Jackson, Alison Margaret (2006) *Day-to-day variability in bipolar disorders.* PhD thesis.

http://theses.gla.ac.uk/6326/

Copyright and moral rights for this thesis are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the Author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the Author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Glasgow Theses Service
http://theses.gla.ac.uk/
theses@gla.ac.uk

Day-to-day Variability in Bipolar Disorders

Alison Margaret Jackson

BA Honours Psychology & Marketing

Submitted for the Degree of PhD

in the Faculty of Medicine, University of Glasgow

August 2006

Section of Psychological Medicine

Division of Community Based Sciences

University of Glasgow

Acknowledgements

The Joan Searle Research Legacy provided the funds to conduct this research project, through Jan Scott's successful bid to investigate research into the early symptoms of relapse in bipolar disorder. I would like to thank my principal supervisor Jan Scott, for providing the opportunity to work on this project and for her expertise and knowledge in the write up of the thesis. I would like to thank Colin Espie and Keith Millar for their support and advice as secondary supervisors. Thanks also to my advisor, Jonathan Cavanagh for his approachability and helpful advice. Thanks to the Staff Psychiatrist at Westbank Day Unit, Elaine McCabe for supporting the research project and helping to recruit participants with bipolar disorder, to Forth Valley Primary Care NHS Trust who provided ethical approval for the project and to Medical Records for providing follow-up admission data on participants. Finally, the time and patience of all participants who completed the daily questionnaires and actigraph monitoring for the current study is greatly appreciated.

List of contents

List of figures and tables

Publications

Jackson, A. Cavanagh, J.C. & Scott, J. (2003) A systematic review of manic and depressive prodromes. *Journal of Affective Disorders* 74 209-217.

(Provided in Appendix H)

Jackson, A. McCabe, E. Espie, C. & Scott, J. (2004) Variability in bipolar disorders. *Regional Mental Health Programme Research Meeting Poster,* West of Scotland Research and Development Consortium, University of Glasgow.

(Provided in Appendix H)

Abbreviations

ALI	Activity level index
BAS	Behavioural Activation System
BIS	Behavioural Inhibition System
BIS/BAS	Behavioural Inhibition System and Behavioural Activation System Scales
DALI	Daily Activity Level Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth revised edition
EEG	Electroencephalogram
ESM	Experience Sampling Method
IS	Interdaily Stability
IV	Intradaily Variability
L5	Night time activity level
MANOVA	Multivariate analysis of variance
M10	Day time activity level
NA	Negative Affect
PA	Positive Affect
PACF	Partial autocorrelation function
PANAS	Positive And Negative Affect Schedule
PSG	Polysomnographic
RA	Relative Amplitude
RSEQ	Rosenberg Self Esteem Questionnaire

SE	Self Esteem
SRM	Social Rhythm Metric
SPSS	Statistical Package for Social Sciences

Glossary

Actigraphy	A method for the objective estimation of the sleep-wake cycle. An actigraph is worn on the wrist with sleep and wake variables estimated from the level of activity recorded.
Actiwatch	An actigraphy-measuring device, similar in size to a digital watch that is worn on the non-dominant wrist.
Autonomy	A tendency to be independent and achievement oriented.
Behavioural activation system	An appetitive motivational system that responds to reward.
Behavioural inhibition system	An aversive motivational system that responds to punishment.
Bipolar I disorder	A mood disorder characterised by one or more manic and/or mixed episodes and at least one major depressive episode.
Bipolar II disorder	A mood disorder characterised by at least one hypomanic episode and one or more major depressive episodes.
Circadian rhythms	Recurring patterns of variation in behaviour and physiology that occur over a 24 hour period.
Cognition	An individual's psychological thought processes.
Cognitive vulnerability	Cognitive or personality characteristics that influence an individual's vulnerability to stress.
Day time activity level	The mean of the ten hour period with the highest activity level in the average day.
Dysphoria	A state of mental discomfort or unease.

Electroencephalogram	A method that utilises electrodes to record cortical activity.
Entrainment	The coupling between the timing of a circadian rhythm (e.g. sleep-wake cycle) and an external zeitgeber (e.g. light).
Interdaily stability	The regularity of the rest-activity rhythm to environmental zeitgebers across time.
Intradaily variability	The fragmentation of the rest-activity rhythm.
Movement and fragmentation index	The percentage of time spent moving during the estimated sleep period plus the percentage of immobility phases of one minute, as a proportion of the number of immobile phases with no activity recorded.
Negative affect	The experience of negative emotions, such as guilt and fear.
Night time activity level	The mean of the five hour period with the lowest activity level in the average 24 hour pattern.
Night waking time	The proportion of time spent in bed awake.
Onset time of day time activity level	The start time of the ten hour time period with the highest activity level.
Onset time of night time activity level	The start time of the five hour period with the lowest activity level.
Partial autocorrelation function	A partial autocorrelation function (PACF) measures the serial dependency of data across time. A correlation coefficient is provided for each time lag once the effects of smaller time lags have been removed.

Polysomnography	A method that comprises electroencephalogram recording in combination with eye movement and muscle activity monitoring to estimate the sleep-wake cycle. Monitoring typically occurs within the laboratory.
Positive affect	The experience of positive emotions, such as enthusiasm and alertness.
Rapid cycling	Bipolar disorder when four or more episodes occur within a given year.
Relative amplitude	The amplitude of the rest-activity rhythm across time.
Self esteem	An individual's psychological view of them-self.
Sleep duration	The proportion of time spent in bed sleeping.
Sleep efficiency	The percentage of time spent asleep whilst in bed.
Sleep latency	The amount of time elapsed after going to bed before sleep onset.
Social rhythms	Behaviours that individuals conduct on a daily basis, such as getting up or going to bed, and eating or drinking.
Sociotropy	A tendency to be dependent on others.
Subsyndromal	Symptoms that do meet the threshold criteria for an acute episode.
Time in bed	The time between bedtime and get up time.
Zeitgeber	A regular environmental signal that synchronises circadian rhythms to the 24 hour day.
Zeitstorer	A time disturber that may act as a source for circadian rhythm disruption.

Summary of day-to-day variability in bipolar disorders

Background. Bipolar disorder is characterised by recurrent acute episodes of mania and depression with the common occurrence of subsyndromal symptoms between episodes. Episode recurrence and frequent inter-episode symptoms have made identification of the factors that influence relapse an important focus for research in bipolar disorder.

Objective. To determine whether dysregulation in bipolar disorder would be exhibited, outwith acute mania, in day-to-day variability and whether variability was associated with risk of relapse.

Design. A prospective daily monitoring study was conducted with bipolar disorder and general population samples. Twenty participants with a bipolar episode experienced in the previous two years were recruited from a Lithium Clinic. A control group of ten participants from the general population were recruited by opportunity sampling.

Main outcome measures. Biological, behaviour, cognition, and affect measures included self-report measures of behavioural activation/inhibition, social rhythms, self esteem, positive affect, negative affect, elation, depression and objective actigraph estimation of the sleep-wake cycle and circadian rhythms.

Results. Lower self esteem, lower positive affect, higher negative affect, higher depression levels and greater variability in self esteem, night waking and sleep efficiency across 14 days were evident in bipolar disorder. Survival analyses suggested greater variability in self esteem and sleep efficiency predicted earlier admission in bipolar disorder.

Conclusions. Greater day-to-day variability in bipolar disorder was observed compared to the general population. Underlying disturbances in biological, cognition and affect measures were evident in bipolar disorder. Findings were clinically important since sleep and self esteem disturbances may be considered as potentially modifiable in reducing risk of relapse in bipolar disorder.

Chapter 1 The longitudinal course of bipolar disorder

In order to prepare for the study, a comprehensive review of the research literature with regard to psychobiosocial functioning in bipolar disorders was conducted. Psychological, biological, and social factors, which may influence the course of bipolar disorder, were examined. Key searches of computerised databases were conducted: MEDLINE (1966-2001); PsycINFO (1985-2001); EMBASE (1980-2001). Reference lists in key papers and review articles were also searched. Ongoing internet access to key journals ensured being kept abreast of current issues and new research. Key journals that published research for bipolar disorder samples included: British Journal of Psychiatry; American Journal of Psychiatry; Archives of General Psychiatry; and the Journal of Affective Disorders. Review papers outlining diathesis stress models of bipolar disorder as well as research investigating specific diathesis-stress associations were obtained. The search criteria for daily variability were focused on affect, cognition and behavioural fluctuations. Although the present study recruited a bipolar disorder sample, publications with a wide range of participant samples were obtained for daily variability. This criterion reflected the limited research conducted to date on inter-episode variability in bipolar disorders. The literature on day-to-day variability will be critiqued in chapter two. This chapter will provide a critique of the literature obtained for diathesis stress models of bipolar disorder. Firstly, a description of bipolar disorder, including symptoms of the disorder, current treatment and long term prognosis will be outlined.

1.1. Description of bipolar disorder

Bipolar disorder is a severe and chronic mood disorder characterised by recurrent episodes of depression and mania. Bipolar disorder subtypes include: bipolar I disorder, characterised by one or more manic and/or mixed episodes and at least one major depressive episode; and bipolar II disorder, characterised by at least one hypomanic episode

and one or more major depressive episodes (Muller-Oerlinghausen et al, 2002). Rapid cycling of mood, in which four or more episodes occur within a given year, occurs in 10 to 15% of individuals with bipolar disorder (Muller-Oerlinghausen et al, 2002). Rapid cycling tends to be more common in bipolar II disorder (Tondo & Baldessarini, 1998; Kilzieh & Akiskal, 1999). Rapid cycling tends to disappear over time indicating that this pattern may be a transient phase in the course of the disorder rather than a distinct subtype per se (Winokur et al, 1994; Kilzieh & Akiskal, 1999; Akiskal et al, 2000). Less severe bipolar disorder symptoms are evident in cyclothymia (DSM-IV; American Psychiatric Association, 1994); these symptoms are sub-threshold and do not meet criteria for bipolar I or bipolar II disorders. Cyclothymia can be characterised by chronic hypomanic and depressive mood swings with infrequent euthymia (Akiskal et al, 2000). Age at onset for bipolar disorder tends to range from late teens to late twenties (Miklowitz et al, 1996; Weissman et al, 1996; Muller-Oerlinghausen et al, 2002), although onset can occur later (Bebbington & Ramana, 1995; Hays et al, 1998). There is no significant gender difference in the prevalence of bipolar disorder (Kessler et al, 1994; Bebbington & Ramana, 1995; Weissman et al, 1996; Muller-Oerlinghausen et al, 2002). The UK lifetime prevalence of bipolar disorder is uncertain (DasGupta & Guest, 2002), but can be estimated at around one to two per cent of the adult population (Bebbington & Ramana, 1995).

1.2 Symptoms of bipolar depression and mania

Heterogeneity exists in the expression of bipolar disorder symptoms (Johnson et al, 2000c). Core symptoms include changes in mood, cognition and behaviour. Bipolar depression tends to be characterised by hypersomnia and psychomotor retardation although insomnia and psychomotor agitation may also occur in some instances (Leibenluft & Frank, 2001). Mania and hypomania are characterised by elevated or irritable mood, racing thoughts, rapid speech, increased psychomotor activity, and decreased sleep (Cassidy et al, 1998; Leibenluft

& Frank, 2001). Criteria for depressive and manic episodes are provided in Tables 1.1 and 1.2. Episodes of bipolar depression tend to be more frequent and have a longer duration compared to episodes of mania (Sachs et al, 2000). Mixed episodes may also occur; the criterion for a mixed episode is a period lasting at least one week when symptoms of both mania and depression are present nearly every day (DSM-IV; American Psychiatric Association, 1994).

Table 1.1: DSM-IV Diagnostic criteria for a major depressive episode

1. Two week period during which at least five of the following symptoms have been present nearly every day and represent a change from previous functioning; at least one symptom is either depressed mood or loss of interest or pleasure: • Depressed mood most of the day • Decreased interest or pleasure in all, or almost all, activities most of the day • Significant change in appetite or weight • Sleep disturbance: insomnia or hypersomnia • Psychomotor agitation or retardation (observable by others) • Fatigue or loss of energy • Feelings of worthlessness or excessive / inappropriate guilt • Diminished ability to think or concentrate, or indecisiveness • Recurrent thoughts of death or recurrent suicidal ideation, a suicide attempt or specific plan for committing suicide.
2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. The symptoms are not due to the direct physiologic effects of a substance or a general medical condition.

Table 1.2: DSM-IV Diagnostic criteria for manic episode and hypomanic episode

1. A distinct period of abnormally or persistently elevated, expansive, or irritable mood lasting at least one week (or any duration if hospitalisation is required).
2. During the period of mood disturbance, three (or more) of the following symptoms have persisted and have been present to a significant degree: • Inflated self esteem or grandiosity • Decreased need for sleep (e.g. feels rested after only three hours of sleep) • Talkativeness: increase in both speech rate and amount • Flight of ideas or a sense that thoughts are racing • Distractibility • Increase in activity or psychomotor agitation • Excessive involvement in pleasurable activities with potential for painful consequences e.g. unrestrained buying sprees, sexual indiscretions, and foolish business investments.
3. In a manic episode, the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning, usual activities or relationships with others, to necessitate hospitalisation, or be associated with the presence of psychosis.
4. A hypomanic episode requires a minimum of only four days of symptoms; in addition, a hypomanic episode is associated with an unequivocal change in function observable by others, but it is not associated with marked impairment, hospitalisation, or psychosis.
5. Symptoms not due to direct physiologic effects of a substance/general medical condition.

In addition to bipolar disorder symptoms experienced during acute episodes, inter-episode symptoms may also occur. Causes of inter-episode or subsyndromal symptoms may be categorised as: prodromal/early symptoms of relapse; residual symptoms from previous episode; co-morbidity with Axis I or Axis II disorders; stress; medication side effects; and inter-episode cyclothymia and minor mood cycling (Fava, 1999; Morriss, 2002).

Subsyndromal symptoms are not severe enough to meet criteria for an episode, although such symptoms may still cause considerable distress (Lam et al, 1999). The existence of subsyndromal symptoms between episodes is common in bipolar disorder (Keller et al, 1992; Gitlin et al, 1995). Recent prospective studies reported participants with bipolar I disorder were symptomatically ill 47.3% of weeks over a mean 12.8 year follow-up period (N=146 bipolar I disorder; Judd et al, 2002), whilst participants with bipolar II disorder were symptomatic 53.9% of weeks over a mean 13.4 year follow-up (N=86 bipolar II disorder, Judd et al, 2003b). Subsyndromal symptoms were present for 74% of symptomatic weeks in bipolar I disorder and 40.9% in bipolar II disorder (Judd et al, 2002, 2003b). The presence of subsyndromal symptoms has been associated with an increased likelihood of relapse in bipolar disorder (Keller et al, 1992).

1.3 Current treatment of bipolar disorder

The primary treatment of bipolar disorder is pharmacotherapy; lithium carbonate is the prophylactic treatment of choice in the UK (Prien & Potter, 1990; Gershon & Soares, 1997; Schou, 1997; Keck et al, 2000). Approximately 20 to 40% of individuals with bipolar disorder do not respond to lithium treatment or experience intolerable side effects (Prien & Potter, 1990; Maj, 2000); anticonvulsants, such as carbamazepine and sodium valproate, tend to be utilised for such individuals (Prien & Potter, 1990). Lithium carbonate and anticonvulsants tend to be more effective in stabilising symptoms of mania than symptoms of depression (Keck & McElroy, 1996), although no differential effect of lithium in preventing depressive or manic relapses has been reported (Coryell et al, 1997). Antidepressant medication may be utilised for bipolar depression, with combined use of a mood stabiliser. Since antidepressants may precipitate mania, most clinicians believe it is contraindicated to utilise antidepressants in the absence of a mood stabiliser (Leibenluft & Suppes, 1999). Non-adherence to medication may have a substantial impact on the course

of bipolar disorder with around 75% of relapses associated with non-adherence (Scott, 1995; Silverstone et al, 1998). Although pharmacotherapy is the primary treatment for bipolar disorder, 25 to 50% of individuals do not adhere to medication (Prien & Potter, 1990).

Relapse may occur in bipolar disorder even when pharmacotherapy is optimal which leads to the need for adjunctive intervention. Historically, intervention research had primarily focused on pharmacotherapy, but in recent years reviews of randomised controlled trials have reported promising findings that psychotherapy may be a useful additional treatment to pharmacotherapy in bipolar disorder (Jones, 2004; Scott & Gutierrez, 2004). Published findings from several randomised controlled trials of psychotherapy for bipolar disorder to date include cognitive therapy (Cochran, 1984; Perry et al, 1999; Zaretsky et al, 1999; Lam et al, 2000, 2003, 2005; Scott et al, 2001, 2006; Ball et al, 2006), family focused psycho-education (Miklowitz et al, 2000, 2003; Rea et al, 2003), group psychoeducation (Colom et al, 2003a, 2003b) and interpersonal and social rhythm therapy (Frank et al, 1994, 1999, 2005). Overall, most of the evidence suggests that psychological interventions can improve outcome in bipolar disorder.

Cognitive therapy trials have reported reduced relapse rates and improvement in symptoms following intervention. An early investigation by Cochran (1984) observed fewer bipolar relapses at six month follow up for a six session cognitive behavioural intervention compared to treatment as usual (N=14 cognitive behavioural intervention, N=14 treatment as usual). Zaretsky et al's (1999) pilot study found a 20 session cognitive behaviour therapy intervention improved both bipolar depressed and unipolar depressed symptoms to a similar extent; follow-up impact of the intervention on relapse rate was not assessed (N=8 bipolar depression, N=8 age and gender matched unipolar depression). A median nine

session early symptom monitoring intervention was found to significantly reduce relapse into mania, but not depression, at 18 month follow up (N=34 early symptom monitoring, N=35 treatment as usual; Perry et al, 1999). Lam et al (2003) reported a significantly lower bipolar relapse rate at 12 month follow up for approximately 20 sessions of cognitive therapy compared to treatment as usual; 44% compared to 75% relapsed (N=51 cognitive therapy, N=52 control). When participants were followed up after 30 months, the intervention had no impact on relapse rate after the first year, although the time spent in bipolar episodes was reduced in the cognitive therapy group (Lam et al, 2005). Scott et al's (2001) pilot study observed a 60% reduction in relapse rate at 18 month follow up compared to the 18 month period preceding cognitive therapy; the intervention comprised a maximum of 25 sessions (N=29). Subsequently, Scott et al's (2006) multi-centre trial for 22 sessions of cognitive behavioural therapy reported the intervention had no significant impact on relapse at 18 month follow up (N=127 cognitive behavioural therapy, N= 126 treatment as usual). However, subgroup analyses suggested the intervention was effective in reducing relapse for individuals who had experienced less than 12 previous bipolar episodes. Finally, Ball et al (2006) recently reported a 20 session cognitive therapy intervention did not have a significant impact on relapse rate at 12 month follow up, although the intervention was observed to decrease depressive symptoms at post-treatment (N=25 cognitive therapy, N=27 treatment as usual). There has been some indication that the benefits of cognitive therapy may diminish over time and be differentially effective according to length of history (Ball et al, 2006; Scott et al, 2006). However, cognitive therapy may still be considered a useful intervention to reduce relapse and improve subsyndromal symptoms over the chronic course of bipolar disorder.

Randomised controlled trials for other psychological interventions for bipolar disorder include family focused psycho-education, group psycho-education, and interpersonal and

social rhythm therapy. A 21 session family focused psycho-education intervention for bipolar disorder significantly reduced relapse both at 12 months (N=31 family focused psycho-education, N=70 crisis management; Miklowitz et al (2000) and 24 month follow up (Miklowitz et al, 2003) compared to a less intensive two session crisis management intervention. Furthermore, Rea et al (2003) reported 21 session family focused psycho-education for bipolar disorder significantly reduced relapses and hospitalisations at 12 month follow up compared to individually focused treatment (N=28 family focused psycho-education, N=25 individually focused treatment). Colom et al (2003a) compared 21 session group psycho-education for bipolar disorder to a control intervention that comprised 21 sessions of non-structured group meetings (N=60 group psycho-education, N=60 age and gender matched control). Group psycho-education was reported to significantly reduce bipolar relapse at two year follow up (Colom et al, 2003a). Another investigation by Colom et al (2003b) reported a 20 session group psycho-education for highly compliant individuals with bipolar disorder significantly reduced relapse at two year follow up , compared to 20 sessions of non-structured group meetings (N=25 group psycho-education, N=25 control). Finally, interpersonal and social rhythm therapy has also been indicated to reduce depressive symptoms in bipolar disorder at 12 month follow up compared to intensive clinical management (N=90; Frank, 1999). The two year follow-up (Frank et al, 2005) reported interpersonal and social rhythm therapy as an acute treatment was effective in reducing bipolar relapse; no difference was observed in the effectiveness of interventions as maintenance treatments for bipolar disorder (N=61 acute interpersonal and social rhythm therapy, N=64 acute intensive clinical management). Overall, these findings indicate these psychosocial interventions, along with cognitive therapy, may improve outcome in bipolar disorder. However, adjunctive interventions may be most effective at the early stages of the disorder, have less impact as the disorder progresses (Scott et al, 2006) with diminishing effects over time (Ball et al, 2006) .

