tentative
contribution to the use of this program in the clinical setting. The strong prospective
relationship found between time spent in bed and mood the following day suggests that
ChronoRecord may be an important education tool for patients with BD. Patient
education is an increasingly common element of adjunctive psychotherapy for BD that
has been shown to reduce long-term relapse rates (Colom et al., 2009; Goodwin, 2009).
The use of ChronoRecord to highlight the potentially harmful relationship between sleep
and mood may be particularly important in the early stages of a BD diagnosis when
education about the illness is a key part of the therapeutic process (Chengappa &
Williams, 2005).

Beyond the use of ChronoRecord as a psychoeducation tool, the software may also
have potential application in long-term outpatient care. Some patients with BD can
display poor insight into their own mood and behaviour at times of significant mood
distress (Dell'Osso et al., 2002). This can make the task of maintaining an accurate and complete clinical history difficult. The record of mood self-reports in ChronoRecord can be used to trigger recall of episodes in outpatients during consultations with doctors and case managers. Indeed, improving the clinical utility of long-term self-report monitoring strategies in BD was a key motivation behind the development of the ChronoRecord program (see Bauer, Grof, Rasgon, Glenn et al., 2006).

The ability to recognise potential episodes of depression is a particular strength of the ChronoRecord program. Mood self-ratings in people with BD have demonstrated good concurrent validity with clinician-rated scores on the HAM-D (Bauer et al., 2004). ChronoRecord may serve as a potentially valid indicator of depressive episodes in outpatients with BD. Mania may be more difficult to accurately self-report. In contrast to the heightened level of self-awareness in depression, the hypo/manic state is characterised by reduced self-awareness (Dell'Osso et al., 2002). The ability to provide accurate self-reports of mania would therefore seem to be severely compromised. While Bauer, Wilson et al. (2008) showed that blind clinician ratings on the YMRS correlated well with inpatient and outpatient mood ratings in ChronoRecord, validation with larger samples is necessary, as well as a deeper exploration of the concurrent validity of mood ratings over the longer term. Twenty-five out of the 27 inpatients to give mood ratings during a hypo/manic episode in the Bauer et al. study provided only a maximum of three ratings. Further investigation is necessary to evaluate the ability of mood self-reports to indicate instances of hypo/mania in a longer term prospective investigation.

The feasibility of using ChronoRecord for long-term monitoring (>1 year) of mood and sleep is an unresolved matter. According to published studies, the maximum time for which it has been used with BD outpatients is 169 ± 59 days (Bauer, Grof, Rasgon, Bschor et al., 2006). In Study 3 an element of data entry fatigue was noted amongst some participants. The validity of some mood and sleep reports in the longer-term may therefore be questionable. Perhaps the most efficacious use of ChronoRecord is with patients in the early stages of recovery, particularly if they have recently been hospitalised for a serious mood episode. The daily connection with their doctor or case manager, albeit via electronic means, may be a useful intermediary step in the recovery
process. For longer term applications, use of the monitoring software during limited periods of known vulnerability (for example, winter for depression and summer for mania; Lee, Tsai, & Lin, 2007) may be indicated. Limited use may lessen the impact of data entry fatigue and moderate the potential for associated reductions in data quality.

7.3.4 Limitations of the self-report method for collecting daily mood and sleep data in the clinical setting

The limitations of self-report data are generally well-known. Minor interpretive difficulties such as standardisation of self-reports that do not submit easily to external validation is a key limitation. Idiosyncratic interpretations of the language used in self-reports and under- or overestimation of symptom severity have also been reported (Corruble, Legrand, Zvenigorowski, Duret, & Guelfi, 1999; Pinard & Tetreault, 1974; Prusoff, Klerman, & Paykel, 1972; Snaith, 1993). Such limitations are inherent to the self-report technique and, as such, are tolerable consequences of using this method of collecting information.

A major limitation of self-report data specifically as it relates to daily reporting in prospective designs is the presence of retest artifacts (e.g., Durham et al., 2002). A common finding in studies using repeated measures of self-report to monitor changes in psychological processes is that, over time, self-report ratings show a tendency for regressing to the mean. Henderson, Byrne, and Duncan-Jones (1981) for example, showed that the number of self-reported neurotic symptoms in a general population survey declined over time. Moreover, this decline was not apparent on other personality measures that did not rely on self-report. Similarly, Ormel, Koeter, and Van Den Brink (1989) demonstrated substantial retest effects in a study of the General Health Questionnaire amongst a psychiatric outpatient population. Significant practice effects were also described in a longitudinal study involving several self-report neuropsychological instruments, including the Profile of Mood States (Salinsky,
The issue of retest artifacts in the long-term use of ChronoRecord has yet to be addressed.

Two prominent explanations for unexplained improvements in self-report scores over time have been proposed (Durham et al., 2002). The first explanation concerns social desirability factors, with baseline reports potentially exaggerated by respondents for reasons of attention and need, and subsequent reports potentially used by respondents to represent themselves in a more favourable light. The second explanation centered on the potential therapeutic effect of increased self-awareness as the number of repeated measures increased. Both explanations are plausible and the latter in particular is an important therapeutic outcome in intervention studies. Nevertheless, the repeated administration of self-report measures over the long-term carries interpretational caveats that require consideration in the evaluation of patient outcomes.