1.4 Prognosis in bipolar disorder

Bipolar disorder tends to have a progressive course. With each new episode, there is an increased likelihood of future relapse as well as a tendency for the severity of each episode to increase (Post et al, 1981, 1986; Goodwin & Jamison, 1990; Koukopoulos et al, 1995; Kessing et al, 1998). Even with prophylactic treatment, the risk of future episodes remains high with a relapse rate of around 25 to 50% in one year following an episode of mania (Prien & Potter, 1990; Keller et al, 1992; Gitlin et al, 1995; Kessing et al, 1998; Maj et al, 1998). The likelihood of relapse in bipolar disorder increases over time: 65% relapse rate over two years (N=128; Silverstone et al, 1998), 82% relapse rate over seven years (N=181; Coryell et al, 1995), and 95% relapse rate over the course of ten years (N=206; Judd et al, 2003a).

Bipolar disorder has a profound effect on long term functioning. Coryell et al's (1993) prospective five year study indicated mania and depression were associated with enduring psychosocial impairment, even when remission was sustained. Individuals with bipolar disorder were less likely to be in employment, and if employed, earned significantly less than a matched comparison group (N=148 bipolar disorder, N=148 first degree relatives with no lifetime history of affective disorder; Coryell et al, 1993). Coryell et al (1993) also reported bipolar disorder had an impact on long term relationships; individuals with bipolar disorder were less likely to get married, but if marriage did occur, divorce or separation was more likely than in the comparison group. Indeed, a recent review of 19 studies (total N=1450 bipolar disorder) reported approximately 30 to 60% of individuals with bipolar disorder have impaired social and occupational functioning (MacQueen et al, 2001).

The importance of genetic factors in the aetiology of bipolar disorder has been robustly demonstrated by family, twin and adoption studies (Craddock & Jones, 1999, 2001;

McGuffin et al, 2003). However, genetic factors do not entirely explain the variance in the expression of bipolar disorder. Severity and frequency of episodes are two independent dimensions, which determine the clinical course of bipolar disorder. The severity of a bipolar episode is likely to vary as a consequence of the combination of biological and psychosocial factors (Depue et al, 1987). Psychosocial factors may play an important role in determining the timing and frequency of symptoms and the type and outcome of bipolar episodes (Depue et al, 1987; Ellicott et al, 1990; Malkoff-Schwartz et al, 1998; Lam et al, 1999). Recent reviews of psychosocial treatment approaches for bipolar disorder have reported that such interventions may decrease relapse risk (Jones, 2004; Scott & Gutierrez, 2004). Further, evidence from randomised controlled trials suggests the effectiveness of psychological interventions may depend on the timing of treatment (Frank et al, 2005) and the individual's history of bipolar disorder (Scott et al, 2006). Thus, prognosis in bipolar disorder may require an understanding of the interaction between biological, psychological and social factors. The current study postulated that as bipolar disorder is primarily a biological disorder, change in biological vulnerability would precede change in psychological and social factors. The preceding sections outlined a description of the symptoms, treatment and prognosis in bipolar disorder. In brief, the key issues raised are provided in Table 1.3.

Table 1.3: Summary of symptoms, treatment and prognosis in bipolar disorders

♦ Bipolar disorder is characterised by acute episodes of mania and depression.
♦ Inter-episode symptoms are common in bipolar disorder and increase risk of relapse.
♦ Pharmacotherapy is the primary treatment for bipolar disorder; psychosocial interventions may be an effective adjunct.
♦ Biological, psychological and social factors influence the course of bipolar disorder.

1.5 A psychobiosocial model of bipolar disorder

The course of bipolar disorder may be influenced by biological, psychological and social factors. These factors may also interact with each other to determine the disorder's course. Psychobiosocial models of bipolar disorder provide a theoretical description of the interaction between biological vulnerabilities and psychosocial factors. Weak regulation has been theoretically postulated as the diathesis for bipolar disorder (Depue et al, 1987). Stress may activate the diathesis: the underlying biological vulnerability. In turn, a diathesis prior to activation may not be latent, thus influencing stress generation (Monroe & Simons, 1991). There are three major diathesis-stress models for bipolar disorder: behavioural sensitisation and kindling; life events and circadian rhythm disruption; and biological dysregulations and the behavioural activation system. Life events and circadian rhythm disruption may occur together or in isolation. Each diathesis-stress model will be discussed in turn before pulling the evidence together.

1.5.1 Behavioural sensitisation and kindling

The behavioural sensitisation and kindling model proposed sensitisation to stress and episode sensitisation occur over time (Post, 1992). Behavioural sensitisation describes sensitisation to stress, whereby repeated exposure leads to increased vulnerability to less stress. Episode triggers (e.g. loss of a close relationship) may become conditioned over time to the extent that anticipation of stress (e.g. concern over losing relationship) may trigger an episode. In addition, stress that would not initially precipitate an acute episode, on repeated exposure over time, may become sufficient to induce relapse (Post & Weiss, 1995). Kindling describes episode sensitisation whereby an episode was hypothesised to increase vulnerability to future relapse (Post, 1992). Previous episodes leave 'scars' which eventually lead to episodes occurring in the absence of exogenous precipitating factors and becoming autonomously driven (Post et al, 1986; Post & Weiss, 1995).

Post et al (1986) suggested evidence for kindling included the tendency for bipolar disorder to originate with episodes of depression and progress to mania, the increasing severity and frequency of episodes over time and the decreasing influence of life events in precipitating episodes as length of time from disorder onset increases. However, longitudinal evidence has indicated that kindling may not necessarily occur. Winokur et al (1994) reported no increase in cycle frequency over a prospective ten year follow-up as well as indicating that rapid cycling may cease over time (N=131 bipolar disorder). Ambelas' (1987) retrospective case note review starting from the first episode of mania reported later manic episodes were precipitated by less stress (N=50 first manic episode). In contrast, more recently conducted retrospective (N=64 bipolar disorder; Hlastala et al, 2000) and prospective (N=58 bipolar disorder; Swendsen et al, 1995) studies with larger samples have reported the number of prior episodes does not appear to impact on reactivity to stress. Indeed, Johnson and Roberts' (1995) review concluded evidence of stress or episode sensitisation was preliminary. Naturalistic longitudinal studies may in future provide a better understanding of this model. For instance, longitudinal within-individual analysis over several years would be necessary to determine whether episodes later in the course of bipolar disorder are more independent of stress (Hammen & Gitlin, 1997). Overall, support for behavioural sensitisation and kindling in bipolar disorders is mixed, with the more robust evidence from prospective studies with larger samples not providing empirical support for this diathesis-stress model.

1.5.2 Life events

Stressful life events have been proposed to activate biological vulnerability and precipitate relapse in bipolar disorders. Life stress may include both positive (e.g. getting married, moving house) and negative events (e.g. losing job, death of family member). The psychological meaning of a life event, particularly an event that was not anticipated, may be

strong enough to directly affect an individual's mood (Frank et al, 1994). One difficulty in measuring life events is determining whether the life event is independent or a consequence of a developing bipolar episode (Hunt et al, 1992; McPherson et al, 1993). For example, the onset of mania tends to be associated with impulsive behaviour that may result in the experience of a stressful event (Johnson & Roberts, 1995). Numerous studies investigating life events and their association with bipolar relapse have been conducted to explore this proposed diathesis-stress association.

Retrospective evidence has provided some evidence supporting an association between life events and bipolar relapse with other evidence suggesting no association. Retrospective evidence has suggested life events may be more critical in precipitating manic relapse up to four months prior to episode onset (N=20 bipolar disorder, Kennedy et al, 1983; N=50 first manic episode, N=50 surgical controls, Ambelas, 1987) and bipolar relapse within two weeks of a hurricane, particularly in individuals with subsyndromal symptoms (N=69 bipolar disorder, Aronson & Shukla, 1987). Life events occurring six to 12 months prior to a manic episode do not appear to have influenced onset, when considered in retrospect (N=28 bipolar disorder, Joffe et al, 1989; N=24 bipolar disorder, Sclare & Creed, 1990). The difficulty in collating evidence from this retrospective evidence includes the small sample sizes, different comparisons of groups (i.e. within-person and between-person comparisons) and life events measured over a range of time periods. Furthermore, retrospective evidence may be limited by recall bias; in particular, as episode length tends to differ across mania and depression, with mania having a shorter duration, individuals may find it easier to recall life events prior to mania (Johnson, 2005). Thus, although some retrospective evidence suggests life events may be associated with subsequent bipolar relapse, findings are limited by methodological shortfalls.

Prospective evidence may be considered to be methodologically stronger than retrospective evidence, particularly since retrospective investigation may be polluted by the effort to find potential triggers after an episode has occurred (Johnson, 2005). However, prospective investigations have also been inconsistent; some studies have reported an association between life events three months prior to bipolar relapse (N=61 bipolar disorder, Ellicott et al, 1990; N=62 bipolar disorder, Hunt et al, 1992; N=52 bipolar disorder, Hammen & Gitlin, 1997), whereas others have reported no significant relationship of life events two to three months prior to bipolar relapse (N=58 bipolar disorder, McPherson et al, 1993) or specifically for bipolar depressive relapse (N=27 bipolar disorder, Pardoen et al, 1996). Similar to retrospective studies, prospective investigations may have limited by the small samples recruited and by not investigating episode polarity separately (e.g. Ellicott et al, 1990). Overall, investigation of life events in bipolar disorder have observed either non-significant or small effects, perhaps due to small sample sizes, but may also be due to the interaction between life events and relapse in bipolar disorder requiring consideration of other characteristics.

1.5.2.1 Life stress and cognitive vulnerability

The interaction between life stress and relapse in bipolar disorder may require consideration of cognitive vulnerability. For instance, Swendsen et al's (1995) one year prospective study reported personality factors interacted with life stress to predict relapse in bipolar disorder (N=58 bipolar disorder). Cognitive vulnerability may be considered as personality or cognitive characteristics that influence an individual's vulnerability to stress. Stressful life events, with personal meaning for an individual, may activate negative thoughts about the self that precipitate or exacerbate symptoms (Robins & Block, 1988; Hammen et al, 1989, 1992). Cognitive vulnerability has been reported to interact with life stress to predict increases in manic and depressive symptoms for bipolar disorder (N=49 bipolar disorder;

Reilly-Harrington et al, 1999) and subsyndromal mood disorder samples (N=43 subsyndromal mood disorder; Alloy et al, 1999). Some research investigating cognitive vulnerability and life stress measured sociotropy and autonomy as stable cognitive characteristics. Sociotropy reflects the tendency to be dependent on others, and high levels have been proposed to increase vulnerability to interpersonal life stress (Robins & Block, 1988; Hammen et al, 1989; Robins, 1990). Autonomy reflects the tendency to be independent and achievement oriented; high levels have been proposed to increase vulnerability to life stress involving perceived personal failure or lack of control (Robins & Block, 1988; Hammen et al, 1989; Robins, 1990). Both sociotropy and autonomy are cognitive styles that vary in the extent to which they dominate an individual's psychological functioning; an individual's response to congruent life stress may be influenced by their respective level (Clark & Beck, 1991). For instance, in a bipolar disorder sample, symptom exacerbation was significantly associated with the interaction between sociotropy and interpersonal events, although no relationship was reported for symptom onset (N=49 bipolar disorder, Hammen et al, 1992). No association between autonomy and achievement-related events was evident. Therefore, the presence of activated cognitive vulnerability in combination with congruent life stress may exacerbate symptoms and increase the risk of relapse.

1.5.2.2 Life stress and bipolar disorder

Although evidence has suggested life events may precipitate relapse in bipolar disorders, previous research (e.g. Hammen et al, 1992; Ellicott et al, 1990) may have obscured the life events association by not considering manic and depressive relapses separately. More recent investigations have considered episode polarity and life events since different types of life stress may precipitate mania and depression. A recent review of life events in bipolar disorder concluded negative life events appear to impact on bipolar depression, whilst goal

attainment life events appear to impact on mania (Johnson, 2005). However, it is not yet conclusive if a life event type may be linked specifically to an episode polarity; the critical determinant of polarity may be the underlying biological vulnerability. To illustrate, bereavement is a negative life event that may cause depressive symptoms in the general population, although clinical evidence suggests mania may follow bereavement. The relationship between episode polarity and life stress requires further investigation, with consideration of cognitive vulnerability (Johnson & Roberts, 1995; Johnson, 2005).

1.5.3 Circadian rhythm disruption

Circadian rhythm disruption has been proposed to cause relapse in bipolar disorders. Circadian rhythms are recurring patterns of variation in behaviour and physiology that occur over a 24 hour period (Thomson, 1984; Wehr, 1984). Examples of circadian rhythms include the sleep-wake cycle and daily variations in body temperature (Wehr, 1984). Circadian rhythms are entrained to a 24 hour period by regular and recurrent environmental signals: exogenous zeitgebers (Wirz-Justice, 1995). An example of a zeitgeber is natural light from the daily rising and setting of the sun. Individuals with bipolar disorder are theoretically predisposed to circadian rhythm disruption, sleep-wake cycle abnormalities in particular (Frank et al, 2000). Features such as diurnal mood variation, early morning wakening, a seasonal pattern of relapse and the recurrence of mania and depression have been suggested to be associated with circadian rhythm disruption in bipolar disorder (Wehr & Goodwin, 1983; Haug, 1992; Ehlers et al, 1993). Some interventions that manipulate the circadian system (e.g. partial sleep deprivation) may decrease depressive symptoms, whereas others (e.g. extended bed rest) may decrease manic symptoms, indicating circadian rhythm disruption may be involved in the pathogenesis of mood disorders (Szuba et al, 1991; Wirz-Justice, 1995).

Observations have suggested that social rhythms, such as the timing of eating, sleeping, and exercising, maintain the timing of circadian rhythms (Monk et al, 1991; Ehlers et al, 1993; Malkoff-Schwartz et al, 1998). For instance, Monk et al (1994) observed greater regularity of daily social rhythms was associated with fewer perceived sleep problems in the general population (Study 1; N=96 general population). Consequently, since social rhythms maintain circadian rhythms, it is likely that social rhythm disruption may cause disruption in circadian rhythms. To illustrate, a long distance flight may disrupt social rhythms (e.g. mealtimes, bedtime) leading to circadian rhythm disruption (changes in sleep-wake cycle). Endogenous circadian rhythms (e.g. melatonin, temperature) do not instantly change with the shift in the sleep-wake cycle from a long distance flight (Wirz-Justice, 1995). Thus, circadian rhythms require synchronisation or entrainment to the time zone of the new environment. Flights with more than two hours time change have been reported to precipitate an acute episode in vulnerable individuals; flights from east to west were associated with depression, whilst mania was associated with west to east flights (N=186 hospital admissions from Heathrow airport; Jauhar and Weller, 1982). Flying east to west may be considered as lengthening the day, whereas flying west to east, time may be considered as lost as the day is effectively shortened. However, since psychiatric information was obtained retrospectively with no information on a participant's mental state prior to admission, relapse may have occurred regardless of whether a flight was taken. Thus, social rhythm disruption that leads to circadian rhythm disruption has been tentatively associated with relapse in bipolar disorder. Larger, prospective longitudinal studies may provide more understanding of social and circadian rhythm disturbances and the initiation, exacerbation and maintenance of bipolar relapse.

1.5.3.1 Theoretical descriptions of circadian rhythm disruption and bipolar relapse

Ehlers et al's (1988) theoretical review proposed circadian rhythm disruption has a causal role in the precipitation of depression. Ehlers et al proposed a model that integrated biological and psychosocial factors of depression. The main proposition was social zeitgebers (personal relationships, social demands, tasks) may entrain circadian rhythms. Changes in social zeitgebers may disrupt social rhythms and therefore lead to disruption in circadian rhythms. To illustrate, loss of a partner (social zeitgeber) may change bedtime and get out of bed times (social rhythms) leading to changes in the timing of sleep and wake (circadian rhythms), resulting in a mood change. Ehlers et al (1993) revised their hypothesis of circadian rhythm disruption in depression to include the concept of a zeitstorer. A zeitstorer was defined as a time disturber and was proposed to act as a source for circadian rhythm disruption. Zeitstorers include physical, chemical, or psychosocial events. Ehlers et al provided examples of social zeitstorers ranging from temporary (long distant flight) to more permanent disturbance (shift work; newborn baby). The presence of a zeitgeber entrains circadian rhythms to the 24 hour day, whereas the occurrence of a zeitstorer disturbs circadian rhythms (Frank et al, 2000). Although Ehlers et al (1988, 1993) focused on the implications of social zeitgebers and zeitstorers for depression, more recent theoretical descriptions by these authors have emphasised social zeitgebers and zeitstorers may also be related to mania (Frank et al, 2000).

Healy and Williams' (1988) theoretical review also proposed circadian rhythm disruption has a causal role in the precipitation of depression; a routine may be important in maintaining mood balance whereas circadian rhythm disruption may cause persistent dysphoria. Circadian rhythm disruption may interact with psychological variables through a tendency for individuals to cognitively distort experiences. Cognitive distortions were hypothesised to lead to activation of dysfunctional attitudes and decreases in self esteem.

Dysfunctional attitudes may be considered as negative beliefs and assumptions that an individual holds. For example, an individual may believe that he/she should perform well at all activities. Circadian rhythm disruption may cause tiredness or diminished concentration that an individual could negatively attribute to being lazy or stupid. This misattribution of internal states may cause the rhythm disruption to lead to depression, with misattributions maintaining the depression. Healy and Williams' (1989) subsequently proposed a theoretical interaction of biological and psychological factors in the pathogenesis of mania. Disruptions in circadian rhythms were proposed to have a tendency to lead to mild dysphoria, psychomotor activation, and thought disorder. Healy and Williams' hypothesised such changes lead to an episode of mania when cognitive distortions, similar to those found in depression, occurred. For instance, over-activity produced by circadian rhythm disturbance may result in an individual making misattributions of increased personal effectiveness and self esteem. Cognitive distortions have been posited to lead to features of mania such as grandiosity and euphoria (Johnson & Roberts, 1995). Dysphoria tends to be the primary affective disturbance in both mania and depression. An implication from Healy and Williams' model is that mania and depression may be precipitated by similar psychosocial factors. Furthermore, Jones' (2001) more recent conceptualisation also suggested an individual's psychological appraisal of dysphoria caused by circadian rhythm disruption may determine whether symptoms of depression or mania are initiated in bipolar disorder.

1.5.3.2 Life stress and circadian rhythms

Life stress may disrupt social rhythms leading to circadian rhythm disruption that may result in a mood disturbance (Ehlers et al, 1988; Healy &Williams, 1989; Johnson & Roberts, 1995; Brown et al, 1996). In some instances, the extent of schedule disruption that occurs from life stress may be more important than the emotional threat/loss experienced (Johnson

& Roberts, 1995). Accordingly, preservation of normal social rhythms may buffer individuals from relapsing following life stress (Ehlers et al, 1993; Brown et al, 1996). For example, bereavement is a life stress that may cause both emotional distress and schedule disruption, leading to relapse in vulnerable individuals. Maintaining a routine following bereavement may minimise the risk of relapse from circadian rhythm disruption. A retrospective study reported higher rates of social rhythm disrupting life stress, during eight weeks prior to episode onset, was associated with onset of mania compared to a control eight week period (N=39 bipolar disorder; Malkoff-Schwartz et al, 1998). Although no association was evident for depressive episodes, Malkoff-Schwartz et al (1998) suggested this may be due to more gradual disruption of social rhythms prior to onset of depression.

Research evidence has suggested life stress and circadian rhythm disruption may occur prior to episode onset in bipolar disorder. Future research needs to identify whether life stress can precipitate bipolar relapse in isolation. Circadian rhythm disruption subsequent to life stress may be the critical factor in determining relapse. Also, life stress and circadian rhythm disruption may vary in the extent to which they precipitate each bipolar polarity. A large number of studies have investigated life events and bipolar relapse. Fewer studies investigating circadian rhythm disruption and bipolar disorder were identified suggesting further prospective investigation is necessary to clarify their association.

1.5.4 Behavioural activation system dysregulation

The third diathesis-stress model for bipolar disorder posits the dysregulation of a behavioural activation system. Gray (1989, 1990, 1994) proposed the existence of two neurologically based emotion systems that influence mood and mood-related behaviour: a behavioural activation system (BAS) and a behavioural inhibition system (BIS). Although a third emotion system, a fight/flight system (FFS) had also been postulated by Gray, the

FFS has not been theoretically linked to bipolar disorder, and thus will not be discussed further. Gray's theory proposed the BAS is an appetitive motivational system, which responds to rewards (e.g. praise from another individual). In contrast, the BIS is an aversive motivational system that responds to punishment (e.g. physical threat from another). An emotional experience is postulated to reflect the current combination of activity within these emotion systems (Gray, 1994). Biological and self report measures have been used to assess behavioural activation and inhibition levels. Although research has suggested associations between neurological activity and BAS/BIS levels (Sutton & Davidson, 1997; Gotlib et al, 1998) such evidence is beyond the scope of this thesis and will not be discussed further. The following sections provide a more detailed outline of the BAS and BIS.

1.5.4.1 Behavioural Activation System (BAS)

Activation of an individual's BAS is postulated to cause movement towards goals, since the BAS is proposed to be sensitive to signals of reward, non-punishment, and escape from punishment (Depue & Iacono, 1989; Harmon-Jones & Allen, 1997; Corr, 2001). Theoretically, the BAS is related to positive affect (PA), and is responsible for the experience of positive feelings (e.g. hope, elation). High BAS levels have been significantly associated with higher average daily PA across a 14 day period, although BAS levels were not associated with greater reactivity to positive events (N=86 undergraduates; Study 2, Gable et al, 2000). This suggests that individuals who self-report higher cross-sectional behavioural activation also report higher PA from day-to-day. The theoretical direction of BAS being responsible for the experience of PA was supported by a further study that observed the BAS significantly predicted average PA (N=155 undergraduates; Study 3, Gable et al, 2000). However, Gable et al's (2000) samples were not assessed for risk of bipolar affective disorders (e.g. Hypomanic Personality Scale; Eckblad & Chapman, 1986),

which may have contributed to the strength of the associations observed. The BAS has also been theoretically related to anger (Depue & Iacono, 1989; Harmon-Jones et al, 2002). Self-report high BAS levels have been significantly associated with high levels of anger, with BAS being a predictor of anger (N=164 undergraduates, Study 1; N=41 undergraduates, Study 2; Harmon-Jones, 2003). Thus, theoretical postulation and empirical evidence have suggested BAS activation may be responsible for the experience of both PA and anger, in the context of goal pursuit.

1.5.4.2 Behavioural Inhibition System (BIS)

Activation of an individual's BIS is postulated to inhibit behaviour that may lead to negative outcomes. The BIS is proposed to be sensitive to signals of punishment, non-reward, novelty and innate fear stimuli (Harmon-Jones & Allen, 1997; Corr, 2001). The BIS is theoretically related to negative affect (NA) and is responsible for the experience of negative feelings (e.g. fear, sadness). High BIS levels have been significantly associated with higher average daily NA across a 14 day period and greater reactivity to negative events (N=86 undergraduates; Study 2, Gable et al, 2000). This suggests that individuals who self-report higher cross-sectional behavioural inhibition also report higher NA from day-to-day. The BIS also significantly predicts average NA (N=155 undergraduates; Study 3, Gable et al, 2000). Higher BIS levels were also associated with lower average PA (Study 2), although BIS levels were not found to significantly predict average PA (Study 3, Gable et al, 2000).

1.5.4.3 The BAS and BIS as joint subsystems

Corr (2001, 2002a) described the joint subsystems hypothesis whereby the BIS and BAS may potentially influence both punishment and reward-mediated behaviours. Mutual inhibition has been proposed to exist between the two systems with facilitatory and

antagonistic effects exerted by both systems (Pickering et al, 1999). The BIS is suggested to antagonise responses made by the BAS and vice versa (i.e. the BIS inhibits the BAS). Corr (2001) highlighted experimental animal evidence has suggested the link from BIS to BAS may be stronger than the BAS to BIS link; the threat of punishment outweighing the incentive of reward. In any given situation, punishment and reward signals may be present to varying degrees, suggesting each system will concurrently facilitate and inhibit behaviour; the overall BIS and BAS level may determine the behaviour that occurs. For instance, an individual's BAS may be activated when meeting a desirable individual; behaviour to initiate a relationship may then occur. However, if the individual has previously tried unsuccessfully on several occasions to maintain a serious relationship, then the BIS may be activated and the individual may be less likely to pursue a relationship that may ultimately fail. The activation level of each system may determine which behaviour is exhibited. Engagement of the motivational systems leads to the experience of affect, whereas disengagement may be considered as an absence of affect (Carver et al, 2000). Disengagement of the BAS suggests an individual will not be experiencing positive feelings such as excitement or enthusiasm, whilst BIS disengagement suggests absence of nervousness and other negative feelings.

1.5.4.4 Behavioural activation and bipolar disorder

Individuals with dysregulated behavioural activation systems have been suggested to be vulnerable to extreme biological, affective and behavioural variability (Depue et al, 1987; Depue & Iacono, 1989; Lovejoy & Steuerwald, 1995). Depue and Gray have both suggested that bipolar disorder is associated with BAS dysregulation (Depue et al, 1987; Gray, 1990). Bipolar disorder is characterised by episodes of mania and depression; extremes of biological, behaviour, cognition and affect levels are evident across episode polarities. The course of the disorder as well as the presence of symptoms may be

determined by an individual's behavioural activation level (Depue et al, 1987). Individuals theoretically vary in their average level of behavioural activation and inhibition, and also in their variability around these levels. The average level of activation or inhibition may determine the resulting mood when dysregulation occurs (Depue & Zald, 1993). Research evidence has reported the BIS played a less important role for mania or depression, compared to the BAS in major depressive and at risk bipolar disorder samples (Meyer et al, 1999; Kasch et al, 2002). This evidence supports Depue et al's (1987) theoretical proposal that the BAS is responsible for the experience of mania and depression in bipolar disorder.

Bipolar depressive and manic symptoms have been suggested to be a consequence of extreme BAS levels; high behavioural activation may facilitate mania whilst low behavioural activation may facilitate depression (Depue & Zald, 1993). Individuals who are prone to BAS dysregulation and greater variability are posited to be more sensitive to signs of reward, which promotes goal directed activity; extreme sensitivity to reward may cause mania if behaviour, cognition and affect are influenced by the pursuit of goals (Harmon-Jones & Allen, 1997). Mania can be characterised by either irritable mood or elated mood (DSM-IV; American Psychiatric Association, 1994). Since the BAS has been associated with both PA and anger (e.g. Gable et al, 2000; Harmon-Jones, 2003), BAS dysregulation theory provides a logical explanation that in goal pursuit either irritated or elated mania may occur. Depression may occur with low BAS sensitivity (Harmon-Jones & Allen, 1997; Kasch et al, 2002), since individuals who are insensitive to reward signals may experience less positive affect.

The dysregulations model suggests mania and depression may be precipitated by different environmental events. Johnson et al's (2000c) prospective study reported increased manic symptoms in the two month period following goal-attainment life events with no observed

change in depressive symptoms (N=43 bipolar disorder). Goal-attainment events include passing exams and being offered a job. This finding provides support for BAS activation by positive rewarding events, which may then become hyperactive in mania. In contrast, goal-attainment life events do not appear to impact on depression (Johnson, 2005). Negative life events have been reported in a recent review (Johnson, 2005) to increase bipolar depressive symptoms; negative life events do not appear to impact on mania. Thus, some evidence suggests that mania may be precipitated by goal attainment events whilst bipolar depression may be precipitated by negative life events.

Expectancies may play a role in affective responses to appetitive and aversive stimuli (Carver et al, 2000). Corr's (2002b) theoretical analysis suggested the relationship between individual differences in BAS sensitivity and reaction to reward is moderated by reward expectancies. Corr (2002b) proposed that if actual reward is equal to or greater than expected reward, the BAS is activated; with lower actual reward than expected, the BIS is activated. For instance, if an individual attending a job interview is offered the position at a higher grade and salary than expected, then the BAS may be activated. Conversely, a job offer at a lower grade/salary than expected may cause BIS activation. Similarly, Carver et al (2000) suggested BAS and BIS may be able to yield both positive and negative affect through the interaction of future expectancies. For instance, high BAS sensitivity may lead to high levels of positive affect when appetitive stimuli are present. High negative affect, however, may be produced instead, when expectancies to obtain rewards are low. Cross-sectional research has suggested a lack of positive experiences and positive expectancies mediates the relationship between BAS responsiveness and depressive symptoms (N=171 undergraduates; Beevers & Meyer, 2002). If an individual has few positive experiences and also has low positive expectancies, the extent of BAS activation in response to reward may consequently be lower. Low BAS responsiveness was related to

higher anhedonic depressive levels, but structural equation modelling indicated this direct effect was not significant, when positive experiences and positive expectancies were considered as mediating variables (Beevers & Meyer, 2002). Further investigation, particularly with prospective monitoring, may be necessary to indicate whether the moderating role of reward expectancies is supported.

Meyer et al's (1999) cross-sectional study reported BAS sensitivity was related to symptoms of mania whereas both BIS and BAS sensitivities were related to symptoms of depression. The sample comprised 357 undergraduates, of which 63 were categorised as at risk for a mood disorder (N=13 depression-prone, N=6 hypomania-prone, N=44 cyclothymia-prone). Behavioural activation (BAS) levels, but not BIS levels, predicted symptoms of mania; BAS and mania symptoms were positively correlated. Both BAS and BIS levels predicted symptoms of depression; BAS was negatively correlated whilst BIS was positively correlated with depressive symptoms. Associations between behavioural activation/ inhibition and current hypomanic/depressive symptoms were weaker for the 'not at risk' subgroup (N=294); BAS was significantly correlated with hypomanic symptoms but not with depressive symptoms, whilst no significant correlations were evident between BIS and hypomania or depression.

Meyer et al's (2001) prospective study assessed symptoms of mania and depression monthly and BIS/BAS levels bi-monthly (N=59 bipolar disorder, mean 20 month follow-up). The BAS was analysed as three subscales: reward responsiveness, drive and fun seeking (Section 3.4.2 provides more description of the self report BIS/BAS Scales used by Meyer et al). Cross-sectional analyses found no relationship between the three BAS subscales and manic or depressive symptom severity. The BIS was not related to mania, but a positive correlation between BIS and depressive symptoms was reported. Furthermore,

longitudinal analyses found the BIS fluctuated with changes in depressive symptoms. No fluctuations were observed with BAS and manic/depressive symptoms, or with BIS and manic symptoms. However, higher BAS reward responsiveness following recovery predicted manic symptom intensification over six months; BAS drive and fun seeking subscales were not significant predictors, nor was the BIS level. Neither the BIS nor BAS scale predicted change in depression over time. Meyer et al highlighted methodological differences were evident between the bipolar disorder sample and a previous 'at risk' sample (Meyer et al, 1999). Meyer et al (1999) used self report measures of symptoms in contrast to clinician interviews, and also collected BIS/BAS and symptom measures at the same time-point; these differences may account for the stronger associations observed by Meyer et al (1999). Thus, further prospective investigation of behavioural activation/inhibition and bipolar symptoms is necessary to identify whether an association does exist.

1.5.5 A psychobiosocial model of bipolar disorder revisited

The diathesis-stress models described emphasise an underlying instability or dysregulation in the pathogenesis of bipolar disorders. Behavioural activation dysregulation, circadian rhythm disruption, occurrence of life stress and illness duration/previous episodes have all been suggested to influence the course of bipolar disorder. Each model is supported by research evidence, although at this time-point, evidence is not conclusive as to whether the models are competing or complementary conceptualisations (Lam et al, 1999). Summary points about the diathesis stress models are available in Table 1.4. Cross-sectional or retrospective small sample studies can be considered methodologically weak compared to prospective longitudinal investigations with larger samples. In brief, the evidence suggests a multivariate approach may be necessary to determine the most likely conceptualisation of the diathesis stress associations in bipolar disorder: further prospective within-person investigations are required.

Table 1.4: Summary of diathesis stress models of bipolar disorder

♦ The behavioural sensitisation and kindling model has a strong theoretical base, although supportive empirical evidence has been limited.
♦ Life stress and circadian rhythm disruption may precipitate relapse in bipolar disorder.
♦ Behavioural activation may precipitate symptoms of mania and depression

Chapter 2 Variability in behaviour, cognition and mood in bipolar disorders

Temporal variability may reflect vulnerability to bipolar disorder in the absence of an acute episode. Chapter two will outline research findings on variability in behaviour, cognition and affect. Research evidence for interactions between affect and behaviour, and between affect and cognition will also be reviewed. A greater understanding of inter-episode variability may aid the identification of factors that predict relapse in bipolar disorder. Determining the aspects of variability associated with symptoms of depression and mania respectively may be critical. Bipolar symptoms may be associated with a general overall variability or with specific variation. Firstly, a brief review of subsyndromal symptoms in bipolar disorders will be provided. The clinical importance of subsyndromal symptoms, particularly as early symptoms of relapse, suggests an improved understanding of inter-episode variability is an essential area of research in bipolar disorder.

2.1 A systematic review of manic and depressive prodromes

A systematic literature review of prodromal symptoms in bipolar and unipolar disorders has suggested individuals can identify early symptoms of relapse (Jackson et al, 2003; Appendix H). Prodromes can be described as cognitive, affective, and behavioural early symptoms of a disorder that appear before an episode of depression or mania (Altman et al, 1992; Keitner et al, 1996). Seventeen studies published between 1964 and 2001, met inclusion criteria for the review. Results indicated a median 82% (range 70-100%) of individuals can identify early symptoms of bipolar depression (Molnar et al, 1988; Smith & Tarrier, 1992; Lam & Wong, 1997). The median prevalence of early bipolar depressive symptoms was: mood change (48%), psychomotor change (41%), increased anxiety (36%), appetite change (36%), suicidality (29%), sleep disturbance (24%), and other symptoms (22%). A median 93% (range 75-100%) of individuals were able to identify early symptoms of mania (Molnar et al, 1988; Sclare & Creed, 1990; Smith & Tarrier, 1992; Lam & Wong, 1997; Wong &

Lam, 1999). The median prevalence of early manic symptoms was: sleep disturbance (77%), psychotic symptoms (47%), mood change (43%), psychomotor change (34%), other symptoms (30%), appetite change (20%), and increased anxiety (16%). While most individuals identified early symptoms of mania and bipolar depression, no consistent early symptom of bipolar depression was evident. In contrast, sleep disturbance was identified as a robust early symptom of mania. Thus, inter-episode symptoms can be identified by individuals with bipolar disorder.

Prospective monitoring of subsyndromal symptoms may provide an improved understanding of specific symptoms associated with manic and depressive prodromes. Inter-episode symptoms commonly occur in bipolar disorder (Judd et al, 2002, 2003b) and may include changes in individuals' behaviour, cognition, or affect levels. Fluctuations may be considered as ongoing biological vulnerability to bipolar disorder. Accordingly, inter-episode variation in bipolar disorder may differ from fluctuations observed over time in the general population. The following three sections provide brief literature reviews for variability in behaviour, cognition, and affect in mood disorders and the general population.

2.2 Variability in behaviour

Since bipolar disorder is a biological disorder with recurrent episodes over time, it is possible that recurrent patterns of behavioural variation may influence prognosis. Disruption in circadian rhythms, as described earlier, may be implicated in the pathogenesis of depression and mania. Vulnerability to circadian rhythm dysregulation in mood disorders may be characterised by day-to-day instability in inter-episode periods (Siever & Davis, 1985; Wirz-Justice, 1995). Thus, variability in behaviour may be considered as an important indicator of underlying circadian rhythm dysregulation during inter-episode

periods. Variation in behaviour will be discussed in terms of social rhythm variability and sleep-wake cycle variability.

2.2.1 Variability in social rhythms

The regularity of social rhythms in unipolar and bipolar disorder samples may differ from the regularity observed in the general population. Lower social rhythm regularity has been observed in individuals during a depressive episode compared to general population individuals over five days (N=19 unipolar or bipolar depression, N= 19 general population; Szuba et al, 1992). Although Szuba et al's (1992) clinical sample comprised individuals with either current unipolar or current bipolar depression, social rhythm regularity was not analysed separately for each diagnostic group (N=11 unipolar depression, N=8 bipolar depression). It is therefore unclear whether lower regularity would have been observed in both unipolar and bipolar disorders samples compared to the general population, if the analysis had considered three participant groups. Brown et al (1996) also reported lower social rhythm regularity in individuals with current major depression who had experienced a spousal bereavement (N=44), compared to general population (N=45), bereaved with minor depression (N=26), and bereaved, but not depressed, samples (N=24) over 14 days. The current major depression sample comprised 34 individuals who were experiencing a first episode of depression and ten individuals who were experiencing a recurrence of depression. It was unclear whether this clinical sample included any individuals with bipolar depression. Although social rhythm disruption is evident in the presence of an acute depressive episode, regularity over a 12 week period, does not appear to differ from the general population when unipolar depression is in remission (N=20 recurrent unipolar depression, in remission, N=15 general population; Monk et al, 1991). However, larger intraindividual variability in weekly social rhythm regularity was reported in remitted unipolar depression compared to the general population (Monk et al, 1991). Furthermore,

a recent investigation by Ashman et al (1999) observed that social rhythm regularity did not appear to vary systematically across different mood states in bipolar disorder over a mean 95 days monitoring (N=9 rapid cycling bipolar disorder, N=9 general population). In comparison to individuals from the general population who were monitored for 14 days, individuals with rapid cycling bipolar disorder displayed less regularity in their social rhythms. This finding suggests greater variability in social rhythms may be observed during inter-episode periods in bipolar disorder compared to the general population. Overall, prospective investigations, albeit with small sample sizes over relatively brief monitoring periods, have observed social rhythm disturbances in mood disorders compared to the general population.

The impact of depression on the number of daily activities that individuals perform is less clear. Brown et al (1996) reported fewer activities were performed by individuals with major depression and recent spousal bereavement, compared to non-bereaved general population individuals. In contrast, two studies suggest no differences in the number of activities performed by individuals with current depression (Szuba et al, 1992) or remitted depression (Monk et al (1991) compared to the general population. Although Ashman et al (1999) did not observe the number of activities performed to vary across bipolar mood states, fewer activities were completed by bipolar disorder compared to general population individuals. Differences between the general population and bipolar disorder, but not between different bipolar mood states, in social rhythms may suggest the presence of general social rhythm disturbance. Thus, some evidence suggests differences in the frequency of activities performed between mood disorders and the general population, whilst other evidence suggests no difference in activity frequency. In general, social rhythm studies in mood disorders have been completed with fairly small samples, sometimes with mixed diagnoses (e.g. Szuba et al, 1992); future research should address these

limitations to elucidate social rhythm disturbance in mood disorders. In particular, further prospective research with bipolar disorder samples across inter-episode periods as well as during acute episodes is necessary to identify the robustness of Ashman et al's (1999) initial observations.

2.2.2 Variability in sleep and wake

Variability in the sleep-wake cycle may represent an underlying dysregulation of circadian rhythms. Sleep may be considered as a biologically driven behaviour: the timing and duration of sleep is regulated by the circadian system as well as by the behaviour of the individual (Wehr, 1984). External circumstances, the occurrence of life stress (Wehr, 1992; Riemann & Berger, 1998), or social rhythm disruption (Ashman et al, 1999) may cause sleep disturbance. Sleep disruption may include difficulty in falling asleep, maintaining sleep, increased time spent awake, and early morning wakening (Riemann & Berger, 1998).

Sleep patterns during bipolar episodes have been indicated to differ from sleep patterns observed for the general population. Indeed, sleep disruption is used as a diagnostic criterion for both mania and depression (DSM-IV; American Psychiatric Association, 1994). A sleep electroencephalogram (EEG) study reported individuals with current major depression displayed greater sleep latency and night waking time, with lower sleep efficiency and sleep duration compared to the general population, with no observed differences for time spent in bed (N=67 unipolar and bipolar depression, N=66 general population; Mendlewicz & Kerkhofs, 1991). Hudson et al's (1992) polysomnographic (PSG) study observed individuals with current mania or depression displayed lower sleep duration and sleep efficiency compared to general population individuals (N=19 current mania, N=19 current depression, N=19 general population). Hudson et al (1992)

highlighted similar sleep disruption across mania and depression suggested the same underlying mechanism may be responsible. Furthermore, prospective longitudinal studies suggest a relationship between the sleep-wake cycle and prognosis in bipolar disorder. Regulating the timing and duration of sleep through extended bed rest and darkness has been indicated to stabilise rapid cycling bipolar disorder in two recent case studies (Wehr et al, 1998; Wirz-Justice et al, 1999). Similarly, an 18 month investigation of the day-to-day relationship between sleep and mood reported decreased sleep duration was the best predictor of mania/ hypomania the following day; the relationship between sleep duration and depression was less consistent (N=11 rapid cycling bipolar disorder; Leibenluft et al, 1996). Thus, prospective evidence has consistently suggested an association between the sleep-wake cycle and mood in bipolar disorder.