The frequency with which self-reports are sought from participants may differentially affect the impact of retest effects. Longwell and Truax (2005), for example, assessed depressive symptomatology amongst a nonclinical population using the self-report BDI-II. A decrease in scores was apparent for the group completing the BDI-II on a weekly basis only. No decrease in scores was apparent for groups completing the instrument on a monthly or bi-monthly basis, indicating a possible frequency effect on retest artifacts. This finding has implications for self-report data collected on a daily basis, including that collected via ChronoRecord. Again, the possibility of retest effects in longitudinal self-report investigations requires careful consideration, a consideration that should also extend to the use of self-report for therapeutic purposes and evaluation of remedial interventions.

In summary, longitudinal monitoring of mood via self-report appears to be a critical psychoeducation tool for people with BD, encouraging greater awareness of mood patterns and the association between sleep behaviour and mood changes in this population. ChronoRecord represents a significant advance on traditional pen-and-paper methods by automating the self-report process and limiting the influence of missing and poor quality data on interpretation. The program may be particularly useful in the early stages of recovery after a manic or depressive episode. From a clinical research
perspective however, some aspects of the ChronoRecord program may benefit from consideration of alternative mood rating methodologies to better match what is becoming known about daily mood phenomena in BD.

7.4 Limitations of project design

Many of the limitations in the design of the studies in this project have already been presented at the end of the chapters dedicated to each study. Limitations associated with the practical use of self-report and actigraphy for the purposes of clinical monitoring have also been presented. Limitations underpinning the overall project have yet to be addressed however, and are presented in this section.

Environmental influences on trait vulnerability to BD were not measured in the current project. Study 1 assumed that vulnerability to BD was subject to a trait, or series of traits, that determine an individual’s risk for developing the disorder. However, myriad developmental, environmental, and social influences have been shown to affect individual vulnerability to BD (see review by Miklowitz & Johnson, 2009), and these were not considered in Study 1. Similarly, in Study 2, the influence of environmental considerations such as social and family factors were not measured. It is of course impractical to expect that individual studies can account for all sources of variance in the expression of human behaviour. Nevertheless, it is important to acknowledge that the investigation of trait vulnerability to mental disorder is subject to significant environmental influence.

Situational influences on vulnerability to BD states were also not measured in Study 3. The same environmental, social, and family factors that may affect trait vulnerability to BD may also have a role to play in within-subject vulnerability to BD. Life events for example, particularly those involving goal attainment, have been shown to predict an increase in manic symptoms over a period of 3 years (Johnson et al., 2008). Negative life events were shown to predict an increase in depressive symptoms in the same study. Much of the current research on psychosocial treatment of BD emphasises a stress-
diathesis model of vulnerability to the disorder (Leahy, 2007), so consideration of environmental effects is warranted. Again, however, given the large number of potential environmental effects in vulnerability to BD, it is impractical to measure them all. Nevertheless, their impact is acknowledged.

### 7.5 Concluding remarks

Within the context of the theoretical and methodological limitations in the design of the current project some important outcomes emerged from the data. Further support and clarification of the 2-dimension structure of trait vulnerability to BD was provided in Study 1. The circadian instability hypothesis of trait vulnerability to BD was tentatively supported by the findings of Study 2. In Study 3, daytime activity was positively associated with daily mood change in BD, supporting previous research. Hypothesised associations between objective measures of circadian rhythm instability and sleep as predictors, and mood deterioration as an outcome were not found however in the same study. Nevertheless, the findings from Study 3 provided impetus for suggestions of how longitudinal monitoring of the 24-hour activity rhythm may be applied in the clinical setting. This was the ultimate aim of the overall project.

Actigraphic monitoring of daytime activity may be an important relapse prevention strategy for BD. Previous studies have already suggested that changes in psychomotor activation are potentially important indicators of manic and depressive onset. The findings from Study 3 supported such associations, and indicated the suitability of actigraphy for their identification. A key advantage of the actigraphic method of longitudinal monitoring is the objective nature of the collected data. Activity data derived from actigraphy is therefore not subject to the potential difficulties associated with self-reports. The actigraphic method of collecting data is also non-intrusive, limiting the potential for interference in naturalistic settings.

Given the strong relationships often reported between sleep problems and manic or depressive onset, the negative findings for prospective associations between objective
measures of sleep and self-reported mood deterioration were surprising. The lack of significant associations may be due to concerns regarding the validity of actigraphy in detecting sleep disturbance. Alternatively, self-reported increases and decreases in total bedrest were significantly associated with mood (lower and higher, respectively) the next day. These findings were consistent with previous research (e.g., Bauer, Grof, Rasgon, Bschor et al., 2006; Harvey et al., 2005; Millar et al., 2004). Self-reports of sleep may therefore provide a better indication of the sleep disturbances associated with mood deterioration in BD, although, as outlined in Chapters 6 and 7, there are caveats to the interpretation of this association.

For the identification of manic onset, monitoring of sleepless nights may be actigraphy’s most significant contribution to the long-term clinical management of BD. The case study of manic onset in Study 3 demonstrated the potential utility of an objective measure of sleep in detecting sleep loss. If objective sleep data can be observed in a timely manner, the potential for successful relapse prevention is increased. Relapse prevention was not an outcome variable in the current project, but there is impetus for such a study based on the case study observations in Study 3.