Prospective investigations using actigraphy to monitor the sleep-wake cycle have reported inconsistent sleep disturbances in bipolar disorder during inter-episode periods (Millar et al, 2004; Harvey et al, 2005; Jones et al, 2005). Actigraphy is a method that objectively estimates the sleep-wake cycle from movement detected by a device worn on the wrist (Section 3.4.1 provides further information on actigraphy). Millar et al (2004) reported no significant differences in averaged sleep measures but greater variability in night waking and sleep duration in bipolar disorder over five days (N=19 bipolar disorder, in remission, N=19 general population). Harvey et al (2005) observed increased sleep duration and reduced sleep efficiency in bipolar disorder over eight days (N=14 bipolar disorder, in remission, N=20 insomnia, N=20 general population). Variability in sleep measures were not reported by Harvey et al (2005). Finally, although Jones et al (2005) did not observe any differences in the average level or variability of sleep measures over seven days, circadian rhythm disturbance of the rest-activity cycle was evident in bipolar disorder (N=19 bipolar disorder, in remission, N=19 general population). Actigraph studies that have investigated the sleep-

wake cycle during inter-episode bipolar disorder have been limited by monitoring small samples of individuals over relatively brief prospective time periods. However, preliminary evidence suggested some sleep disturbance may be apparent in two of the three studies. Larger studies over longer time periods may elucidate the extent of inter-episode sleep disturbance in bipolar disorder.

2.2.3 Sleep disruption and symptoms of depression

Sleep disruption has been indicated in recent meta-analysis studies to be a risk factor for depression (Cole & Dendukuri, 2003; Riemann & Voderholzer, 2003) and has also been reported as a common early symptom of depression (Breslau et al, 1996; Perlis et al, 1997). Furthermore, research has indicated that a night of total sleep deprivation can induce a temporary improvement in mood in around 60% of individuals experiencing depression (Wu & Bunney, 1990; Riemann et al, 1993; Szuba et al, 1994; Berger et al, 1997; Riemann & Berger, 1998; Emilien & Maloteaux, 1999). However, depression reappears in most individuals following recovery sleep, even for as little as two hours sleep (Gillin et al, 1984; Wehr, 1989; Wu & Bunney, 1990). Antidepressant effects of sleep deprivation tend to be more marked in the early morning, which suggests that circadian rhythms may also be involved in mood regulation (Boivin et al, 1997). In addition, diurnal mood variation has been associated with greater mood change following sleep deprivation (Gillin et al, 1984; Roy-Byrne et al, 1984; Haug, 1992; Leibenluft & Wehr, 1992; Wehr, 1992). In contrast, sleep deprivation has not been found to produce mood elevation in individuals from the general population (Roy-Byrne et al, 1984; Wirz-Justice, 1995). The antidepressant effect of sleep deprivation has led to the proposal that sleep disturbance may not only be a symptom, but also be related to the pathogenesis of mood disorders (Wu & Bunney, 1990; Wehr, 1992).

2.2.4 Sleep disruption and symptoms of mania

Sleep disruption is a common symptom of mania, which frequently involves decreased sleep duration, (Bunney et al, 1972; Wehr, 1984, 1990; Hudson et al, 1988; Riemann & Berger, 1998) although total insomnia can sometimes occur at the onset of mania (Wehr, 1990). Serretti and Olgiati (2005) reported a reduced need for sleep was a symptom of mania in approximately 98% of individuals with bipolar disorder (N=280 bipolar disorder). The most robust early symptom of mania identified by a systematic review was sleep disturbance (Jackson et al, 2003). Sleep deprivation can trigger the onset of a manic episode in bipolar disorder (Wehr et al, 1987; Wehr, 1991, 1992; Van den Hoofdakker, 1997; Barbini et al, 1998). Furthermore, sleep loss may even trigger a switch from depression to mania or hypomania, at least in rapidly cycling individuals (Wehr et al, 1982; Wehr, 1989; Wu & Bunney, 1990). Thus, research has consistently indicated that sleep disruption may be a triggering factor in the pathogenesis of mania.

Wehr et al (1987) outlined a hypothesis regarding sleep reduction as a final common pathway in the pathogenesis of mania. Wehr et al (1987) proposed a self-reinforcing mechanism of sleep loss and progressive mood improvement: sleep disruption has the capacity to cause mania, and mania in turn to reduce sleep and so on. This mechanism may create an ongoing vicious circle resulting in mania becoming autonomous (Wehr, 1992; Wehr et al, 1987). Support for Wehr et al's hypothesis is evident from Barbini et al's (1996) recent findings, where sleep loss appeared to act as both a precipitant of mania and as an augmenting factor during an episode of mania. Barbini et al (1996) investigated sleep loss in 34 individuals with bipolar disorder, who were currently experiencing an episode of mania. Sleep loss and mania were monitored over a consecutive three day period. The results indicated a significant inverse relationship between sleep duration and symptoms of mania: the shorter the sleep duration, the greater the level of manic symptoms observed the

following day. Thus, sleep disturbance has been theoretically and clinically linked to manic relapse in bipolar disorder.

2.2.5 Variability in behaviour and bipolar disorder

Overall, evidence suggests variability in social rhythms may differ between bipolar disorder and the general population. Lower social rhythm regularity has been observed in currently depressed (Szuba et al, 1992; Brown et al, 1996) and rapid cycling bipolar disorder (Ashman et al, 1999) samples. There is no indication that social rhythms may vary with mood state, at least in rapid cycling bipolar disorder, but this can only be considered a preliminary finding. Variability in the sleep-wake cycle may also differ between the general population and acute bipolar episodes. For instance, sleep disturbance is evident in both elated and depressed states in comparison to the general population (Hudson et al, 1992). During inter-episode periods, some studies (Millar et al, 2004; Harvey et al, 2005) have observed sleep disturbances in bipolar disorder, whilst others (Jones et al, 2005) have not. Although previous investigations of behavioural variability in bipolar disorder had the methodological advantage of being conducted prospectively, findings are preliminary as small samples were recruited and monitored over relatively short time periods.

2.3 Variability in cognition

Cognition may be defined as an individual's psychological thought processes. The course of bipolar disorder reflects variation in cognition, with acute episodes characterised by cognitive distortions. Cognitive symptoms of depression may include feelings of worthlessness/low self esteem, whereas grandiosity/inflated self esteem may be present in elation or mania. Retrospective studies indicate early symptoms of bipolar relapse may include cognitive changes, such as lowered concentration and self esteem (Smith & Tarrier, 1992; Keitner et al, 1996). Cognitive theories (e.g. Beck, 1987) have postulated

individuals with depression have a generalised negative view of the self. Psychoanalytic theories (e.g. Neale, 1988) also postulate individuals with bipolar disorder have a negative view of self and that mania occurs as a defence against low self esteem and the associated depression. Thus, self rated cognition may be considered a theoretically important construct for depression and mania. Changes in self esteem are included as diagnostic criteria for bipolar relapse in DSM-IV (Tables 1.1 and 1.2). Thus, the literature review for variation in cognition focused on the self esteem construct.

Self esteem (SE) may be considered as an individual's view of the self: what an individual thinks about them-self. For instance, an individual may view them-self as an attractive, interesting, likeable person. The stability of this self view may vary since an individual may have a different view of them-self in different situations. To illustrate, an individual who is popular within their family, but has difficulty making friends at work may have lower SE in the workplace. A multidimensional SE model of depression has proposed four different aspects of the SE construct: level, regulation, reactivity and variability (Roberts & Monroe, 1994, 1999). The level and regulation of SE over time may influence mood. Self esteem regulation includes strategies to maintain SE as well as reactivity and variability of SE. Deficits in these aspects may represent increased cognitive vulnerability to mood change (Roberts & Monroe, 1999). Each SE aspect will be outlined in turn and research evidence for a role in precipitating mood change discussed.

2.3.1 Level of self esteem

Differences in SE emerge between the general population and individuals with bipolar disorder during acute episodes. Research evidence has also suggested differences in SE exist during inter-episode periods in bipolar disorder compared to the general population. Although Pardoen et al's (1993) cross-sectional investigation reported no significant

differences in SE level between individuals with bipolar disorder and general population individuals (N=27 bipolar disorder, minimum remission six months; N=26 general population), more recent cross-sectional studies, with larger samples, indicate differences in SE level. Lower SE levels in euthymic bipolar disorder compared to the general population have been reported by Shapira et al (1999; N=27 bipolar disorder, N=27 general population), Serretti et al (1999; N=99 bipolar disorder, N=100 general population), and Blairy et al (2004; N=144 bipolar disorder, N=144 general population). The minimum remission periods for the bipolar disorder samples were three months (Serretti et al, 1999; Blairy et al, 2004) and 12 months (Shapira et al, 1999). The four studies used the same SE measure (Rosenberg Self Esteem Questionnaire). Two studies matched each bipolar disorder individual to a general population individual for age and gender (Shapira et al, 1999; Blairy et al, 2004). No evidence has suggested the inter-episode SE level for bipolar disorder may be higher than in the general population. Thus, evidence has indicated the SE level for individuals with bipolar disorder, during inter-episode periods, are similar or lower than general population SE levels.

The presence of low SE levels during inter-episode periods of bipolar disorder may explain low SE in bipolar depression, but it is less evident how inflated SE associated with mania may occur. One explanation was provided by Healy and Williams (1989), who proposed that individuals misattribute dysphoria from circadian rhythm disturbance, which could lead to mood elevation (Section 1.5.3.1). Alternatively, psychodynamic explanations have also been postulated. For instance, Neale (1988) hypothesised unstable self esteem was a characteristic of bipolar disorder. When life stress threatens to lower SE, grandiosity or inflated SE was proposed to occur to defend against negative cognitions; this defence was hypothesised to lead to mood elevation. Some research evidence may support this theoretical defensive function of mania. Winters and Neale (1985) observed that whilst

general population and bipolar disorder individuals reported similar SE levels, individuals with unipolar and bipolar disorders made similar internal inferences regarding the cause of failures, which suggests the presence of a low self worth schema (N=16 bipolar disorder, in remission, N=16 unipolar depression, in remission, N=16 general population). Lyon et al (1999) also concluded their findings were consistent with the manic defence hypothesis; participants with current bipolar depression or mania both attributed more negative events to internal factors and recalled more negative words compared to general population participants (N=15, current mania, N=15 current bipolar depression, N=15 general population). Thus, these findings suggest individuals with bipolar disorder may possess a cognitive schema of low SE in both bipolar depressive and manic episodes, as well as during inter-episode periods.

2.3.2 Self esteem regulation

Regulation may be necessary to keep an individual's SE at the same level. Structural deficits in an individual's SE regulation processes have been proposed to increase vulnerability to mood change (Roberts & Monroe, 1994, 1999). Deficits may include over-reliance on limited personal or social sources of SE. For instance, Lam et al (1999) highlighted from clinical observation, that some individuals with bipolar disorder concentrate on one domain in their life (e.g. work) and derive SE specifically from this domain. Lowered SE may arise as a consequence of loss of status associated with bipolar disorder, particularly in terms of long term employment problems (Scott, 1995). Furthermore, the extent of awareness of daily activity performance and the resulting change in how the individual views them-self following task success or failure, has also been suggested as an important factor in SE regulation (Greenier et al, 1999). Heightened awareness of daily activity performance may hinder the regulation of stable SE. In this way, relatively small stressors may have a large impact on SE (e.g. spilling a drink at a

meeting). An individual with heightened awareness may interpret this accident as evidence of incompetence, with a resulting negative impact on their SE level. Individuals with strong SE regulation may be less likely to let a small accident influence how they view them-self overall. Deficits in SE regulation would therefore contribute to SE variability. Kernis et al (1993a) reported variability in specific self-evaluations (competence, social acceptance, physical attractiveness) were associated with SE variability in a general population sample (Study 2, N=104 undergraduates). Furthermore, SE variability was positively associated with greater self-ratings of the importance of physical attractiveness and competence in determining self-worth; importance of social acceptance and SE variability were not significantly associated. These findings suggest deficits in SE regulation through heightened awareness of how individuals consider they perform in day-to-day life, may lead to temporally variable SE.

Self esteem regulation processes may also describe strategies used to maintain and protect SE (Roberts & Monroe, 1999). Social comparison, interpersonal feedback, self-verification and self-enhancement strategies may all be utilised for SE regulation. The use of strategies has been associated with different SE levels (e.g. Kernis et al, 1997) indicating that aspects of the SE construct interact. Roberts & Monroe (1999) provide a more comprehensive review of the research evidence outlining strategies for SE regulation.

2.3.3 Variability and reactivity of self esteem

Self esteem variability refers to the magnitude of short term fluctuations over time, whilst reactivity refers to the extent that SE changes in response to stimuli, such as life stress and dysphoric mood (Kernis, 1993; Roberts et al, 1995). The reactivity and variability of SE may be considered as a continuum whereby moderate reactivity would occur in the general population (Roberts & Monroe, 1992; Kernis et al, 1993a; Butler et al, 1994). Research

evidence has suggested positive associations between SE variability and SE reactivity, and negative associations between SE variability/reactivity and SE level (Kernis et al, 1992, 1998; Greenier et al, 1999). Kernis and Waschull (1995) reported their previous findings (Kernis et al, 1993b; paper presentation, N=60 undergraduates) whereby SE variability was positively associated with greater self-reported impact of negative events. Similarly, Greenier et al's (1999) prospective investigation observed individuals who exhibited greater SE variability reported greater reactivity to both positive and negative daily events (N=130 undergraduates). A prospective self report study observed daily life stress had a greater impact on mood in low SE individuals (N=67 undergraduates; Campbell et al, 1991). Similarly, Brown and Mankowski's (1993) three studies consistently found negative mood led to negative self-evaluations in low SE, but not high SE, individuals (Study 1, N=51 undergraduates; Study 2, N=73 undergraduates; Study 3, N=102 undergraduates). In contrast, positive mood had no differential impact on self-evaluations in low SE compared to high SE individuals (Study 1, N=51 undergraduates; Brown and Mankowski, 1993). Thus, prospective studies with undergraduate samples have suggested the impact of life stress and dysphoric mood on an individual may depend on the individual's variability and level of SE.

Prospective investigations, using undergraduate samples, have consistently reported high SE variability individuals were more likely to experience depressive symptoms following life stress than low SE variability individuals (N=192 undergraduates, Roberts & Monroe, 1992; N=122 undergraduates, Roberts & Gotlib, 1997; N=213 undergraduates, Roberts & Kassel, 1997; N=98 undergraduates, Kernis et al, 1998). Associations between SE variability and depressive symptoms were evident for individuals initially low in symptoms in two studies (Roberts & Monroe, 1992; Roberts & Kassel, 1997); this suggests SE variability may be more important in onset, rather than persistence, of mood symptoms.

Furthermore, prospective investigation has observed greater SE reactivity to daily life stress in current and previously depressed individuals compared to never depressed individuals (N=57 current major depression, N=76 previous major depression, N=72 never depressed undergraduates; Butler et al, 1994). Thus, SE variability may be considered as a diathesis for depressive symptoms; SE variability in combination with life stress or daily hassles has been associated with onset of depressive symptoms.

A mood-state hypothesis has been suggested by some authors (e.g. Teasdale, 1988) which postulates individuals with a biological vulnerability for mood disorders have stronger associations between cognition and mood than the general population. Research evidence to support the mood-state hypothesis has been mixed. Roberts and Kassel's (1996) cross-sectional study reported SE level was mood-state dependent in depression-prone individuals, but this was not evident in control individuals (N=88 remitted dysphoria, N=74 non-dysphoric undergraduates). In particular, SE level was significantly correlated with negative affect, but not positive affect, in depression-prone individuals. In contrast to the mood-state hypothesis, Roberts and Gamble's (2001) cross-sectional study reported a stronger association between SE level and negative affect in never depressed individuals (N=11 previously depressed; N=99 never depressed adolescents). Although a significant positive correlation between SE level and positive affect was evident, this association did not differ between previously depressed and never depressed individuals. Prospective investigation of mood and SE in clinical samples compared to the general population may provide improved understanding of associations between mood and cognition.

Despite the extensive investigation of SE variability and depressive symptoms in the general population, little research has been conducted with individuals with current clinical depression or mania. A recent cross-sectional study reported SE level varied across

individuals with hypomania, bipolar depression or bipolar disorder in remission; higher SE levels were observed in individuals with remitted bipolar disorder compared to individuals with current hypomania or depression (N=26 remitted bipolar disorder, N=13 hypomania, N=38 bipolar depression; Scott & Pope, 2003). Further investigation of the temporal relationship between SE and mood is necessary to improve understanding of how SE fluctuations relate to elevation or depression of mood in clinical samples. Future investigations monitoring SE prospectively across different mood states within individuals would provide a stronger method to detect differences in bipolar disorder, although longitudinal monitoring may be required to observe individuals across all clinical mood states.

2.4 Variability in mood

Bipolar disorder is characterised by acute episodes of extreme mood as well as mood fluctuations during inter-episode periods. Theoretical models of mood (e.g. Batson et al, 1992; Larsen, 2000) have differentiated three aspects of emotional experience: affect, emotion, and mood. Affect may be considered as the individual affective components or tone associated with a mood or emotion state (Larsen, 2000). Moods and emotions have been posited by these theoretical models to differ in their duration and intensity. Mood duration may be longer than emotion since mood is thought to be influenced by future expectations (Batson et al, 1992; Larsen, 2000). Emotion intensity may be greater than mood intensity as emotions are thought to occur over more discrete time periods (Batson et al, 1992; Larsen, 2000). The onset and maintenance of elated and depressed moods in bipolar disorder is of more clinical interest than the experience of emotions per se. Affect is necessary for the creation of mood, although changes in affect may not always lead to changes in mood (Batson et al, 1992). Thus, day-to-day fluctuations in affect may be critical in understanding variability between elation, depression and euthymia in bipolar

disorder. Affect is comprised of both valence (positive-negative) and intensity (strong-weak) (Batson et al, 1992). The literature review will focus on variability in affect, but will briefly discuss mood variability in clinical samples.

2.4.1 Level of positive and negative affect

Two dominant dimensions of subjective emotional experience are positive affect (PA) and negative affect (NA); each affect can be measured as either a trait or a state (Watson & Clark, 1984; Watson & Tellegen, 1985; Watson, 1988; Watson et al, 1988b; Clark & Watson, 1991). Positive affect refers to the level of enthusiasm, activity, and alertness that an individual feels; negative affect refers to the level of subjective distress, and includes aversive mood states, such as anger, disgust, guilt, fear, and nervousness (Watson et al, 1988b; Lonigan et al, 1999). High levels or intensity of PA and NA represent states of emotional arousal whereas low levels represent a relative absence of affect (Watson & Tellegen, 1985; Watson, 1988).

Differences in PA and NA levels have been demonstrated. Cross-sectional investigations have reported higher PA than NA levels in general population (N=4217; Watson et al, 1988a) and undergraduate (N=153; Roberts & Gamble, 2001) samples. Gable et al's (2000) prospective studies observed higher daily PA than NA level across seven days (Study 2, N=50) and 14 days (Study 3, N=155) in undergraduate samples. Egloff et al (1995) also reported higher PA level compared to NA, when affect was prospectively measured three times a day for a seven day period (N=49 undergraduates). Furthermore, Lovejoy and Steuerwald's (1995) prospective investigation indicated higher daily PA compared to daily NA over 28 days in undergraduates with either no psychiatric diagnosis or a subsyndromal mood disorder (N=16 intermittent depression, N=12 cyclothymia, N=19

undergraduates, no current psychiatric diagnosis). Overall, cross-sectional and prospective evidence has indicated the average PA level tends to be higher than the average NA level.

Prospective studies have observed differences in affect levels between mood disorders and the general population. Lovejoy and Steuerwald (1995) reported higher daily NA in subsyndromal mood disorders in comparison to the general population; daily PA did not differ between groups across 28 days (N=16 intermittent depression, N=12 cyclothymia, N=19 undergraduates, no current psychiatric diagnosis). Myin-Germeys et al (2003) conducted an experience sampling method (ESM) study whereby affect was self-rated on ten occasions per day, following unpredictable alarms from a wristwatch device, across a six day period. Myin-Germeys et al (2003) reported higher NA and lower PA in currently depressed individuals compared to the general population (N=46 current major depression, N=49 general population). No difference for NA level was evident between the general population and remitted bipolar disorder, although PA level was significantly lower in bipolar disorder (N=38 bipolar disorder, full or partial remission for minimum 2 months; Myin-Germeys et al, 2003). Thus, preliminary evidence has suggested affect levels during acute episodes and inter-episode periods may differ across mood disorders and general population samples.

Positive and negative affect levels are likely to be different during acute episodes of depression and mania, in comparison to inter-episode periods. Episodes of depression may be characterised by high NA and low PA (Watson et al, 1988b; Clark & Watson, 1991; Lonigan et al, 1999; Gencoz, 2002). A prospective general population study reported higher NA and lower PA in depressed compared to non-depressed individuals (N=37 undergraduates; Hopko et al, 2003). In contrast, episodes of mania may be characterised by high NA and high PA. For instance, Cassidy et al (1998) reported symptoms of mania

that may be considered as high NA (e.g. irritability, guilt) and high PA (e.g. increased humour). Lovejoy and Steuerwald's (1992) cross-sectional investigation of subsyndromal affective symptoms and trait affect reported depressive symptoms were positively correlated with NA and negatively correlated with PA, when hypomania was controlled for. Although a positive correlation between hypomanic symptoms and NA was evident, this was reported to be due to shared variance with depressive symptoms; hypomanic symptoms and PA were positively correlated, when depression was controlled for (N=53 subsyndromal affective disorder, N=268 undergraduates, no psychiatric diagnosis; Lovejoy & Steuerwald, 1992). Thus, the high NA-low PA characteristic of depression has been supported (Lovejoy & Steuerwald, 1992; Hopko et al, 2003) but not the high NA-high PA characteristic of mania (Lovejoy & Steuerwald, 1992). However, since a subsyndromal samples were used with one cross-sectional investigation, stronger associations may be observed with prospective monitoring of a clinical sample. Prospective investigation of affect levels in mood disorders may provide a better understanding of how affect varies during acute episodes as well as across inter-episode periods.