In conclusion, several biological rhythm features derived from the 24-hour activity rhythm demonstrated potential importance for the identification of trait and state vulnerability to BD in the current project. Circadian activity rhythm instability, measured in reduced amplitude of the 24-hour activity rhythm, was a significant between-subjects factor in two groups of students at high- and low-risk of BD in Study 2. The higher risk group had lower amplitude as predicted by theory. No other features of the 24-hour activity rhythm were found to differ between the two groups. In Study 3, daytime activity was a significant within-subject predictor of daily mood amongst a group of outpatients with BD. The association was positive, with higher activity levels associated with higher mood, and lower activity levels associated with lower mood, again as predicted by theory. No other features of the 24-hour activity rhythm were significantly associated daily mood change in Study 3. Although the findings of the current project were largely negative, an important contribution to the identification and
clinical management of BD has been provided, including a sharpened focus for future research on this most complex psychiatric disorder.
References


Dell'Osso, L., Pini, S., Cassano, G. B., Mastrocinque, C., Seckinger, R. A., Saettoni, M., et al. (2002). Insight into illness in patients with mania, mixed mania, bipolar...
depression and major depression with psychotic features. Bipolar Disorders, 4(5), 315-322.


Appendix A

DSM-IV criteria for Manic and Major Depressive Episodes

A Manic Episode is defined by DSM-IV as one in which abnormally and persistently elevated, expansive, or irritable mood is present for at least 1 week. In addition, at least three of the following symptoms must be reported:

1. inflated self-esteem or grandiosity
2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

A MDE is defined by DSM-IV as one in which there is depressed mood or the loss of interest or pleasure in nearly all activities. In addition, five (or more) of the following symptoms must have been present for a 2-week period:

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Appendix B

Questionnaire used in Study 1

Adaptations of this questionnaire were used at baseline for Study 2 and Study 3. To avoid repetition, the questionnaires used for these two studies are not presented as appendices.

Mood, Personality and Temperament Questionnaire

The following survey will take approximately 30-40 minutes to complete. Please respond to all questions. Do not spend too much time on any item – it is your first impressions we are interested in.

<table>
<thead>
<tr>
<th>General Information</th>
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<tbody>
<tr>
<td>1. Age _____</td>
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<tr>
<td>2. Gender MALE FEMALE (please circle appropriate response)</td>
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</table>

This first set of questions asks about behaviours that occur in the general population. Using the scale below as a guide, circle the number that best describes how often you experience these behaviours:

<table>
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<tr>
<td></td>
<td>Never or Hardly Ever</td>
<td>Sometimes</td>
<td>Often</td>
<td>Very Often or Almost Constantly</td>
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</table>

Keep the following points in mind when responding to these questions:

**Frequency:** If you first noticed a behavior when you were young, and you have experienced it repeatedly since then, mark your answer "often" or "very often – almost constantly". However, if you have experienced a behavior during only one isolated period in your life, but not outside that period, mark your answer "never – hardly ever" or "sometimes".

**Changeability:** What matters is not whether you can get rid of certain behaviors if you have them, but whether they have occurred at all. So even if you can get rid of these behaviors, you should mark your answer according to how frequently you experience them.
<table>
<thead>
<tr>
<th></th>
<th><strong>Question</strong></th>
<th>** Never or Hardly Ever**</th>
<th><strong>Sometimes</strong></th>
<th><strong>Often</strong></th>
<th><strong>Very Often or Almost Constantly</strong></th>
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<tbody>
<tr>
<td>1</td>
<td>Have there been periods in your life when it was almost impossible to make even small decisions, even though this may not be generally true of you?</td>
<td>1</td>
<td>2</td>
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<td>2</td>
<td>Have you found that your enjoyment in being with people changes – from times when you enjoy them immensely and want to be with them all the time, to times when you don’t want to see them at all?</td>
<td>1</td>
<td>2</td>
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<td>3</td>
<td>Have you become sad, depressed, or irritable for several days or more without really understanding why?</td>
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<td>4</td>
<td>Have you experienced periods of several days or more when, although you were feeling unusually happy and intensely energetic (clearly more than your usual self), you also were physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?</td>
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<td>5</td>
<td>Have there been periods of several days or more when you felt you needed more sleep, even though you slept longer at night or napped more during the day (not including times of exercise, physical illness, or heavy work schedules)?</td>
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<td>6</td>
<td>Have people said that you looked sad or lonely?</td>
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<td>7</td>
<td>Have there been periods of several days or more when you were almost constantly active such that others told you they couldn’t keep up with or that you wore them out?</td>
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<td>8</td>
<td>Have there been periods of several days or more when you could not keep your attention on any one thing for more than a few seconds and your mind jumped rapidly from one thought to another or to things around you?</td>
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<td>9</td>
<td>Have there been periods lasting several days or more when you lost almost all interest in people close to you and spent long times by yourself?</td>
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<td>10</td>
<td>Have you had periods of several days or more when food seemed rather flavorless and you didn’t enjoy eating at all?</td>
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<td>11</td>
<td>Have there been periods of several days or more when your friends or family told you that you seemed unusually happy or high, clearly different from your usual self or from a typical good mood?</td>
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<td>12</td>
<td>Have there been times when your memory or concentration seemed especially poor and you found it difficult, for example, to read or follow a TV program, even though you tried?</td>
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<td>13</td>
<td>Have there been periods of time when you lost almost all interest in the things that you usually like to do (such as hobbies, school, work, entertainment)?</td>
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<td>Question</td>
<td>Never or Hardly Ever</td>
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<td>14</td>
<td>Have you had periods of sadness and depression when almost everything gets on your nerves and makes you irritable or angry (other than related to the menstrual cycle)?</td>
<td>1 2 3 4</td>
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<td>15</td>
<td>Have there been times of several days or more when you did not feel the need for sleep and were able to stay awake and alert for much longer than usual because you were full of energy?</td>
<td>1 2 3 4</td>
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<td>16</td>
<td>Have you had long periods in which you felt you couldn’t enjoy life as easily as other people?</td>
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<td>17</td>
<td>Have you had periods of several days or more when you wanted to be with people so much of the time that they asked you to leave them alone for a while?</td>
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<td>18</td>
<td>Have there been times of several days or more when you were so tired and worn out that it was very difficult or even impossible to do your normal everyday activities (not including times of intense exercise, physical illness, or heavy work schedules)?</td>
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<td>19</td>
<td>Has your mood or energy shifted rapidly back and forth from happy to sad or high to low?</td>
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<td>20</td>
<td>Have there been periods lasting several days or more when you spent much of your time brooding about unpleasant things that have happened?</td>
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<td>21</td>
<td>Have there been times when you felt that you were physically cut off from other people or from yourself, or felt as if you were in a dream, or felt that the world looked different or had changed in some way?</td>
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<td>22</td>
<td>Have you had periods of extreme happiness and intense energy lasting several days or more when you also felt much more anxious or tense (jittery, nervous, uptight) than usual (other than related to the menstrual cycle)?</td>
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<td>23</td>
<td>Have there been times of several days or more when you were so sad that it was quite painful or you felt that you couldn’t stand it?</td>
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<td>24</td>
<td>Have you found that your enjoyment in eating changes – from periods of two or more days when food tastes exceptionally good, clearly better than usual, to other periods of several days or more when food seems rather flavorless and perhaps you don’t enjoy eating at all?</td>
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<td>25</td>
<td>Have there been times of several days or more when you wake up much too early in the morning and have problems getting back to sleep?</td>
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<td>26</td>
<td>Have you had periods when you were so down that you found it hard to start talking or that talking took too much energy?</td>
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<td>27</td>
<td>Have there been times of several days or more when, although you were feeling unusually happy and intensely energetic (clearly more than your usual self), you also had to struggle very hard to control inner feelings of rage or an urge to smash or destroy things?</td>
<td>Never or Hardly Ever</td>
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<td>Have there been periods other than when you were physically ill that you had more than one of the following: (a) headaches or feelings of tightness, pressure, or &quot;wooziness&quot; in your head; (b) dizziness; (c) constipation or diarrhea; (d) aches and pains; (e) nausea, vomiting, or stomach aches; (f) blurred vision; (g) trembling or shaking hands, or (h) feeling too hot or too cold?</td>
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<td>Have you experienced periods of several days or more when you were feeling down and depressed, and you also were physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?</td>
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<td>Have there been times lasting several days or more when you felt you must have lots of excitement, and you actually did a lot of new or different things?</td>
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<td>31</td>
<td>Have you had periods of extreme happiness and intense energy (clearly more than your usual self) when, for several days or more, it took you over an hour to get to sleep at night?</td>
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<td>32</td>
<td>Have there been times when you looked back over your life and could see only failures or hardships?</td>
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<td>Have you experienced times of several days or more when you felt as if you were moving in slow motion?</td>
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<td>34</td>
<td>Have there been long periods in your life when you felt sad, depressed, or irritable most of the time?</td>
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<td>35</td>
<td>Has it seemed that you experience both pleasurable and painful emotions more intensely than other people?</td>
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<td>36</td>
<td>Have there been periods of several days or more when you felt guilty and thought you deserved to be punished for something you had or had not done?</td>
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<td>37</td>
<td>Have you had times of several days or more when you woke up frequently or had trouble staying asleep during the middle of the night?</td>
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<td>38</td>
<td>Have you had periods of extreme happiness and high energy lasting several days or more when what you saw, heard, smelled, tasted, or touched seemed vivid or intense?</td>
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<td>39</td>
<td>Have there been times when you were feeling low and depressed, and you also had to struggle very hard to control inner feelings of rage or an urge to smash or destroy things?</td>
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<td>Question</td>
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<td>40</td>
<td>Have you found that your feelings or energy are generally up or down, but rarely in the middle?</td>
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<tr>
<td>41</td>
<td>Have you had periods of several days or more when it was difficult or almost impossible to think and your mind felt sluggish, stagnant, or &quot;dead&quot;?</td>
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<td>42</td>
<td>Have there been times when you had a strong urge to do something mischievous, destructive, risky, or shocking?</td>
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<td>43</td>
<td>Have there been periods of several days or more when your thinking was so clear and quick that it was much better than most other people's?</td>
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<td>44</td>
<td>Have there been times when you exploded at others and afterwards felt bad about yourself?</td>
<td>1</td>
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<td>3</td>
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<tr>
<td>45</td>
<td>Have there been times of several days or more when you were so down that nothing (not even friends or good news) could cheer you up?</td>
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<tr>
<td>46</td>
<td>Have there been times of a couple days or more when you felt that you were a very important person or that your abilities or talents were better than most other people's?</td>
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<tr>
<td>47</td>
<td>Have them been times when you have hated yourself or felt that you were stupid, ugly, unlovable, or useless?</td>
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<td>48</td>
<td>Have you found that your thinking changes greatly -- that there are periods of several days or more when you think better than most people, and other periods when your mind doesn't work well at all?</td>
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<td>2</td>
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<td>49</td>
<td>Have there been times of a day or more when you had no feelings or emotions and seemed cut off from other people?</td>
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<td>50</td>
<td>Have you had sad and depressed periods lasting several days or more when you also felt much more anxious or tense (jittery, nervous, uptight) than usual (other than related to the menstrual cycle)?</td>
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<td>51</td>
<td>Have there been times when you have done things -- like perhaps driving recklessly, taking a trip on the spur of the moment, creating a public disturbance, being more sexually active than usual, getting into fights, destroying property, or getting into trouble with the law -- which you later thought showed poor judgment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>52</td>
<td>Have you had periods of sadness and depression when, for several days or more, it took you over an hour to get to sleep at night, even though you were very tired?</td>
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<td>Question</td>
<td>Never or Hardly Ever</td>
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<td>53</td>
<td>Have you had periods lasting several days or more when you felt depressed or irritable, and then other periods of several days or more when you felt extremely high, elated, and overflowing with energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>54</td>
<td>Have there been periods when, although you were feeling unusually happy and intensely energetic, almost everything got on your nerves and made you irritable or angry (other than related to the menstrual cycle)?</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>55</td>
<td>Have there been times when upsetting or bad thoughts kept going through your mind and you couldn't stop them?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56</td>
<td>Have there been times of several days or more when you really got down on yourself and felt worthless?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>57</td>
<td>Have there been times when you had blank spells in which your activities were interrupted, and you did not know what was going on around you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>58</td>
<td>Have you had sad and depressed periods of several days or more, interrupted by periods lasting between an hour to a day when you felt extremely happy and intensely energetic?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>59</td>
<td>Have there been periods of several days or more when you were slowed down and couldn't move as quickly as usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>60</td>
<td>Have you experienced weight changes (increases, decreases, or both) of two-and-a-half (2.5) kilograms or more in short periods of time (three weeks or less), not including changes due to physical illness, menstruation, exercise, or dieting?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>61</td>
<td>Have there been periods of a couple days or more when sexual feelings and thoughts were almost constant, and you couldn't think about anything else?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>62</td>
<td>Have you had periods when it seemed that the future was hopeless and things could not improve?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>63</td>
<td>Have there been periods lasting several days or more when you were so down in the dumps that you thought you might never snap out of it?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>64</td>
<td>Have you had times when your thoughts and ideas came so fast that you couldn't get them all out, or they came so quickly that others complained that they couldn't keep up with your ideas?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>65</td>
<td>Have there been times of several days or more when you felt very down and depressed during the early part of the day, but then less so during the evening?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>66</td>
<td>Have there been times when you began many new activities with lots of enthusiasm and then found yourself quickly losing interest in them?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Have you found that your mood consistently follows the seasons, where you have long periods of depression during the winter, but mostly happy periods during the summer?</td>
<td>Never or Hardly Ever</td>
<td>Sometimes</td>
<td>Often</td>
<td>Very Often or Almost Constantly</td>
</tr>
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<td>---</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<td>-------------------------------</td>
</tr>
<tr>
<td>67</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have you had long periods when you were down and depressed, interrupted by brief periods when your mood was normal or slightly happy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have there been times of several days or more when you have struggled to control an urge to cry, have had frequent crying spells, or found yourself crying without really understanding why (other than related to the menstrual cycle)?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>69</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have there been times of several days or more when almost all sexual interest was lost?</td>
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<tr>
<td>70</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have you found yourself at times feeling fearful or suspicious of your environment or people around you?</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>71</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Have there been periods of time when you felt a persistent sense of gloom?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>72</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have there been times when you have felt that you would be better off dead?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Would you say you were one of those people who have frequent ‘ups and downs’?  