2.4.2 Variability and reactivity of affect

Affect variability may be considered as the extent of fluctuations in affect over time, whilst affect reactivity refers to the extent that affect changes in response to life stress or events. Evidence has indicated that affect variability is a stable dispositional characteristic in the general population (Cooper & McConville, 1990; Penner et al, 1994; McConville & Cooper, 1997), with observed individual differences in variability (Cooper & McConville, 1990). For instance, Penner et al (1994) reported intraindividual affect variability exhibited temporal stability over a 14-day monitoring period, when the first five day and last five day periods were compared (N=54 general population). Positive associations between PA/NA level and PA/NA variability have been reported by a prospective study, suggesting

individuals who experience relatively high affect may also exhibit greater variability in affect over time (N=29 undergraduates; Hepburn & Eysenck, 1989). Consistent variability across positive and negative affects has been observed. Prospective general population investigations have reported positive associations between PA and NA variability, which suggests individuals who display large PA variability also display large variability in NA (N=29 undergraduates, Hepburn & Eysenck, 1989; N=17 general population, McConville & Cooper, 1995; N=78 general population, McConville & Cooper, 1997). Thus, while intraindividual stability in affect variability has been indicated, interindividual differences in affect variability may exist, particularly when comparing the general population to clinical populations.

Investigation of affect variability in general population and mood disorder samples has not been extensive. A study by Lovejoy and Steuerwald (1995) prospectively compared PA and NA in subsyndromal unipolar or bipolar disorder and general population individuals (N=47 undergraduates; N=16 intermittent depressive disorder; N=12 cyclothymia, N=19 no current psychiatric diagnosis). Greater daily PA variability was observed for cyclothymia, compared to general population, individuals; daily NA variability was significantly greater in both cyclothymia and intermittent depression individuals in comparison to the general population (Lovejoy & Steuerwald, 1995). Roberts and Gotlib's (1997) prospective study reported affect variability (PA and NA) did not predict depressive symptoms, either alone or in interaction with life stress (N=122 undergraduates). This may suggest that affect variability may be a vulnerability factor for mood disorders, but not for mood change in the general population. Further research is necessary in both general and clinical populations to determine the clinical significance of affect variability.

Day-to-day fluctuations or variability in affect may be influenced by the extent that affect is reactive to life stress. For instance, Bolger et al's (1989) prospective investigation reported approximately 20% of negative mood variability was accounted for by negative daily stress (N=332 general population). Other research has reported both positive and negative affect reactivity to life stress is evident in the general population. Negative events have been associated with increased NA (Clark & Watson, 1988; David et al, 1997; Van Eck et al, 1998; Gable et al, 2000), whereas reactivity of PA to negative events has been less substantial (David et al, 1997; Van Eck et al, 1998; Gable et al, 2000). Positive events have been associated with increased PA (Clark & Watson, 1988; David et al, 1997; Gable et al, 2000). Negative affect reactivity to positive events has not been observed (David et al, 1997; Gable et al, 2000). Overall, evidence has suggested specific affect reactivity with negative events impacting on NA and positive events impacting on PA in the general population.

Individuals with mood disorders experience extremes of affect during episodes of mania and depression. Consequently, it is possible that affect reactivity to daily life stress may be greater in mood disorders compared to the general population. Peeters et al's (2003) experience sampling method investigation (ten ESM ratings each day over a six day period) reported affect reactivity to daily life stress differed between currently depressed and general population individuals (N=46 current major depression, N=39 general population). Currently depressed individuals displayed greater affect reactivity to positive events/ situations; larger increases in PA and larger decreases in NA were evident in current depression compared to the general population. In contrast, affect reactivity to negative events/situations was observed to be greater in the general population group, with larger increases in NA and decreases in PA. Another ESM study by the same authors, investigated affect reactivity to current daily life stress by comparing Peeters et al's current

depression sample with bipolar disorder participants and a different general population sample (N=46 current major depression, N=38 bipolar disorder, minimum two months full/partial remission, N=49 general population; Myin-Germeys et al, 2003). Myin-Germeys et al (2003) reported greater NA reactivity to life stress in currently depressed compared to general population individuals, with no difference in PA reactivity. Furthermore, greater PA reactivity to life stress was observed in remitted bipolar disorder compared to the general population group, with no difference in NA reactivity. Thus, preliminary evidence suggests affective reactivity may differ between mood disorders and the general population, and may also depend on the valence (positive or negative) and intensity (life events vs. daily life stress) of life stress.

Although evidence has indicated affect reactivity to life stress may occur in both general population and mood disorder samples, differences in affect recovery have been suggested to exist. Affect recovery following reactivity, whereby affect stabilises and returns to the prior level, may be slower in individuals with mood disorders. Goplerud and Depue (1985) observed longer duration of mood recovery following life stress in dysthymia and cyclothymia compared to the general population (N=4 dysthymia, N=31 cyclothymia, N=24 general population). Similarly, Peeters et al (2003) observed longer affect recovery in currently depressed compared to general population individuals; prior negative events were reported to have a persistent effect on NA level in current depression. Thus, longer affect recovery following reactivity to life stress has been suggested in mood disorders.

2.5 Literature review conclusions

Individuals experience biological, behaviour, self esteem and affect day-to-day variability. Preliminary evidence has suggested the extent of this variability differs between the general population and individuals with mood disorders. Greater day-to-day variability has been

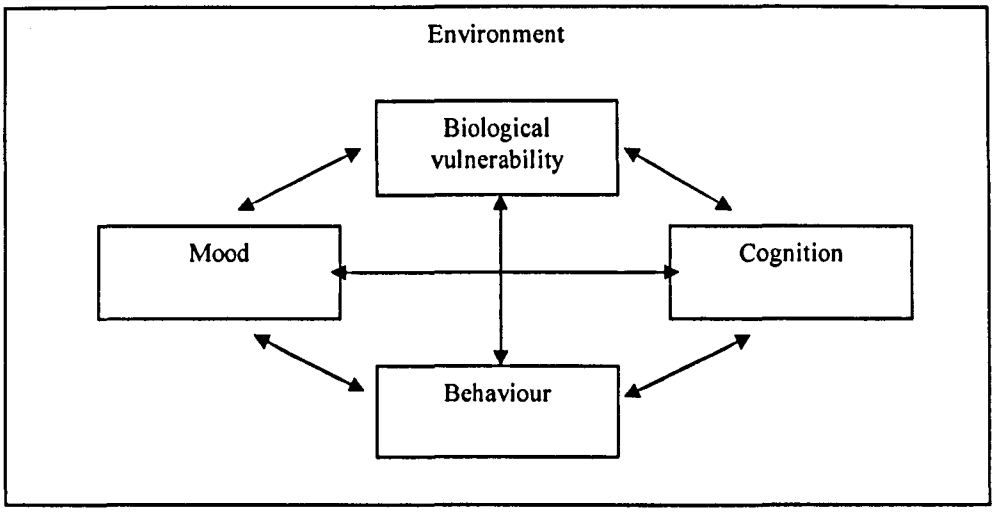
observed in unipolar and bipolar disorders, as well as in subsyndromal mood disorders. The difference between bipolar disorder and the general population may be the ability to regulate behaviour, cognition and mood following psychosocial stress (Depue & Iacono, 1989; Johnson et al, 2000c). Whereas general population individuals may be influenced by stress temporarily, greater variability in bipolar disorders may increase reactivity to stress or delay mood recovery (Goplerud & Depue, 1985; Myin-Germeys et al, 2003). Indeed, some previous investigations have suggested that mood fluctuations might be an indirect measure of life stress (Kennedy-Moore et al, 1992; Gable & Nezlek, 1998). Research to date, however, has not concurrently monitored inter-episode variability in biological, behaviour, self esteem and affect measures in bipolar disorders.

Although similar psychological processes have been postulated to increase vulnerability to depression and mania (Healy & Williams, 1988; Reilly-Harrington et al, 1999), research findings suggest different psychosocial factors are important for each polarity. Evidence has reported psychosocial factors (e.g. social support, self esteem, life events involving loss) may be important in the course of bipolar depression, whilst factors important to the course of mania may include sleep, social rhythms and life events involving goal attainment (Johnson et al, 2000b, 2000c; Malkoff-Schwartz et al, 2000). Most research has concentrated on psychological models of unipolar depression, and while this may be extended to refer to bipolar depression, there is no psychological model that presently exists which provides a comprehensive explanation for onset of mania (Scott, 2001). Understanding the importance of variability in behaviour, cognition and affect, and how they interact, may provide a step towards understanding why depressive symptoms occur in some instances, whilst manic symptoms present at other times.

2.6 Rationale for the study

The literature review has identified that the biological vulnerability of bipolar disorder interacts with the individual's mood, cognition and behaviour as well as the surrounding environment (e.g. life events). The five systems model provides a simple representation of how these five systems interact and is provided in Figure 2.1. This model has been used in cognitive behavioural self help guides to explain the interaction between different aspects of an individual's life (Greenberger & Padesky, 1995; Scott, 2001; Williams, 2001). This five systems model is applicable to all individuals, and can be used in the current study to describe how variation in the other systems (environment, biological vulnerability, cognition, and behaviour) may lead to variation in mood for bipolar disorder. The sequence of change that precipitates relapse in bipolar disorder is uncertain, perhaps due to the numerous factors that can impact on clinical course and the scarcity of longitudinal studies that monitor the interaction of multiple factors on bipolar disorder. Since bipolar disorder may be considered a biological disorder (Craddock & Jones, 1999, 2001) the current study posited that change in biological vulnerability would precede change in the other systems. Even with prophylactic medication, the biological vulnerability of bipolar disorder has a pervading presence observed through high relapse rates (e.g. Judd et al, 2003a) and commonly experienced subsyndromal symptoms (Judd et al, 2002, 2003b). The impact of the environment (e.g. life events) has been briefly discussed in a diathesis stress context but was not monitored in the current study. The study rationale outlines the importance of the interactions between the four remaining systems: biological vulnerability, behaviour, cognition, and mood.

Figure 2.1: A psychobiosocial model of bipolar disorder



Bipolar disorder is recurrent in nature, and as such identification of the factors that predict relapse has always been an essential element of core research (Ellicott et al, 1990). Research evidence has indicated several factors may play a role in the precipitation of relapse in bipolar disorder. These factors include: biological vulnerability, life stress, social rhythm disruption, medication non-adherence and cognitive vulnerability. Inconsistent findings from previous research may be due to variable interactions, where the effects of one variable depend on the level of another variable (Simons et al, 1995). Whilst research to date has been important in highlighting the relationship between the disorder and certain factors, a more comprehensive model of how several factors interact to influence the course of disorder may provide a greater understanding of bipolar disorder. It is critical for research to investigate several constructs to identify whether general dysregulation or specific instability in one construct underlies vulnerability to mood disorders during inter-episode periods. One investigation reported temporal self esteem variability, but not affect variability, predicted onset of depressive symptoms in a general population sample, suggesting specific instability is critical (N=122 undergraduates; Roberts & Gotlib, 1997). Looking at one construct in isolation may suggest specific dysregulation whereas it is

possible that a more general dysregulation exists across several constructs in bipolar disorder, even during inter-episode periods.

Bipolar disorder is characterised by recurrent episodes of acute mania and depression. Symptoms of bipolar episodes encompass changes in cognition and behaviour in addition to these extremes of mood. A reduced need for sleep during mania has been reported in 97 to 99% of individuals with bipolar I and II disorders (N=158 bipolar I disorder, N=122 bipolar II disorder; Serretti & Olgiati, 2005), whilst social rhythm disruption has also been associated with mania (Malkoff-Schwartz et al, 1998). Furthermore, increased self esteem was reported as a symptom of mania in 87% of individuals with bipolar I disorder and in 64% with bipolar II disorder (Serretti & Olgiati, 2005). However, subsyndromal fluctuations in affect, self esteem and behaviour may also be present in inter-episode periods (Cassano et al, 1999; Akiskal et al, 2000). Subsyndromal fluctuations may play a role in the precipitation of relapse as well as long term outcome (Fava, 1999; Morriss, 2002; Jackson et al, 2003). For instance, sleep disruption has been identified as a robust early symptom of mania (Jackson et al, 2003). Furthermore, ongoing biological dysregulation may represent an underlying vulnerability to bipolar disorder. For instance, a recent study reported individuals with euthymic bipolar disorder had a disturbed sleep-wake cycle compared to the general population (Millar et al, 2004). Monitoring the sleep-wake cycle may be the most clinically useful evaluation of circadian rhythm disruption in bipolar disorder since it is amenable to change. Thus, understanding bipolar mood fluctuation in the context of biological dysregulation as well as fluctuations in affect, self esteem and behaviour may be essential for the investigation of subsyndromal fluctuation in bipolar disorder.

2.7 Aims of thesis

The core vulnerability of bipolar disorders may be represented as instability of biological regulatory control. Diathesis-stress models for bipolar disorder propose the existence of an underlying instability with biological, behaviour, self esteem and affect extremes evident across acute bipolar episodes. Consistent with instability models of bipolar disorder, the current study posited inter-episode instability may be exhibited in day-to-day variability. The research hypothesis was greater day-to-day variability in prospective measures of biological, behaviour, self esteem, and affect would be observed in a bipolar disorder sample in comparison to individuals recruited from the general population. In addition, the average levels of measures were hypothesised to differ between bipolar disorder and general population groups, in line with previous findings. Thus, the present study investigated the average level and variability of biological, behaviour, self esteem and affect measures.

The present study built on previous evidence by addressing gaps in the research conducted to date. Although research interest in temporal variability has rapidly increased in recent years, most studies have recruited general population or subsyndromal samples. It remains unclear to what extent that such findings could be considered representative of clinical mood disorder populations. Furthermore, most research investigations in bipolar disorder have focused on acute episodes whilst relatively few studies have investigated biological, behaviour, cognition, and affect regulation across inter-episode periods. The importance of inter-episode periods in the long term course of bipolar disorder has become evident in light of findings from recent large prospective longitudinal studies investigating weekly symptomatic status in bipolar disorders. Evidence from two longitudinal studies across approximate 13 year periods (Judd et al, 2002, 2003b) reported individuals with bipolar I and bipolar II disorders were symptomatic approximately 47 to 54% of the time; subsyndromal symptoms accounted for 41 to 74% of the time spent symptomatic. The

objective of the current study was to address these gaps in existing knowledge by prospective monitoring of individuals with bipolar disorder across inter-episode periods.

Three research aims were identified. The first aim was to investigate whether greater variability in biological, behaviour, self esteem and affect measures were evident in individuals with bipolar disorder compared to individuals from the general population. The second research aim was to investigate whether mean biological, behaviour, self esteem and affect levels differed between bipolar disorder and the general population. Differences in the variability of measures between bipolar disorder and general population groups may be considered to have clinical importance if variability was associated with outcome in bipolar disorder. The third aim was to investigate the clinical importance of variability in bipolar disorder. Greater variability in individuals with bipolar disorder was hypothesised to be associated with increased vulnerability to relapse across time.

Chapter 3 Methodology

The purpose of the current research was to investigate behavioural, cognitive and affective variability in bipolar disorders. Variability of circadian rhythms and behavioural activation, as measures of underlying diathesis vulnerabilities, were also investigated. Daily self-report measures of the key variables were identified to use in combination with objective monitoring of the sleep-wake cycle. Forth Valley Primary Care NHS Trust Ethics Committee approved the Research Protocol (Appendix A). Management approval was obtained from the Chief Executive and Medical Director of Forth Valley Primary Care NHS Trust. A sample of participants with bipolar disorder and a general population sample were recruited to identify variability between groups and within-individuals.

3.1 Participants

Individuals who met criteria for a clinical diagnosis of bipolar I or bipolar II disorders (fulfilled DSM-IV criteria, according to casenotes) were recruited from a Lithium Clinic in Forth Valley Primary Care NHS Trust between September 2001 and March 2002. A staff psychiatrist confirmed case diagnosis. A control group from the general population was also recruited. Control group individuals were selected through opportunity sampling from personal and occupational sources.

3.1.1 Inclusion criteria for participants with bipolar disorder

1. Currently in contact with general adult psychiatry services.
2. Met DSM-IV criteria for bipolar I or bipolar II disorder
3. Not currently experiencing mania
4. Willingness to provide informed consent.
5. Consultant approval to approach individual to participate.
6. Experienced a recent episode in the past two years.

7. Aged 18 to 65 years.

3.1.2 Exclusion criteria for participants with bipolar disorder

1. Current involvement with another research project.
2. Unable to give written informed consent.
3. Inability to speak English.

3.2 Design

A prospective design was used since retrospective assessment may not reliably reflect actual day-to-day variability. Cross-sectional self-report measures of self esteem variability have not been reported to be strongly associated with self esteem variability obtained from prospective repeated assessments (Kernis, 1993; Kernis et al, 1989, 1992). For instance, Kernis et al (1992) found variability of self esteem, measured at 10am and 10pm over a four day period, was weakly associated with self-report measures of how much individuals estimated their self esteem ratings would vary over time ($r=0.22$, $N=112$, $p<0.03$). Furthermore, the use of a prospective design provided data on both average level and variability of measures over time.

Daily self-report measures were selected to assess variability over time, with interval-contingent monitoring at the end of each day. Prospective research studies with general population samples have reported mood does not tend to carry over across days (David et al, 1997; Suls et al, 1998), making daily monitoring suitable for measuring change across time. Less frequent monitoring may obscure the extent of variability in bipolar disorders (Hennen, 2003). Monthly symptom monitoring has been reported to identify fewer manic and depressive symptoms in comparison to prospective daily monitoring in a bipolar

disorder sample (N=30; Denicoff et al, 1997). Prospective daily monitoring may also minimise the potential bias of retrospective recall (Reis & Gable, 2000; Bolger et al, 2003).

Self-report questionnaires were selected to assess day-to-day variability. Interviews were rejected as time consuming and obtrusive for daily prospective monitoring. A self-report measure of behavioural activation was completed weekly. Actigraphy, a method for objective estimation of the sleep-wake cycle, was used in addition to a self-report measure of time spent in bed to provide a more detailed description of sleep-wake variability across time. The use of self-report measures removed any potential interviewer bias, although validity was dependent on participants' ability and willingness to provide accurate information (John & Benet-Martinez, 2000; Reis & Gable, 2000). Similarly, collection of sleep-wake cycle data was contingent on participants continuously wearing an actigraphy device on their wrist.

3.2.1 Pilot of study design

The measures initially selected for the current study were piloted with volunteers from the general population and the Manic Depression Fellowship (N=2 general population, N=2 bipolar disorder). Questionnaires to measure the factors that may influence relapse in bipolar disorder were identified. Nine questionnaires were selected to pilot the study design. The questionnaires were short listed on the basis of research evidence of their construct's importance in bipolar disorder. Although all nine questionnaires were considered relevant to the research hypotheses, volunteers' feedback indicated the package was too large for people to retain interest in completing. The questionnaire package was reduced following this feedback. Questionnaires considered unlikely to vary on a day-to-day basis were discarded for the current project. Questionnaires piloted but not used in the current study included: Sociotropy Autonomy Scale (Beck et al, 1983; Bieling et al, 2000);

24 item Dysfunctional Attitudes Scale (Power et al, 1994) ; List of Threatening Experiences (Brugha & Cragg, 1990); Multidimensional Perfectionism Scale (Hewitt & Flett, 1999); and an unpublished Tablet and Routines Questionnaire. The daily questionnaires along with a weekly behavioural activation measures were retained to investigate variability from day-to-day. The questionnaires selected for the current study were: Social Rhythm Metric; Rosenberg Self Esteem Questionnaire; Positive And Negative Affect Schedule; and Behavioural Inhibition system and Behavioural Activation System Scales. These measures will be described in more detail in Section 3.4.

3.2.2 Study design modification

Initially, the current study intended to replicate and expand Ashman et al's (1999) study design. Participants were recruited and completed the questionnaires for the current study on this basis. When a participant with bipolar disorder had completed a minimum eight week period of monitoring, an age and gender matched participant from the general population was recruited. Between-group comparisons were intended to compare a two week period in general population participants compared to the full monitoring period in bipolar disorder participants. However, following statistician advice, participant groups were compared over equivalent time periods. Since this decision was taken after data collection had been completed, further participants from the general population were unable to be recruited. The study design modification was considered to be a more conservative investigation of differences between bipolar disorder and general population samples.