**YES**  

**NO**

For each of the statements below, circle the number that best describes how much you agree with each statement.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I am not a worrier.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I like to have a lot of people around me.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>I don’t like to waste my time daydreaming.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I try to be courteous to everyone I meet.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I keep my belongings clean and neat.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>6</td>
<td>I often feel inferior to others.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>I laugh easily.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Once I find the right way to do something, I stick to it.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>I often get into arguments with my family and co-workers.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>I’m pretty good about pacing myself so as to get things done on time.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>When I’m under a great deal of stress, sometimes I feel like I’m going to pieces.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>I don’t consider myself especially “light-hearted”.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>I am intrigued by the patterns I find in art and nature.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>Some people think I’m selfish and egotistical.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>I am not a very methodical person.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>I rarely feel lonely or blue.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>I really enjoy talking to people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>I believe letting students hear controversial speakers can only confuse and mislead them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>I would rather cooperate with others than compete with them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>I try to perform all the tasks assigned to me conscientiously.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>I often feel tense and jittery.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22</td>
<td>I like to be where the action is.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23</td>
<td>Poetry has little or no effect on me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>I tend to be cynical and sceptical of others’ intentions.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>I have a clear set of goals and work towards them in an orderly fashion.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26</td>
<td>Sometimes I feel completely worthless.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>I usually prefer to do things alone.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28</td>
<td>I often try new and foreign foods.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
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</tr>
<tr>
<td>29</td>
<td>I believe that most people will take advantage of you if you let them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30</td>
<td>I waste a lot of time before settling down to work.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>31</td>
<td>I rarely feel fearful or anxious.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32</td>
<td>I often feel as if I’m bursting with energy.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33</td>
<td>I seldom notice the moods or feelings that different environments produce.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34</td>
<td>Most people I know like me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35</td>
<td>I work hard to accomplish my goals.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36</td>
<td>I often get angry at the way people treat me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37</td>
<td>I am a cheerful, high-spirited person.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38</td>
<td>I believe we should look to our religious authorities for decisions on moral issues.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39</td>
<td>Some people think of me as cold and calculating.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40</td>
<td>When I make a commitment, I can always be counted on to follow through.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41</td>
<td>Too often, when things go wrong, I get discouraged and feel like giving up.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42</td>
<td>I am not a cheerful optimist.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43</td>
<td>Sometimes when reading poetry or looking at a work of art, I feel a chill or wave of excitement.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44</td>
<td>I’m hard-headed and tough-minded in my attitudes.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>Sometimes I’m not as dependable or reliable as I should be.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46</td>
<td>I am seldom sad or depressed.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47</td>
<td>My life is fast-paced.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>I have little interest in speculating on the nature of the universe or the human condition.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49</td>
<td>I generally try to be thoughtful and considerate.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50</td>
<td>I am a productive person who always gets the job done.</td>
<td>1</td>
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<td></td>
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</tr>
<tr>
<td>51</td>
<td>I often feel helpless and want someone else to solve my problems.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52</td>
<td>I am a very active person.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53</td>
<td>I have a lot of intellectual curiosity.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54</td>
<td>If I don’t like people, I let them know it.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>55</td>
<td>I never seem to be able to get organised.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56</td>
<td>At times I have been so ashamed I just want to hide.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>57</td>
<td>I would rather go my own way than be a leader of others.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>58</td>
<td>I often enjoy playing with theories or abstract ideas.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>59</td>
<td>If necessary, I am willing to manipulate people to get what I want.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>60</td>
<td>I strive for excellence in everything I do.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

In this next set of questions, we are interested in the kind of person you are. Please circle the following items only if they apply to you for much of your life.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>My ability to think varies greatly from sharp to dull for no apparent reason.</td>
</tr>
<tr>
<td>2</td>
<td>I constantly switch between being lively and sluggish.</td>
</tr>
<tr>
<td>3</td>
<td>I get sudden shifts in mood and energy.</td>
</tr>
<tr>
<td>4</td>
<td>The way I see things is sometimes vivid, but at other times lifeless.</td>
</tr>
<tr>
<td>5</td>
<td>My mood often changes for no reason.</td>
</tr>
<tr>
<td>6</td>
<td>I go back and forth between being outgoing and being withdrawn from others.</td>
</tr>
<tr>
<td>7</td>
<td>My moods and energy are either high or low, rarely in between.</td>
</tr>
<tr>
<td>8</td>
<td>I go back and forth between feeling overconfident and feeling unsure of myself.</td>
</tr>
<tr>
<td>9</td>
<td>My need for sleep varies a lot from just a few hours to more than 9 hours.</td>
</tr>
<tr>
<td>10</td>
<td>I sometimes go to bed feeling great, and wake up in the morning feeling life is not worth living.</td>
</tr>
<tr>
<td>11</td>
<td>I can really like someone a lot, and then completely lose interest in them.</td>
</tr>
<tr>
<td>12</td>
<td>I am the kind of person who can be sad and happy at the same time.</td>
</tr>
<tr>
<td></td>
<td>People tell me I am unable to see the lighter side of things.</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>14</td>
<td>I’m the kind of person that doubts everything.</td>
</tr>
<tr>
<td>15</td>
<td>I am a very skeptical person.</td>
</tr>
<tr>
<td>16</td>
<td>I am by nature a dissatisfied person.</td>
</tr>
<tr>
<td>17</td>
<td>I’m a sad, unhappy person.</td>
</tr>
<tr>
<td>18</td>
<td>I think things often turn out for the worst.</td>
</tr>
<tr>
<td>19</td>
<td>I give up easily.</td>
</tr>
<tr>
<td>20</td>
<td>I complain a lot.</td>
</tr>
<tr>
<td>21</td>
<td>People tell me I blow up out of nowhere.</td>
</tr>
<tr>
<td>22</td>
<td>I can get so furious I could hurt someone.</td>
</tr>
<tr>
<td>23</td>
<td>I often get so mad that I will just trash everything.</td>
</tr>
<tr>
<td>24</td>
<td>When crossed, I could get into a fight.</td>
</tr>
<tr>
<td>25</td>
<td>When I disagree with someone, I can get into a heated argument.</td>
</tr>
<tr>
<td>26</td>
<td>When angry, I snap at people.</td>
</tr>
<tr>
<td>27</td>
<td>I am known to swear a lot.</td>
</tr>
<tr>
<td>28</td>
<td>I have been told that I become violent with just a few drinks.</td>
</tr>
<tr>
<td>29</td>
<td>I have a gift for speech, convincing and inspiring to others.</td>
</tr>
<tr>
<td>30</td>
<td>I often get many great ideas.</td>
</tr>
<tr>
<td>31</td>
<td>I love to tackle new projects, even if risky.</td>
</tr>
<tr>
<td>32</td>
<td>I like telling jokes, people tell me I’m humorous.</td>
</tr>
<tr>
<td>33</td>
<td>I have abilities and expertise in many fields.</td>
</tr>
<tr>
<td>34</td>
<td>I am totally comfortable even with people I hardly know.</td>
</tr>
<tr>
<td>35</td>
<td>I love to be with a lot of people.</td>
</tr>
<tr>
<td>36</td>
<td>I am the kind of person who likes to be the boss.</td>
</tr>
<tr>
<td>37</td>
<td>I am often fearful of someone in my family coming down with a serious disease.</td>
</tr>
<tr>
<td>38</td>
<td>I’m always thinking someone might break bad news to me about a family member.</td>
</tr>
<tr>
<td>39</td>
<td>When someone is late coming home, I fear they may have had an accident.</td>
</tr>
</tbody>
</table>
Have you ever been diagnosed with clinical depression by a doctor or mental health professional?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

If YES, please indicate how long ago this occurred and whether or not you sought professional treatment (i.e. medication, counselling) in the comments box below.