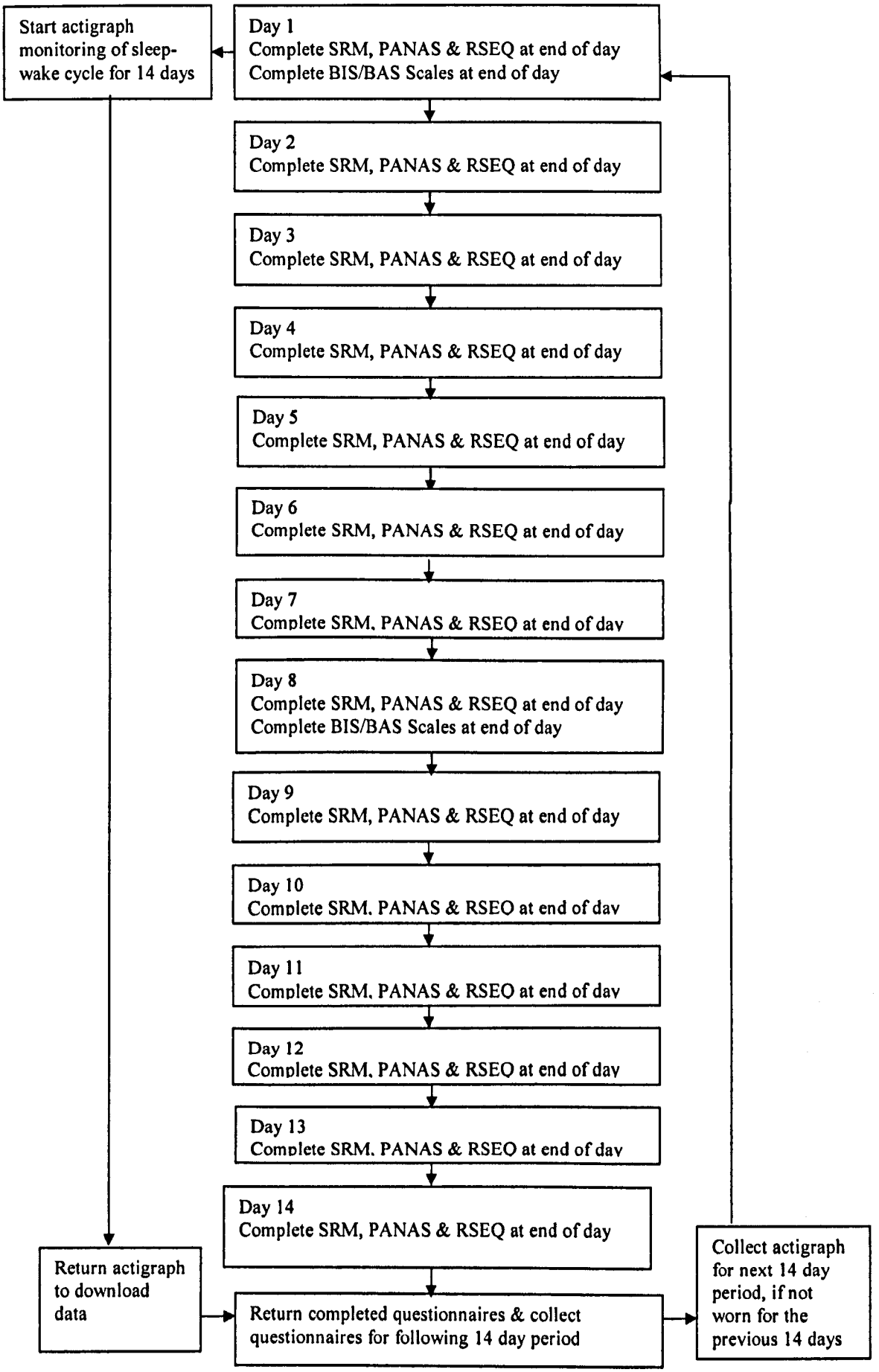
3.3 Procedure

Prior to recruitment, a list of individuals with bipolar disorder identified as suitable for inclusion was sent to the treating consultant psychiatrist. An information sheet describing the research project was provided (Appendix B). Only individuals with written consent

from their consultant psychiatrist were approached regarding the project. Individuals were initially provided with a patient information sheet, which outlined the purpose of the study and described what participating would involve. Individuals who agreed to participate were asked to sign a consent form and received a copy of this for their own records (Appendix B). The information sheet and consent form both explicitly stated that individuals were free to withdraw from the research at any point and that there were no direct benefits to individuals in participating in the project. General population participants were recruited following recruitment of the bipolar disorder participants (Section 4.1.3 provides additional information on the recruitment of individuals from the general population). Individuals, if interested, were provided with feedback regarding the questionnaires and actigraphic assessments they completed.

Figure 3.1 provides a flowchart for the completion of questionnaires and actigraph monitoring over a two week period. Individuals completed the first day of self-report questionnaires with the research assistant (Alison Jackson) present. The procedure for completing questionnaires and how to use the actigraph- measuring device were explained in detail. Individuals then completed three daily questionnaires to measure behaviour, self esteem and affect at the same time at the end of each day. A self-report measure of behavioural activation and inhibition was completed once a week. Completion of measures at the same time each evening was an attempt to control for the effect of diurnal variation in bipolar disorder participants. The time of day has been reported to impact on how mood ratings are completed in a bipolar disorder sample; mood ratings in the evening were higher than morning ratings (Feldman-Naim et al, 1997). If individuals failed to complete a daily rating, they were asked to complete it immediately on rising the following morning. If more than one day had elapsed, the questionnaires for the missed day were not used. Completed questionnaires were collected from the participants every two weeks.

Figure 3.1: Flowchart of questionnaire completion and actigraph monitoring



Individuals were requested to continuously wear an actiwatch (an actigraphy-measuring device worn on the wrist) to monitor sleep and activity patterns. Although the general population participants were monitored with actigraphy for their entire participation period (two to four week periods), this was not possible for the bipolar disorder participants due to the limited availability of actiwatch models during the time period of the study. Data collection occurred over 11 months, from 19th September 2001 to 19th August 2002. The monitoring period for bipolar disorder participants ranged from two to 24 weeks. Since variability in the rest-activity rhythm in addition to mean levels of sleep-wake variables was of interest, it was decided to monitor bipolar participants on alternative two week periods to coincide with the collection of completed questionnaires. This method was expected to provide more information on rest-activity variability across time rather than measuring the rest-activity cycle on one occasion only. Furthermore, the generation of circadian rhythm variables from actiwatch data required a minimum consecutive seven day period (Section 3.4.1.1 provides more information on circadian rhythm variables). Actiwatch data were downloaded at regular intervals and the actiwatch reset.

3.4 Measures

Biological, behaviour, cognition and affect changes are characteristic of bipolar episodes. However, subsyndromal symptoms also occur in a large proportion of individuals with bipolar disorders during inter-episode periods (Keller et al, 1992; Gitlin et al, 1995; Judd et al, 2002). Biological, behaviour, cognition and affect regulation may differ between individuals with bipolar disorder and the general population, with bipolar disorder characterised by dysregulation and greater variability over time (Depue & Iacono, 1989; Johnson et al, 2000c). The presence of subsyndromal symptoms may therefore indicate ongoing dysregulation. Furthermore, previous investigations with general population samples have reported associations between depressive symptoms and self esteem variability

(e.g. Kernis et al, 1998) and affect variability (McConville & Cooper, 1996). This evidence suggested the importance of investigating the role that variability may play in the clinical course of mood disorders. Measures were selected for the current study that could potentially go on to be used to monitor an individual's variability in clinical practice if inter-episode day-to-day variability was found to be of clinical importance in bipolar disorder.

Measures were selected to investigate biological, behaviour, self esteem and affect variation across time. Diathesis-stress models of bipolar disorder have theoretically postulated underlying biological vulnerabilities: dysregulations in circadian rhythms (Healy & Williams, 1988, 1989) and behavioural activation (Depue et al, 1987; Gray, 1990). Accordingly, circadian rhythms and behavioural activation measures were used to assess whether this postulated diathesis dysregulation in bipolar disorder exists during inter-episode periods. The circadian rhythm of the sleep-wake cycle and self-report behavioural activation and inhibition levels were monitored.

Daily variability in behaviour, cognition and affect were monitored to investigate the extent of inter-episode fluctuation. Measures of sleep and social rhythms were used to assess variability in behaviour. Diathesis-stress models have also theoretically postulated self-rated cognition as an important factor in the onset of symptoms in mood disorders (Healy & Williams, 1988, 1989). Furthermore, cognitive theories of depression have proposed a negative view of self as a distinctive characteristic of depression (e.g. Beck, 1987). Since bipolar episodes are characterised by self esteem fluctuations, self esteem was therefore selected as the most pertinent cognitive measure of how individuals with bipolar disorder view themselves. Affect variability in both positive and negative affect as well as ratings of elation and depression were measured. Although the measures selected have been widely used for daily monitoring in general population samples, less evidence exists for use in

bipolar disorder samples. This may reflect the limited interest to date in considering inter-episode periods relative to acute bipolar episodes. Research interest for general population day-to-day variability, particularly for self esteem and affect, has rapidly increased in recent years. Interest in variability in bipolar disorder across inter-episode periods has also burgeoned recently. The present study aimed to contribute to increased understanding of daily variability by applying established measures in a bipolar disorder sample across inter-episode periods where day-to-day variability was hypothesised to exceed that reported by a sample drawn from the general population.

3.4.1 Measures of the sleep-wake cycle

The present study monitored the sleep-wake cycle as an objective evaluation of circadian rhythms. Other circadian rhythm measures, such as temperature and melatonin levels, were considered impractical for daily monitoring in an individual's normal environment. Furthermore, sleep disturbance has been indicated as an early symptom of bipolar relapse (Jackson et al, 2003), suggesting that disturbances in the sleep-wake cycle may be evident during inter-episode periods. Methods for the objective estimation of the sleep-wake cycle include polysomnography (PSG) and actigraphy. The PSG method utilises electrodes to record cortical activity as an estimate of sleep and wake. Monitoring typically occurs within the laboratory although home PSG recording also occurs. Although PSG is regarded as the gold standard for evaluating sleep, limitations include its relative expense, cumbersome and physically intrusive procedure and impracticality for longitudinal monitoring, particularly for monitoring an individual's wake period throughout the day (Blood et al, 1997; Lockley et al, 1999). Thus, whilst PSG may be ideal for measuring sleep over a few days, PSG was not considered suitable for the present study which aimed to measure both sleep and wake over a longer time period.

Actigraphy is a method that allows continuous, relatively unobtrusive estimation of the sleep-wake cycle in the environment of an individual's daily life and may be a particularly useful method for the longitudinal monitoring of circadian rhythms (Royant-Parola et al, 1986; Sadeh et al, 1995; Kushida et al, 2001). An actigraph comprises a sensitive accelerometer microprocessor unit that is worn on the wrist. Physical motion is translated to numeric representation through an acceleration sensor; the intensity, amount and duration of movement is integrated and recorded (Sadeh et al, 1995). An actigraph identifies sleep periods from the level of physical activity detected (Lockley et al, 1999) and can also differentiate between sedentary and physical activities (Patterson et al, 1993). Actigraphy was selected to provide an objective estimation of sleep. Sleep-wake cycle monitoring also provided data on circadian rhythms.

The sleep-wake cycle may also be measured by an individual's subjective estimation. Although actigraphy has high sensitivity in comparison to self-reports (Teicher, 1995), actigraphy has been indicated to report a longer sleep period and greater sleep disturbance compared to subjective sleep measurement (Lockley et al, 1999). Actigraphy and subjective measurement agree when determining sleep rhythms and changes in sleep patterns (Lockley et al, 1999). The Social Rhythm Metric provided subjective estimation of time in bed; participants recorded the time they went to bed and the time they got out of bed (Section 3.4.3.1).

3.4.1.1 Actigraphy (Appendix C)

The present study used continuous actigraph monitoring of motor activity and sleep over a 14 day period for each individual. The American Sleep Disorders Association (1995) recommended actigraphy should be conducted over a minimum three day period. Application of a longer 14 day period provided circadian rhythm data and was also

consistent with the collection of questionnaires. Each participant wore an actiwatch on their non-dominant wrist for 14 consecutive days and nights. The non-dominant wrist was used as significantly higher mean activity levels from the dominant wrist during both sleep and wakefulness have been reported (Sadeh et al, 1994). The "Actiwatch-score" and "Actiwatch-plus" models were used (developed by Cambridge Neurotechnology Ltd.). The "Actiwatch-score" model is displayed in Figure 3.2. The recommended one minute epoch length was used for accuracy, which is a practice standard for actigraph monitoring (American Sleep Disorders Association, 1995; Cambridge Neurotechnology Ltd, 2000). The epoch comprised the activity counts for each one minute time period. Raw actigraphic data were downloaded using the Actiwatch Sleep Analysis software programme. The actiwatch, with raw data collected, was placed face down on a reader, and data were downloaded to the computer.

Figure 3.2: Actiwatch-score model

Bed-time and Get up time were manually inputted according to the daily time recorded on the Social Rhythm Metric (Section 3.4.3.1). Diary estimates of bed-time and wake-time have been reported as reliable compared to actigraph based times (Monk et al, 1994). If

the Bed-time or Get up time were not recorded on the Social Rhythm Metric, visual inspection of the actigraph data provided an estimated time. A similar method to estimate time in bed was employed by Mendlowicz et al (1999). In addition to recording bed-time and get up times on the Social Rhythm Metric, participants used this questionnaire to record the occasions when the actiwatch was removed (e.g. to have a bath). The actiwatch software sleep-wake scoring algorithm computed each epoch as 'sleep' or 'wake.' The time at which sleep started each night and the time when sleep ended each morning were also automatically calculated with the sleep-wake scoring algorithm. Sleep was estimated to start when a minimum ten minute period, with one or less minutes of movement following bedtime occurred. The 'Sleep Start' variable was calculated as the time when this period began. For example, if an individual went to bed at 11pm and the first ten minute period meeting the criteria occurred between 11:40 to 11:50pm, Sleep Start was calculated as 11:40pm. Sleep was estimated to end when a ten minute consecutive period of activity, preceding the recorded 'Get up time' occurred. The 'Sleep End' variable was calculated as the time when this period began. For example, if an individual got out of bed at 8:30am and a ten minute period of activity occurred between 8:20 to 8:30am, Sleep End was calculated as 8:20am. Finally, the recommended medium default sensitivity was used. The sensitivity setting refers to the use of activity scores by the sleep-wake scoring algorithm to estimate sleep and wake.

The Actiwatch sleep analysis software (Cambridge Neurotechnology Ltd.) calculates a large number of variables. An example of the sleep variables calculated by the actiwatch software is provided in Appendix C. Time in bed was calculated from the Social Rhythm Metric daily getting up and going to bed times whilst the remaining sleep variables were calculated for each night of actiwatch monitoring. The sleep variables of interest to the present study were those identified in the literature as being disrupted in acute bipolar

episodes. Decreased sleep duration, decreased sleep efficiency and increased night waking time have been associated with both mania and depression (Hudson et al, 1992; Leibenluft et al, 1996; Serretti & Olgiati, 2005). Subsyndromal sleep disruption may also exist during inter-episode periods. A previous study by Millar et al (2004) reported the sleep of individuals with bipolar disorder during inter-episode periods differed from the sleep of individuals from the general population across measures of sleep duration, latency, efficiency and night waking time. Published means and standard deviations for sleep variables are available in Table 3.1.

The sleep variables investigated in the present study were:

- Time in bed: the difference between self-report bed-time and get up times.
- Sleep duration: the total amount of sleep between sleep start and sleep end, minus night waking time.
- Night waking time: the amount of time spent awake between the recorded bed-time and get up time.
- Sleep efficiency: the percentage of time spent asleep whilst in bed. Sleep efficiency at 85% or less marks the criterion for disrupted sleep (Wicklow & Espie, 2000).
- Sleep latency: the amount of time elapsed before sleep onset following bed-time.
- Movement and Fragmentation index: the percentage of time spent moving during the estimated sleep period (sleep start to sleep end) plus the percentage of immobility phases of one minute, as a proportion of the number of immobile phases with no activity recorded. Higher scores on the movement and fragmentation index indicate more restlessness or sleep disruption.

Table 3.1: Actigraph published means and standard deviations for sleep variables

Values are means (standard deviations), in minutes unless stated otherwise

Study	Time in bed	Sleep latency	Sleep duration	Night waking	Sleep efficiency (%)
Mendlowicz et al (1999) N=32 general population	516 (84)	24 (11)	470 (72)	26 (16)	-
Kushida et al (2001) N=100 sleep disorders	-	-	414 (60)	-	86 (7)
Millar et al (2004) N=19 bipolar I disorder, euthymic	-	20 (22)	434 (92)	59 (26)	83 (9)
N=19 general population	-	8 (7)	388 (53)	49 (18)	87 (4)

In addition, weekly variables were calculated to provide the circadian rhythm of the rest-activity cycle. Circadian rhythm disruption has been posited to underlie the precipitation of bipolar relapse (Ehlers et al, 1988; Healy & Williams, 1988, 1989). Circadian rhythm disruption during mania and depression has been prospectively observed (Wehr et al, 1980). Subsyndromal disruption of circadian rhythms may also exist during inter-episode periods; melatonin secretion disruption has been observed in individuals with euthymic bipolar disorder (N=29 euthymic bipolar disorder; Nurnberger et al, 2000). Circadian rhythm disruption has been indicated to occur over several variables, measured by actigraphy, in Alzheimer's disease (Witting et al, 1990; Van Someren et al, 1999) and in seasonal affective disorder (Teicher et al, 1997; Winkler et al, 2005). For instance, disruption in the rest-activity rhythm may be indicated by elevated activity levels during the night. An example of the variables calculated with the non-parametric circadian rhythm analysis is provided in

Appendix C. The variables investigated in the present study for the presence of rest-activity disruption in bipolar disorders were:

- Interdaily stability (IS): indicates the strength or regularity of the rest-activity rhythm to environmental zeitgebers across time (Van Someren et al, 1999). Interdaily stability was calculated as "the ratio between the variance of the average 24-hour pattern around the mean and the overall variance" (Van Someren et al, 1996, 1997). Interdaily stability measures the consistency of rest and activity between days. Higher day-to-day variability of activity is associated with decreased IS (Witting et al, 1990).
- Intradaily variability (IV): indicates the fragmentation of the rest-activity rhythm. Intradaily variability was calculated as "the ratio of the mean squares of the difference between consecutive hours (first derivative) and the mean squares around the grand mean (overall variance)" (Van Someren et al, 1996, 1997, 1999). Intradaily variability measures the consistency of waves of rest and activity across the day. Daytime naps or night-time restlessness may increase IV (Witting et al, 1990).
- Night time activity level (L5): calculated as "the mean of the five hour period with the lowest activity level in the average 24-hour pattern" (Van Someren et al, 1996). Higher scores represent more night time restlessness.
- Onset time of night time activity level (L5 onset): the start time of the five hour period with the lowest activity level.
- Day time activity level (M10): calculated as "the mean of the ten hour period with the highest activity level in the average day" (Van Someren et al, 1996). Higher scores represent a more active lifestyle.
- Onset time of day time activity level (M10 onset): the start time of the ten hour period with the highest activity level.
- Relative amplitude (RA): calculated as (M10-L5) / (M10 + L5) (Van Someren et al, 1997, 1999). Relative amplitude represents the wave between day time and night time

activities. Higher scores indicate greater amplitude in the rest-activity rhythm (Witting et al, 1990).

Disturbance in the rest-activity rhythm may be suggested by interdaily stability, intradaily variability, night time activity level, and relative amplitude variables. Lower interdaily stability, lower relative amplitude, higher intradaily variability and higher night time activity levels may suggest rest-activity rhythm disturbance. In contrast, day time activity level shows the extent of day time activity with higher levels indicating a more active lifestyle. Day time activity level does not provide an indication of rhythm disturbance, since high day time activity levels could equally be due to actions such as pacing in individuals with Alzheimer's disease (Van Someren et al, 1996) or having an active occupation where individuals are constantly walking (e.g. bar staff). The onset times of day time and night time activity levels were calculated to observe whether a rhythm disturbance was due to a phase delay/advance where rest and activity occur later/earlier in individuals with bipolar disorder.

3.4.1.2 Reliability and validity of actigraphy

Actigraphy has been established as a reliable and valid method of assessing the rest-activity cycle. High agreement rates (88 to 93%) between actigraph measurements and PSG recordings of sleep-wake activity are evident (Cole et al, 1992; Sadeh et al, 1994, 1995; Kushida et al, 2001). However, poor actigraph prediction of PSG-determined sleep-wake has been reported (Pollak et al, 2001). One limitation of actigraphy is overestimation of sleep in individuals who lie in bed quietly when awake; similarly sleep may be underestimated in individuals who are very restless when asleep (Cole et al, 1992; American Sleep Disorders Association, 1995; Sadeh et al, 1995; Blood et al, 1997; Verbeek et al, 2001). Environmental factors may determine levels of sleep and motor activity (Sadeh et

al, 1995). Environmental factors which may disrupt sleep include: noise; temperature; sleep restriction; sleep setting; and psychological factors (e.g. anxiety). Factors such as externally induced movement (e.g. travelling in a train) and artefacts such as placing the wrist on the chest while sleeping can make sleep indistinguishable from wake with actigraph recording (Patterson et al, 1993; Sadeh et al, 1994). However, the factors involved in actiwatch over- or underestimation of sleep may be relatively consistent for a given individual (Verbeek et al, 2001). Although the limitations outlined may reduce reliability and validity in some instances, actigraphy remains a useful assessment tool that is widely used to measure rest-activity cycles in both general population and clinical samples.