Comments:

The following statements describe a number of behaviours. Please indicate those that you have experienced by ticking the appropriate box to the right of each statement.

<table>
<thead>
<tr>
<th>Has there ever been a period of time when you were not your usual self and…</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. …you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. …you were so irritable that you shouted at people or started fights or arguments?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. …you felt much more self-confident than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. …you got much less sleep than usual and found you didn’t really miss it?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. …you were much more talkative or spoke faster than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. …thoughts raced through your head or you couldn’t slow your mind down?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7. …you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8. …you had much more energy than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. …you were much more active or did many more things than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10. …you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11. …you were much more interested in sex than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12. …you did things that were unusual for you or that other people might have thought were excessive, foolish or risky?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>13. …spending money got you or your family into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>14. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? Please circle one response only</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
15. How much of a problem did any of these cause you – like being unable to work; having family, money, or legal troubles; getting into arguments or fights? Please circle one response only

<table>
<thead>
<tr>
<th>No problem</th>
<th>Minor problem</th>
<th>Moderate problem</th>
<th>Serious problem</th>
</tr>
</thead>
</table>

Thank you for taking the time to participate in this research. Your contribution is greatly appreciated.

Before returning your completed survey please double-check that you have responded to all questions.
Appendix C

Computational algorithms for calculating the nonparametric 24-hour activity rhythm variables

\[ RA = \frac{M10 - L5}{M10 + L5} \]

\[ *IV = \frac{n \sum (x_i - x_{i-1})^2}{(n - 1) \sum (x_i - \bar{x})^2} \]

\[ *IS = \frac{n \sum (\bar{x}_n - \bar{x})^2}{n \sum (x_i - \bar{x})^2} \]

Note. \( n \) = total number of data points, \( p \) = the number of data points per day.

Appendix D

Mean subscale scores and standard deviations for YSQ-SF and DAS-24.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Subscale</th>
<th>High GBI</th>
<th></th>
<th>Low GBI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>YSQ-SF</td>
<td>Emotional Deprivation</td>
<td>2.78</td>
<td>1.75</td>
<td>1.52</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Abandonment</td>
<td>3.45</td>
<td>1.57</td>
<td>1.74</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Mistrust/Abuse</td>
<td>3.44</td>
<td>1.34</td>
<td>1.76</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Social Isolation</td>
<td>3.15</td>
<td>1.26</td>
<td>1.88</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Defectiveness/Shame</td>
<td>2.28</td>
<td>1.08</td>
<td>1.32</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>2.62</td>
<td>1.20</td>
<td>1.56</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Dependence/Incompetence</td>
<td>2.22</td>
<td>1.00</td>
<td>1.76</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Vulnerability to Harm/Illness</td>
<td>2.77</td>
<td>1.33</td>
<td>1.37</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Enmeshment</td>
<td>2.11</td>
<td>1.10</td>
<td>1.38</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Subjugation</td>
<td>2.71</td>
<td>1.23</td>
<td>1.62</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Self-sacrifice</td>
<td>3.40</td>
<td>1.13</td>
<td>2.74</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Emotional Inhibition</td>
<td>2.96</td>
<td>1.40</td>
<td>2.03</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Unrelenting Standards</td>
<td>3.76</td>
<td>1.08</td>
<td>2.96</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>Entitlement</td>
<td>3.12</td>
<td>0.98</td>
<td>2.19</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Insufficient self-control</td>
<td>3.42</td>
<td>1.05</td>
<td>2.15</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Achievement</td>
<td>37.89</td>
<td>8.21</td>
<td>24.58</td>
<td>7.17</td>
</tr>
<tr>
<td></td>
<td>Dependency</td>
<td>32.97</td>
<td>8.64</td>
<td>24.78</td>
<td>5.14</td>
</tr>
<tr>
<td></td>
<td>Self-control</td>
<td>36.78</td>
<td>6.21</td>
<td>31.36</td>
<td>6.35</td>
</tr>
</tbody>
</table>

*Note. All mean differences were significant at \( p < .003 \) (\( \alpha \) adjusted for multiple comparisons), except for Dependence/Incompetence, Self-sacrifice, and Unrelenting Standards.*
Appendix E

ChronoRecord mood VAS interface
Appendix F

ChronoRecord sleep graphic interface
Appendix G

Multilevel regression analyses not included in hypothesis testing

(a) Within-Subject Parameter Estimates for Zero and -1 Lag Relationships Between Circadian Rhythm Instability and Mood Level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>ratio</th>
<th>Approx. df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Zero lag</td>
<td>-0.05</td>
<td>0.31</td>
<td>0.15</td>
<td>1290</td>
</tr>
<tr>
<td></td>
<td>-1 lag</td>
<td>0.35</td>
<td>0.31</td>
<td>1.13</td>
<td>1287</td>
</tr>
<tr>
<td>IV</td>
<td>Zero lag</td>
<td>-0.54</td>
<td>0.33</td>
<td>1.63</td>
<td>1201</td>
</tr>
<tr>
<td></td>
<td>-1 lag</td>
<td>-0.12</td>
<td>0.31</td>
<td>0.40</td>
<td>1212</td>
</tr>
</tbody>
</table>

Note. IV = intradaily variability, RA = relative amplitude.

(b) Within-Subject Parameter Estimates for -1 Lag Relationships Between Sleep Variables and Mood Level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>ratio</th>
<th>Approx. df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Length</td>
<td>-0.41</td>
<td>0.43</td>
<td>0.95</td>
<td>839</td>
<td>.35</td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>-0.73</td>
<td>0.51</td>
<td>1.44</td>
<td>542</td>
<td>.15</td>
</tr>
<tr>
<td>TST</td>
<td>-0.07</td>
<td>0.30</td>
<td>0.24</td>
<td>1192</td>
<td>.81</td>
</tr>
<tr>
<td>SE</td>
<td>0.03</td>
<td>0.36</td>
<td>0.08</td>
<td>1110</td>
<td>.94</td>
</tr>
<tr>
<td>WASO</td>
<td>-0.38</td>
<td>0.35</td>
<td>1.09</td>
<td>1256</td>
<td>.28</td>
</tr>
</tbody>
</table>

Note. TST = total sleep time, SE = sleep efficiency, WASO = wake after sleep onset.
(c) Within-Subject Parameter Estimates for -1 Lag Relationships Between Sleep Variables and Mood Deviation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Length</td>
<td>0.20</td>
<td>0.32</td>
<td>0.61</td>
<td>1201</td>
<td>.54</td>
</tr>
<tr>
<td>Total Bedrest</td>
<td>-0.51</td>
<td>0.41</td>
<td>1.25</td>
<td>350</td>
<td>.21</td>
</tr>
<tr>
<td>TST</td>
<td>-0.13</td>
<td>0.22</td>
<td>0.60</td>
<td>1246</td>
<td>.55</td>
</tr>
<tr>
<td>SE</td>
<td>-0.18</td>
<td>0.27</td>
<td>0.65</td>
<td>1287</td>
<td>.52</td>
</tr>
<tr>
<td>WASO</td>
<td>0.43</td>
<td>0.26</td>
<td>1.67</td>
<td>1312</td>
<td>.10</td>
</tr>
</tbody>
</table>

Note. TST = total sleep time, SE = sleep efficiency, WASO = wake after sleep onset.

(d) Within-Subject Parameter Estimates for Zero and -1 Lag Relationships Between Total Daytime Activity and Mood Deviation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>t ratio</th>
<th>Approx. df</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M10 Zero lag</td>
<td>-1.26</td>
<td>0.40</td>
<td>3.18</td>
<td>962</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>-1 lag</td>
<td>0.63</td>
<td>0.36</td>
<td>1.75</td>
<td>1238</td>
<td>.08</td>
</tr>
</tbody>
</table>

Note. M10 = average activity during the most active 10-hour period of the day
Appendix H

Possible explanations for the pattern of mood reporting for Participant D

A review of Participant D’s ChronoRecord mood reporting over the 90 days of the data collection period revealed no variation in self-reported mood. Specifically, a score of 50 (the default score in ChronoRecord) was entered for every day of the study period. According to the ChronoRecord Association (T. Glenn, personal communication, December 17, 2007), this pattern of mood reporting is rare, but has been reported previously in participants with chronic schizophrenia who did not have sufficient insight to comprehend the concept of mood. However, there was no evidence of a schizophrenia diagnosis in the medical history for this participant. In addition to the lack of variation in mood reporting there was a similarly invariant pattern in self-report sleep behaviour and medication intake according to the ChronoRecord data. It is conceivable that Participant D does not have sufficient insight to rate his own mood states. Lack of insight is a common feature in BD that tends to be more impaired during a manic phase (Dell'Osso et al., 2002; Yen et al., 2007). There was no external evidence of manic behaviour during the data collection phase for Participant D, but the impact of poor insight during even subsyndromal periods, although unlikely, can not be discounted. There is also a possibility that this participant was experiencing severe attenuation of mood due to his medication. The central action of lithium is to stabilize moods and there is much evidence to support the effectiveness of this mechanism of action (Gould, Chen, & Manji, 2002). It is especially effective in stabilizing day-to-day variability in mood (Folstein, DePaulo, & Trepp, 1982). However, it is highly unlikely that lithium would cause no variation in mood across such a lengthy time frame. It is more likely that Participant D provided his mood and sleep reports ‘by rote’ (i.e., without effortful reflection) though the reasons for this are unclear. Despite the valuable amount of data recorded from this participant the decision was made that his ChronoRecord mood and sleep records could not be considered for further analysis due to a suspected lack of ecological validity in the data.
Appendix I

Actogram example showing arbitrary data

Black lines describe raw activity per minute – the higher the line the more activity has been recorded. Red underlining signifies periods where the level of activity has exceeded the set threshold for the identification of wakefulness. Blue shaded areas are post hoc estimates of the sleep period.

Appendix J

Ethics approval certificates

Study 1: Swinburne University Human Research Ethics Committee Proj 0607/018 “Temperament and personality correlates of the bipolar trait”. Approval received 27/9/06.

Study 2: Swinburne University Human Research Ethics Committee Proj 06/27 “Psychological and biological features of the bipolar trait”. Approval received 13/6/06.

Study 3: Internal: Swinburne University Human Research Ethics Committee Proj 05/41 “Monitoring of mood, sleep and activity in Bipolar Disorder”. Approval received 21/12/05.
External: Bendigo Health Care Group Proj 34/2005 “Monitoring of mood, sleep and activity in Bipolar Disorder”. Approval received 20/04/06.
List of Publications

Listed in reverse chronological order.