Actigraphy has been successfully utilised with a wide range of clinical disorders in which circadian rhythm disturbances are apparent, such as sleep disorders, Alzheimer's disease, seasonal affective disorder and bipolar disorder (Teicher et al, 1997; Van Someren et al, 1999; Kushida et al, 2001; Millar et al, 2004). Actigraphy was selected as the more useful objective estimation of sleep and circadian rhythms for the current study. Actigraphy could be equally useful in both research and clinical settings, although the relative expense of an actiwatch and the necessary software may limit its applicability to clinical practice.

3.4.2 Measures of behavioural activation

Behavioural activation dysregulation has been posited to occur in bipolar disorder (Depue et al, 1987). Behavioural activation dysregulation may be associated with variability in affect, but may also influence behaviour and self esteem. Biological measures (e.g. cortical activity; Harmon-Jones & Allen, 1997) and self-report measures have both been used to assess behavioural activation levels. Biological measurement of behavioural activation was considered impractical for monitoring individuals' in their normal environment from week to week. Accordingly, the current study monitored behavioural activation with a self-report

measure of this neurologically based emotion system. There are several self-report measures which have been designed to measure behavioural activation and inhibition (see Corr, 2001 for a discussion of measures). Consensus as to which scale is the optimal BIS/BAS measure is not evident (Corr, 2001). Indeed, some measures only consider one system (e.g. BIS scale; MacAndrew & Steele, 1991). It was important for the current study to measure both behavioural activation and inhibition, particularly since recent postulation suggests facilitatory and antagonistic effects between the systems (Pickering et al, 1999). The current research selected Carver and White's (1994) BIS/BAS Scales for its brevity and ease of completion. Recent bipolar disorder studies have used the BIS/BAS Scales (Meyer et al, 1999, 2001). Furthermore, previous general population research (e.g. Gable et al, 2000) had used the BIS/BAS Scales with the affect measure selected for the current study (PANAS; Watson et al, 1988b). These similarities in selection of measures may assist between study comparisons of findings. Therefore, the BIS/BAS Scales were selected as the most useful measure of behavioural activation and inhibition in the current study.

3.4.2.1 Behavioural Inhibition System and Behavioural Activation Systems (BIS/BAS) Scales (Carver & White, 1994) (Appendix D)

The BIS/BAS Scales assess an individual's dispositional sensitivities for the two motivational systems of behavioural activation and behavioural inhibition. The BIS/BAS Scales comprises 20 items developed with a college sample (N=732), consisting of one behavioural inhibition system (BIS) subscale and three behavioural activation system (BAS) subscales. The seven item BIS subscale measures reactions to the anticipation of punishment (e.g. "I worry about making mistakes"), with a score range seven to 28. The three BAS subscales are Reward Responsiveness, Drive and Fun Seeking. The five item BAS Reward Responsiveness subscale measures positive responses to the occurrence or

anticipation of reward (e.g. "When I get something I want, I feel excited and energised"); score range five to 20. The four item BAS Drive subscale measures the persistent pursuit of desired goals (e.g. "I go out of my way to get things I want"); score range four to 16. The four item BAS Fun Seeking subscale measures the desire for new rewards and the willingness/impulsiveness to approach potentially rewarding events (e.g. "I'm always willing to try something new if I think it will be fun"); score range four to 16. Items were scored on a four point Likert scale with no neutral response: 4 = strong agreement; 3 = agreement; 2 = disagreement; and 1 = strong disagreement. The score for two items phrased positively for the BIS subscale were reversed (items 5 and 7). Higher scores indicate higher BIS or BAS sensitivity. Reported means and standard deviations for the BIS/BAS subscales are available for undergraduate, community and bipolar disorder samples (Table 3.2).

Table 3.2: BIS/BAS published means and standard deviations

Values are means (standard deviations)

Study	BIS	BAS Reward Responsiveness	BAS Drive	BAS Fun Seeking
Carver & White (1994) N=732 undergraduates	20.0 (3.8)	17.6 (2.1)	12.1 (2.4)	12.4 (2.3)
Harmon-Jones & Allen (1997) N=37 undergraduates	22.1 (2.9)	17.9 (2.0)	12.2 (2.3)	12.8 (2.2)
Meyer et al (1999) N=294 undergraduates, no mood disorder risk	20.6 (3.8)	17.6 (2.1)	11.6 (2.6)	12.2 (2.4)
N=63 undergraduates, at risk for mood disorder	20.6 (4.6)	16.7 (3.2)	11.2 (3.2)	12.2 (2.9)

Study	BIS	BAS Reward Responsiveness	BAS Drive	BAS Fun Seeking
Meyer et al (2001)				
N=59 Bipolar Disorder	23.0 (3.8)	16.9 (2.4)	11.8 (2.6)	11.6 (2.8)
Kasch et al (2002)				
N=41 depression	24.0 (3.3)	14.9 (3.5)	9.2 (2.5)	10.7 (2.4)
N=21 general population	20.0 (3.8)	17.7 (2.3)	11.9 (2.9)	12.6 (2.0)
Beevers & Meyer (2002)				
N=171 undergraduates	20.7 (3.8)	17.3 (2.4)	11.4 (2.5)	12.1 (2.5)

3.4.2.2 Reliability and validity of the BIS/BAS Scales

The BIS/BAS Scales have been indicated to be a reliable and valid measure of behavioural activation and inhibition. Administration of the BIS/BAS Scales with a positive and negative affect questionnaire (PANAS, Watson et al, 1988a; Section 3.4.5.1) has demonstrated convergent and discriminant validity (N=498 undergraduates; Study 2, Carver & White, 1994). Negative affect was related to the BIS scale, but not to any of the BAS subscales. Positive affect was related to the three BAS subscales, but not to the BIS scale. Convergent and discriminant validity of the BIS/BAS Scales have also been demonstrated in further exploratory factor analysis studies (Heubeck et al, 1998; Jorm et al, 1999), and a confirmatory factor analysis study across three countries (Leone et al, 2001). Laboratory experiments by Carver and White (1994) have demonstrated BIS and BAS sensitivity. Higher BIS sensitivity was associated with higher levels of nervousness when punishment cues were introduced (Study 3, N=69 undergraduates). Higher BAS sensitivity (reward responsiveness and drive) was associated with higher levels of happiness when reward cues were introduced (Study 4, N=90 undergraduates). Significant positive correlations (r = 0.30 to 0.44) between the BAS subscales have been consistently reported (Carver & White,

1994; Heubeck et al, 1998; Leone et al, 2001; Ross et al, 2002). Some research studies, however, have also indicated significant positive correlations (r = 0.28 to 0.34) between the BIS and BAS Reward Responsiveness subscale (Heubeck et al, 1998; Leone et al, 2001; Ross et al, 2002).

Four-factor structure (one BIS scale and three BAS subscales) has been demonstrated in a large community sample (N=2725, Jorm et al, 1999) and further student samples (N=336, Heubeck et al, 1998; N=679, Leone et al, 2001; N=476, Ross et al, 2002). Two-factor structure (one BIS scale; one BAS scale) has been supported by research utilising principal component analysis (Jorm et al, 1999) but not by studies utilising confirmatory factor analysis (Heubeck et al, 1998; Leone et al, 2001). Furthermore, structural equation modelling has indicated the BAS subscales are independent and should be considered as separate constructs (Ross et al, 2002). Analyses of the three BAS subscales (but no BAS total score analysis) were conducted in the present study in light of these findings. Adequate reliability has been demonstrated for the BIS/BAS Scales. The BIS scale has reported alpha reliabilities of 0.73 to 0.85. The BAS Reward Responsiveness, Drive and Fun Seeking subscales have reported alpha reliabilities ranging from 0.65 to 0.84 (Carver & White, 1994; Heubeck et al, 1998; Jorm et al, 1999; Meyer et al, 1999, 2001; Beevers & Meyer, 2002; Ross et al, 2002).

3.4.3 Measures of social rhythms

Circadian rhythms comprise 24 hour daily cycles in human physiology and behaviour (Czeisler & Dijk, 2001). Social rhythms are daily behaviours that maintain the timing of circadian rhythms (Monk et al, 1991). Social rhythms, such as mealtimes, can be self-reported. The Social Rhythm Metric (SRM) was selected as a self report measure of social rhythms. The SRM was developed by Monk et al (1990) and has been used in several

studies by the same research group. Although a literature search did not identify any alternative self report measures of social rhythms, the SRM was selected as a useful measure of daily activities in bipolar disorder. In particular, an interpersonal and social rhythm therapy trial (e.g. Frank et al, 1994, 1999) has shown the clinical usefulness of SRM monitoring of social rhythms in bipolar disorder.

3.4.3.1 Social Rhythm Metric (SRM) (Monk et al, 1990, 1991) (Appendix E)

The SRM measures the regularity of an individual's social rhythms by recording the timing of daily events. The SRM consists of 17 daily activities of which 15 are specified (get out of bed; first contact with another person; have morning beverage; have breakfast; go outside for the first time; start work, school, housework, volunteer activities, child or family care; have lunch; take an afternoon nap; have dinner; physical exercise; have an evening snack/drink; watch evening TV news program; watch another TV program; return home for last time; and go to bed). Two activities are idiosyncratic (Activity A, Activity B) to that individual so that they can select activities which they engage in on most days of the week. Typical examples included walking a dog, reading, and having a bath. The SRM requires the individual to record the time at which an activity occurs and the number of people present.

The SRM yields several variables calculated with an outlier elimination algorithm provided by Monk et al (1991) (Appendix E: Algorithm for calculating scores on the Social Rhythm Metric). Data for each week were analysed to give a weekly score of social rhythms. The algorithm calculated a habitual time for each activity for each week. In the example provided (Appendix E), the habitual 'Get out of bed' time calculated from non-outlier data (i.e. excluding the 5:30am early start) was 8:07am. An activity regularity score counted the number of 'hit' times for an activity, which occurred within 45 minutes of the habitual time.

The activity regularity score is from zero (least regular) to seven (most regular). The regularity score for the 'Get out of bed' example was five. Two times (9:30am and 5:30am) were excluded since they occurred more than 45 minutes outwith the habitual 'Get up time' for that week. Habitual times and regularity scores are not calculated for activities with less than three occurrences in a given week. The SRM regularity score provides an indicator of the level of regularity in the timing of all activities over the week. The SRM regularity score is calculated by totalling all the activity regularity scores and then dividing by the number of activities that occurred at least three times over the week. The SRM regularity score range is from zero to seven, with higher scores indicating higher regularity of social rhythms.

In addition to measuring the regularity of activities, the SRM provides a measure of the number of activities that occur. An Activity Level Index (ALI) was calculated by totalling all activities that occur over the week. The ALI maximum score is 119 (17 activities multiplied by seven days). Similar to Ashman et al (1999), a Daily Activity Level Index (DALI) was calculated, which provided a total number of activities completed on a given day, with a DALI maximum score of 17. Table 3.3 provides ALI and SRM regularity scores for general population and mood disorder samples.

The SRM measures the volume and extent of social interaction. A pilot of the monitoring package indicated participants found describing the extent of social interaction to be difficult and onerous (interaction categories were: people just present; people actively involved; other people very stimulating). The SRM was modified to only record the number of people present during each activity. Dividing the total number of activities done alone by the total number of all activities performed for that week provided a solitude ratio. The solitude ratio has a score range from zero to one, with scores closer to one indicating

higher levels of solitude. Although collected for the present study, social interaction findings will not be reported.

Table 3.3: SRM published means and standard deviations

Values are means (standard deviations) * Based on previous samples

Study	Regularity score	Activity level index
Monk et al (1990)		
N=50 general population	3.55 (0.93)	-
Monk et al (1991)		
N=15 general population	3.40 (0.81)	82.60 (6.50)
N=20 unipolar depression	3.45 (0.48)	80.20 (6.35)
Szuba et al (1992)		
N=19 general population	3.9 (0.49)	-
N=19 unipolar or bipolar depression	3.5 (0.49)	-
Monk et al (1994)		
N=96 general population	3.43 (0.82)	83.1 (8.4)
Ashman et al (1999)		
N=9 general population	3.84 (0.85)	94.00 (8.19)
N=9 rapid cycling disorder	2.67 (0.54)	80.18 (7.57)
Monk et al (2002)		
N=293 general population*	3.90 (0.83)	-

3.4.3.2 Reliability and validity of the SRM

The SRM was developed with a general population sample with good test-retest reliability across two week ($r=0.44$, $N=49$, $p<0.001$; Monk et al, 1990) and mean 22 month ($r=0.479$, $N=39$, $p<0.002$; Study 2, Monk et al, 1994) follow up periods. The validity of

retrospective SRM completion at the end of each day, compared to concurrent completion, has been established (Monk et al, 1990). Fifty per cent of Monk et al's (1990) sample completed the SRM retrospectively at the end of each day, whilst the other 25 participants completed the SRM concurrently, when an activity occurred. No significant differences between SRM regularity scores for retrospective and concurrent completion were observed over a two week period (retrospective SRM mean 3.42, standard deviation 0.98; concurrent SRM mean 3.60, standard deviation 0.83, $t<1$). Validity has also been supported by similar SRM-based and actigraph-based bed-time and get out of bed time estimates (Monk et al, 1994). The feasibility of daily SRM monitoring has been indicated in individuals with mood disorders as well as individuals from the general population (Monk et al, 1991; Szuba et al, 1992; Brown et al, 1996; Ashman et al, 1999). In particular, the SRM has been successfully used as a self-report measure of the social rhythms of individuals with bipolar disorder over long monitoring periods (N=9 rapid cycling bipolar disorder monitored for a mean 95 days; Ashman et al, 1999). Thus, the SRM has been indicated to be a reliable and valid prospective measure of daily social rhythms in both general population and mood disorder samples.

3.4.4 Measures of self esteem

The DSM-IV diagnostic criteria for depressive and manic/hypomanic episodes include changes in self esteem. Feelings of worthlessness may be present in depression whilst inflated self esteem may be evident in mania (DSM-IV diagnostic criteria for depression and mania are available in Tables 1.1 & 1.2). Therefore, if self esteem is recognised to fluctuate between episodes of depression and mania, it is possible that subsyndromal variation in self esteem may also be evident during inter-episode periods. Furthermore, cognitive theories of depression postulate a negative view of the self is a distinctive characteristic of affective disorder (Beck, 1987). In order to examine this research question, the Rosenberg Self

Esteem Questionnaire (RSEQ) was selected as the self esteem (SE) measure. Although there are a variety of self report SE measures, the RSEQ is the most widely used measure. In particular, the RSEQ has been used previously for the prospective measurement of daily SE variability (e.g. Kernis et al, 1991; Roberts & Gotlib, 1997). Use of the same measure enables across-study comparison without potential measurement confounding factors. Strengths of the RSEQ include its brevity and scaled response format for ease of completion. Previous studies with clinical samples have also indicated that individuals with bipolar disorder are willing to complete the RSEQ (e.g. Serretti et al, 2005).

3.4.4.1 Rosenberg Self Esteem Questionnaire (RSEQ) (Rosenberg, 1965) (Appendix F) The RSEQ is a ten item self report questionnaire, with five positively worded (e.g. On the whole I am satisfied with myself) and five negatively worded (e.g. At times, I think I am no good at all) items to measure positive and negative self esteem. The total score for both subscales provides a measure of global self esteem. Positively and negatively worded items were listed alternatively to reduce the effect of respondent set (Rosenberg, 1965). The RSEQ Likert scale has ranged from four to ten points in previous research. A four point Likert scale RSEQ has tended to be used in cross-sectional studies where SE level is the variable of interest. Studies investigating SE variability have used seven or ten point Likert scales for the RSEQ (e.g. Kernis et al, 1991; Roberts & Gotlib, 1997). The current study selected a seven point Likert scale for the RSEQ (1 = strongly agree; 2 = agree; 3 = agree slightly; 4 = neutral; 5 = disagree slightly; 6 = disagree; 7 = strongly disagree). Participants rated each item for the 'present moment.' The scores for positively phrased items were reversed (statements 1, 3, 4, 7, 10). Positive and negative self esteem subtotals were calculated, with a score range from five to 35 for each subscale. A RSEQ total score was calculated by adding the negative self esteem subtotal and the positive self esteem subtotal, with a score range from ten to 70. High scores indicate high self esteem. Means and

standard deviations for a seven point Likert scale RSEQ are available for undergraduate and bipolar disorder samples (Table 3.4).

Table 3.4: RSEQ published means and standard deviations

Values are means (standard deviations)

Study	N	Participants	Self esteem
Roberts et al (1995; Study 3)	95	Undergraduates	52.9 (9.2)
Roberts & Gotlib (1997)	92	Undergraduates	55.6 (9.4)
Johnson et al (2000b)	29	Bipolar I Disorder	44.1 (16.4)

3.4.4.2 Reliability and validity of the RSEQ

The RSEQ has a reported alpha reliability of 0.77 for Rosenberg's (1965) New York sample (Wylie, 1989). Alpha reliabilities for the RSEQ rated on a seven point Likert scale have been reported as 0.82-0.92 (Roberts & Gotlib, 1997) and 0.94 (Johnson et al, 2000b). The RSEQ has been reported to have high convergent validity with psychiatrist's SE ratings for an individual and other self-report SE questionnaires; high discriminant validity has also been demonstrated between SE and SE stability (Rosenberg, 1979). Content overlap across measures of self esteem and depression may exist. Indeed, the RSEQ has been observed to correlate with depressive symptoms (e.g. Kernis et al, 1998), which may suggest that the RSEQ could be considered as a proxy measure of mood. However, the RSEQ has been widely used as a measure of self esteem with bipolar disorder samples across inter-episode and acute episodes (e.g. Serretti et al, 1999, 2005; Shapira et al, 1999; Scott & Pope, 2003; Blairy et al, 2004) and the clinical importance of variability rather than level per se was the main focus of the current investigation. The RSEQ was originally scored using a Guttman scale, where the ten RSEQ items are categorised into six scales. A positive score is given for answers indicating positive self esteem and the score range is

from zero to six (Rosenberg, 1965; Rosenberg's Appendix D provides more information on the RSEQ's Guttman scale scoring). The RSEQ has a reported coefficient of reproducibility of 92% and a coefficient of scalability of 72% using a Guttman scale (N=5024; Rosenberg, 1965). The RSEQ has been scored according to the Likert method with a large general population sample (N=2300; Rosenberg, 1979) and yields similar results compared to the Guttman procedure. The Likert scale RSEQ is more typically administered.

3.4.5 Measures of affect

Bipolar disorder is characterised by episodes of mania and depression, although subsyndromal symptoms in inter-episode periods occurs in approximately 50% of individuals with this disorder (Keller et al, 1992; Gitlin et al, 1995). Jackson et al's (2003) systematic review reported individuals identified mood change as an early symptom of relapse for bipolar depression (median 48%) and mania (median 43%). Day-to-day changes in mood may not necessarily be perceived simply as elation or depression. Therefore, a general measure of affect was also selected. Self-report ratings of elation and depression were used in combination with Watson et al's (1988b) Positive And Negative Affect Schedule (PANAS). Although there were several measures of affect available, the PANAS was selected as the most useful prospective measure of affect. The PANAS is a widely used questionnaire for measuring positive and negative affect and has been used in previous investigations (e.g. Roberts & Gotlib, 1997) to measure daily variability in affect. Thus, levels and variability of the PANAS subscales are available from previous research for study comparison. The PANAS has a scaled response format for ease and speed of completion.

3.4.5.1 Positive And Negative Affect Schedule (PANAS) (Watson et al, 1988b) (Appendix G)

The PANAS measures current mood state. The PANAS comprises two scales, consisting of ten items for each scale which measure positive and negative affect. Positive affect items were: interested; excited; strong; enthusiastic; proud; alert; inspired; determined; attentive; and active. Negative affect items were: distressed; upset; guilty; scared; hostile; irritable; ashamed; nervous; jittery; and afraid. Items were rated on a five point Likert scale to indicate the extent to which the individual 'has felt this way today' to measure affect fluctuations. The scale choices included: 1 = very slightly or not at all; 2 = a little; 3 = moderately; 4 = quite a bit; and 5 = extremely. High scores indicate high levels of affect. The score range is from ten to 50 for the positive and negative affect subscales. The PANAS has been used as a prospective measure of daily affect in general population and subsyndromal mood disorder samples (Table 3.5).

Two additional items were included in the PANAS list to measure current mood state relevant to bipolar disorder: 'elated' and 'depressed.' The score range was from one to five for the elated and depressed affect items. It was deemed appropriate to include these items in the PANAS since other studies have used 'elated' as a measure of positive affect (Larsen & Ketelaar, 1991) and 'depressed' as a measure of negative affect (Van Eck et al, 1998). Elated and depressed items were scored as separate subtotals from the positive and negative affect subscales of the PANAS. Co-efficient alpha values for the positive and negative affect subscales were not affected by this modification of the PANAS. The alpha values observed in the current study for positive and negative affect subscales were 0.93 and 0.96, which were similar to previous research (e.g. Watson et al, 1988b; Roberts & Gamble, 2001). Further, reliability analyses of 11 item subscales (positive affect and elated; negative affect and depressed) observed the same alpha values as for the 10 item analyses.

Therefore, the addition of elated and depressed items did not impact the internal consistency of the PANAS.

3.4.5.2 Reliability and validity of the PANAS

The PANAS was developed with large general population samples, using different time instructions for participants to rate how they felt: present moment (N=660); today (N=657); past few days (N=1002); past few weeks (N=586); past year (N=649); and in general (N=663) (Watson et al, 1988b). The PANAS has been reported to be internally consistent, reliable and valid in the measurement of positive and negative affect (Watson et al, 1988b). Watson et al (1988b) reported low PA-NA inter-correlations (r = -0.12 to -0.23) across different time frames. Test-retest reliability was reported to increase as the time frame lengthened from moment to general time instructions. Reported alpha reliabilities for the PANAS range from 0.89-0.90 for moment/today PA and from 0.80-0.87 for moment/today NA (Watson et al, 1988b; Roberts & Gamble, 2001).

Table 3.5: PANAS published means and standard deviations

Values are means (standard deviations)

Study	Time instructions	Positive affect	Negative affect
Watson et al (1988b) Undergraduate & general population samples			
N=660	Moment	29.7 (7.9)	14.8 (5.4)
N=657	Today	29.1 (8.3)	16.3 (6.4)

Study	Time instructions	Positive affect	Negative affect
Lovejoy & Steuerwald (1995)			
N=19 undergraduates	Today	24.2 (8.2)	14.3 (3.4)
N=16, intermittent depressive disorder		21.7 (4.8)	19.4 (3.6)
N=12, cyclothymia		28.1 (3.1)	19.0 (4.0)
Roberts & Gotlib (1997)			
N=92 undergraduates	Moment	27.5 (7.3)	16.1 (4.9)
Scott-Killgore (2000)			
N=302 undergraduates	Moment	26.6 (8.6)	17.5 (7.2)
Roberts & Gamble (2001)			
N=110 adolescents	Moment	26.8 (9.6)	14.5 (5.1)
Hopko et al (2003)			
N=14 mildly depressed	Today	27.1 (5.5)	18.7 (4.4)
N=23 undergraduates		32.7 (3.7)	15.8 (4.4)

3.4.6 Monitoring package selected for present study

In summary, five measures were selected to monitor variability in bipolar disorders. Actigraphy objectively estimated biological variability of the sleep-wake cycle. Daily variability in social rhythms, self esteem and affect were assessed with self-report questionnaires: Social Rhythm Metric (SRM), Rosenberg Self Esteem Questionnaire (RSEQ), and the Positive And Negative Affect Schedule (PANAS), with additional 'Depressed' and 'Elated' ratings included. The Behavioural Inhibition System and Behavioural Activation Systems (BIS/BAS) Scales were rated once per week and provided a self report measure of behavioural activation. The characteristics of the self-report

questionnaires are outlined below (Table 3.6). An example print-out of actigraph monitoring and copies of the four self-report measures are available in Appendices C to G. High internal consistency for the RSEQ, PANAS and BIS/BAS Scales were demonstrated by the present study.

Table 3.6: Characteristics of self-report questionnaires

Measure	No. of items	Scale	Score range	Co-efficient alpha for present study
SRM	17	Time of		-
Regularity score		day	0-7	-
Activity Level Index (ALI)			0-119	-
Daily Activity Level Index (DALI)			0-17	-
RSEQ	10	7-point	10-70	0.96
Positive RSEQ subscale	5		5-35	
Negative RSEQ subscale	5		5-35	
PANAS	20	5-point		-
PA subscale	10		10-50	0.93
NA subscale	10		10-50	0.96
'Depressed' mood rating	1		1-5	-
'Elated' mood rating	1		1-5	-
BIS/BAS Scales	20	4-point		-
BIS subscale	7		7-28	0.85
BAS subscales:				
Reward Responsiveness	5		5-20	0.88
Drive	4		4-16	0.91
Fun Seeking	4		4-16	0.67

3.5 Statistical Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS version 9.0). Sleep variables were calculated with the actiwatch sleep analysis software (version 3.31), and then entered into SPSS for analysis. An overview of the data was conducted prior to statistical analyses. This overview included checking for any inconsistencies in the data, such as incorrectly entered values, which were corrected prior to analyses. Investigation of the extent of missing data was also conducted to inform the strategy for dealing with missing data. This strategy will be discussed next.

3.5.1 Missing data strategy

A disadvantage of longitudinal data collection is the increased likelihood of missing data. In the present study, missing data occurred from participants not completing all assessment items, removing the actigraphy-measuring device, and from participants dropping out of the study. List-wise deletion was applied to missing values that occurred when a participant did not complete a questionnaire or removed the actigraphy-measuring device over the monitoring period (see Streiner, 2002 for a discussion of missing data strategies). Since the analysis of data which excludes missing data may compromise the validity of results (Streiner, 2002), strategies to replace missing data were considered. For instance, Butler et al (1994) substituted missing data with the mean of the participant's score on the two adjacent days, although no more than two consecutive days of missing data in a series were allowed. However, most missing data for the current study were evident for bipolar disorder participants who were unwilling to complete some of the questionnaires daily. For example, some participants reported daily completion of the self esteem questionnaire was too distressing. It was concluded that replacing missing data in these instances would be misleading, as the main focus of the research was to investigate day-to-day variability. These participants continued to be monitored since at least one questionnaire was being

completed daily. Consequently, numbers varied between analyses as data were excluded list-wise.

Questionnaire totals for the SRM, RSEQ, PANAS and BIS/BAS were calculated by SPSS inputted formula. A questionnaire total was allocated a missing value if any item in the formula was missing (e.g. if PA item 'interested' was missing for a specific day, the PA subtotal for that day would also be entered as a missing value. Questionnaire totals may mislead when questionnaire items are missing, leading to lower scores than would otherwise occur. Similarly, a weekly Activity Level Index (ALI) was recorded as a missing value, if any of the seven daily SRM questionnaires were not completed.

Missing data also occurred when participants removed the actiwatch during the continuous monitoring period. For instance, a participant may have removed the actiwatch to have a bath in the evening, but then failed to replace the device on the wrist until the following morning. Participants recorded occasions when the actiwatch was not worn. In addition, visual inspection of actigraph data identified missing data where no activity was recorded over prolonged time periods. Sleep variables were not calculated for nights when the actiwatch was not worn, with the exception of the time in bed variable which was provided by the SRM. Circadian rhythm variables were calculated from seven day consecutive actigraph monitoring periods. This seven day analysis period was shortened on occasions when the actiwatch had been removed (Section 4.2 provides more information on missing questionnaire and actigraph data in the current study).

3.5.2 Computation of group mean and variability levels

The mean level for each measure was calculated as the mean score for each participant across a 14 day monitoring period. Participants had completed varying monitoring periods

(bipolar disorder participants monitored for median 8 weeks, general population participants monitored for median 2 weeks). One possible limitation of aggregating data over different monitoring periods is that bipolar disorder participants may exhibit greater variability due to a longer monitoring period. Thus the first 14 day period when a participant completed the self-report questionnaires and underwent actigraph monitoring was selected. Groups' means and standard deviations were based on the mean of these individual scores; this method is an accepted way of obtaining group means from participants repeated measures (Bolger et al, 2003). Indeed, aggregation of data measured repeatedly has been indicated to improve temporal reliability and may provide a stable level for a given variable (Epstein, 1984). Similar methods for calculating group means from individual participants' means for the SRM, RSEQ and PANAS have been described in previous research using prospective daily monitoring (e.g. Lovejoy & Steuerwald, 1995; Kernis et al, 1997; Monk et al, 1997; Roberts & Gotlib, 1997). Variability in each measure was computed as within-participant standard deviation scores across a 14 day monitoring period. This method was also consistent with previous research (e.g. Kernis et al, 1997; Roberts & Gotlib, 1997; Gruber et al, 2000). Variability for the group was computed as the mean of these standard deviations.

3.5.3 Skewness and kurtosis of group mean and variability levels

The distribution of mean and variability scores for participants was examined by calculating skewness and kurtosis for each variable. The significance of skewness and kurtosis values was ascertained by calculating z scores. A skewness z score was calculated by dividing the skewness value by the standard error for skewness. Similarly, dividing the kurtosis value by the standard error for kurtosis provided a kurtosis z score. Skewness and kurtosis z scores outwith ± 1.96 indicate with 95% confidence that the distribution is not normal (Kerr

et al, 2002). The findings from examination of the assumptions of a normal distribution for the participant sample are available in Section 4.9.2 and in Appendix I.

3.5.4 Effect size, type I and type II errors and statistical power

Effect size was calculated to indicate the extent of the difference between group mean and variability scores. This provides a useful method of interpreting any statistically significant differences between groups. Cohen's d (Cohen, 1988) was computed for the effect size of each dependent variable between-group comparison. The effect size measured the difference between the two participant group means (bipolar disorder group mean minus general population group mean), divided by the sample standard deviation. A d value of 0.8 or greater is considered a large effect size (Cohen, 1988).

Although the experimental hypothesis that greater variability in biological, behaviour, self esteem and affect measures would be evident in bipolar disorder compared to the general population could either be true or false, there were four possible interpretations of the results. These four interpretations are displayed in Figure 3.3. Two possible errors may occur when interpreting research findings: retaining the experimental hypothesis when it is false (Type I error) or rejecting the experimental hypothesis when it is true (Type II error). Consideration was given to minimise the risk of committing a type I or type II error in interpreting the research findings. Alpha (α) is the probability of a type I error occurring, and can only occur when the null hypothesis, no difference between groups, is true (Norman & Streiner, 2000; King & Minium, 2003). A 5% significance level ($p<0.05$) was selected for the current study, which is the usual level of alpha selected. This alpha level means there was a 5% chance that the present study would conclude that there a significant difference between groups, where no differences actually exist in the population. Beta (β) is the probability of a type II error occurring, and can only occur when the null hypothesis,

no difference between groups, is false (Norman & Streiner, 2000; King & Minium, 2003). Beta is the chance that the present study would conclude there was no difference between groups, when a difference did actually exist in the population. The likelihood that the present study committed a type I or type II error in interpretation of the research findings is discussed in Section 5.6.

Figure 3.3: Four interpretations of a research hypothesis

		Experimental hypothesis	
		Hypothesis is true	**Hypothesis is false**
Research decision	**Retain hypothesis**	**True positive**	**False positive (Type I error)**
	Reject hypothesis	**False negative (Type II error)**	**True negative**

Statistical power is the probability of concluding there was a significant difference between groups when a difference exists in the population (Norman & Streiner, 2000; King & Minium, 2003). Power is calculated by subtracting beta from one (power = 1-β). Therefore, a reduction of beta would increase statistical power and vice versa. The recommended 80% minimum level of statistical power was selected (Cohen, 1988) as the desired level of power. Accordingly, the current study would have had a 20% (β=0.20) chance of concluding there was no difference between groups, when a difference occurs in the population, if 80% statistical power was achieved. A prospective power calculation to determine the required sample size for 80% power and alpha level 0.05 was not conducted as the current study was exploratory in nature. Furthermore, at the start of data collection, little published evidence on the variability of distribution and effect size for selected measures in bipolar disorder samples was available, which limited the ability to make a

realistic estimation of the required group sample size to detect differences between bipolar disorder and general population samples. The actual statistical power obtained for the current study compared to the required power of 80% will be discussed in Section 5.6.

3.5.5 Parametric comparisons between the bipolar disorder and general population groups

Between-group analyses of participant mean scores for the level and variability of each measure were conducted between bipolar disorder and general population groups. The present study had one independent variable (participant group) and multiple dependent variables for biological, behaviour, self esteem and affect measures. Consideration was given to the selection of the appropriate analyses to investigate differences in the mean level and variability of measures between the bipolar disorder and general population groups.

3.5.5.1 Parametric analyses rejected by current study

Two parametric tests were considered before being rejected as inappropriate for the current study: an independent t test and a repeated measures analysis of variance (ANOVA). The t test is a relatively simple parametric analysis of differences between group means. However, since several dependent variables were being investigated, this analysis was considered unsuitable as the risk of a Type I error is increased with multiple t tests (Cohen, 2001; Kerr et al, 2002). Repeated measures analysis of variance was the second type of analysis considered. However, a repeated measure ANOVA has limited applicability to time series that are the same length across participants, which do not include missing data and that hold to the compound symmetry assumption (Gibbons et al, 1993; Collins & Sayer, 2000). It was decided not to replace missing data in the present study (Section 3.5.1 provides more information). Compound symmetry assumes that variances between data points across the time series are homogeneous. Compound symmetry may be more likely

with longitudinal data with large time intervals between measurements. However, it is likely that measures collected one day will be more correlated to measures collected on the next day, than to measures collected several days later. Thus, it was decided repeated measures analysis of variance was not suitable for analysing the data for the present study.

3.5.5.2 Multivariate analysis of variance

The third parametric analysis considered was multivariate analysis of variance (MANOVA). Multivariate analysis of variance can be used when two or more dependent variables are being analysed (Bryman & Cramer, 1997; Norman & Streiner, 2000). Multivariate analysis of variance investigates whether the mean level of several dependent variables differs between groups (Tabachnick & Fidell, 2001). Although MANOVA can also be limited by missing data and varying time series across participants, it is suitable to analyse data when the compound symmetry assumption does not hold. Participant mean and variability levels for each variable were computed, and this removed the problem of missing data. Further, each participant now had a mean and variability score for each variable, which also removed the limitation of varying time series (Section 3.5.7 provides details of the time series analyses conducted for each participant). It was therefore decided for the present study that MANOVA analyses of mean and variability levels for biological, behaviour, self esteem and affect measures would be most appropriate for the between group analyses.

Variables were conceptually grouped with correlations between variables hypothesised to be higher within each grouping. Multivariate analyses of variance to investigate group differences in the level or variability of measures were conducted to control for multiple comparisons. Multivariate analyses of variance (MANOVA) were conducted for the following measures:

- Mean scores of sleep variables (time in bed, sleep duration, night waking time, sleep efficiency, sleep latency, fragmentation index)
- Day-to-day variability of sleep variables (time in bed, sleep duration, night waking time, sleep efficiency, sleep latency, fragmentation index)
- Mean scores of social and circadian rhythm variables (social rhythm regularity, daily activity level index, night time activity level, day time activity level, relative amplitude, interdaily stability, intradaily variability)
- Week-to-week variability of social and circadian rhythm variables (social rhythm regularity, daily activity level index, night time activity level, day time activity level, relative amplitude, interdaily stability, intradaily variability)
- Mean scores of behavioural inhibition and activation (BIS, BAS reward responsiveness, BAS drive, BAS fun seeking)
- Week-to-week variability of behavioural inhibition and activation (BIS, BAS reward responsiveness, BAS drive, BAS fun seeking)
- Mean scores of self esteem and affect variables (self esteem, positive affect, negative affect, elated, depressed)
- Day-to-day variability of self esteem and affect variables (self esteem, positive affect, negative affect, elated, depressed)
- Mean scores and day-to-day variability of positive and negative self esteem subscales

Although participants with bipolar disorder had completed varying lengths of prospective monitoring, both bipolar disorder and general population participants had their mean level and variability of measures calculated from a 14 day monitoring period. If data were aggregated over longer monitoring periods for bipolar disorder participants, it could be argued that greater variability was merely an artefact of the longer time frame. Therefore, comparison of 14 day monitoring periods for bipolar disorder and general population

participants was considered a conservative investigation of group differences in variability. However, it was also possible that a longer prospective monitoring period would be necessary to obtain an accurate estimation of the mean level and variability of measures in bipolar disorder. To illustrate, previous studies have reported seven weeks of monitoring was required to identify social rhythm 'traits' in mood disorder samples although two weeks monitoring was adequate for general population samples. Consequently, MANOVA group comparisons were repeated using the full prospective monitoring period for each participant with bipolar disorder.

3.5.5.3 Homogeneity tests for multivariate analyses

Two tests for homogeneity were conducted with each MANOVA. Firstly, homogeneity of variance was examined with Box's M statistic. This homogeneity test examines the equivalence of the covariance matrices of the dependent variables across the groups. Tabachnick and Fidell's (2001) succinct guidelines for interpretation of Box's M suggest significance tests are robust to any deviations from homogeneity when sample sizes are equal and p associated with M is greater than 0.001. Secondly, Levene's homogeneity tests were conducted. Levene's tests are univariate analyses that examine the error variance of the dependent variables across the groups. If the p value associated with Levene's test is less than 0.05, the homogeneity of variance assumption is not met (Cohen, 2001). An advantage of Levene's test is that it remains robust even when the assumption of a normal distribution is not met (Petrie & Sabin, 2000). If the assumptions of the homogeneity tests are not met, the univariate analyses should be used instead of the multivariate analysis to indicate significance (Norman & Streiner, 2000). Whilst analysis of variance is relatively robust to departures from the normal distribution and to unequal sample sizes, it is not robust to unequal variances (Petrie & Sabin, 2000; Cohen, 2001).

3.5.5.4 Holm method for correction of alpha level

Since univariate analyses involved multiple comparisons between the groups, it may be considered necessary to correct the alpha level. For instance, a multivariate analysis of six variables would produce six univariate comparisons between groups. If alpha was set at $p<0.05$, then six comparisons would increase the possibility of obtaining a significant result to approximately $p<0.30$. Therefore, there may be some risk of committing a Type I error in the current study if significant findings were not interpreted with consideration of the number of comparisons conducted. Thus, it was decided to correct the alpha level for the number of univariate comparisons conducted following each multivariate analysis.

A typical post hoc comparison is the Bonferroni correction, where alpha ($p<0.05$) is divided by the number of comparisons. The Bonferroni correction is a conservative method to correct for multiple comparisons. However, this method was not selected for the present study as the Bonferroni correction may be considered as overly stringent (Norman & Streiner, 2000). Instead, Holm's (1979) modification of the Bonferroni correction was applied to univariate analyses. The Holm method orders the probabilities obtained from smallest to largest; the smallest probability is then compared to alpha 0.05 divided by the number of comparisons. If the probability for that dependent variable is significant, the next smallest probability is compared to alpha 0.05 divided by the number of comparison minus one, and so on (Further description of the Holm method is available in Norman & Streiner, 2000). The Holm method to correct the alpha level was subsequently applied to univariate analyses to indicate which differences between bipolar disorder and general population groups remained when this more conservative alpha criteria was applied.

3.5.6 Non-parametric comparisons between the bipolar disorder and general population groups

Although between group differences were initially investigated with parametric analyses, non-parametric comparisons were also utilised. Since parametric analyses are based on certain underlying assumptions regarding the parameters of the normal distribution, any violation of these assumptions impacts on the robustness of the analyses. The parametric homogeneity of variance assumption has already been outlined in Section 3.5.5.3. The normal distribution assumption was investigated by examination of the skewness and kurtosis for each dependent variable to ascertain whether the sample scores did approximate the normal distribution. A skewness or kurtosis score outwith ±1.96 would indicate with 95% confidence that the distribution was not normal (Kerr et al, 2002). Non-parametric analyses may be more robust and powerful than parametric analyses when normal distribution assumptions are violated (King & Minium, 2003). Skewness and kurtosis scores for the dependent variables are provided in Appendix I. Therefore, when parametric assumptions of normally distributed data and homogeneity of variance were not met, non-parametric analyses were selected as the preferred inferential test. The Mann-Whitney U test was selected as the non-parametric analysis to investigate between group differences in the mean level and variability of measures. Variables were retained in the same conceptual groups that they had been allocated for parametric analyses. Holm's correction was applied to the alpha level to control for multiple comparisons; significance was set at $p<0.05$.

3.5.7 Time series analyses in bipolar disorder

Data collected for the study was suitable for time series analyses since equal temporal spacing of measures had occurred (West & Hepworth, 1991; West et al, 2000). Time series analyses were conducted to investigate daily variability for participants with bipolar

disorder. Aggregation of data masks any order effects that may be present within a time series (Epstein, 1984). Furthermore, variability calculated as within-participant standard deviation scores provides average variability, but not any indication of the frequency of change (Larsen, 1987). Further investigation of the measures found to differ between the general population and bipolar disorder groups were thus subjected to time series analyses.

Time series models provide estimates in either the time domain or frequency domain (Larsen, 1990; Shumway & Stoffer, 2000). The time domain approach models future values on current and past values and tends to be utilised as a forecasting tool (Shumway & Stoffer, 2000). The present study utilised the frequency domain approach since variability was the primary focus. Periodic or systematic variation was investigated. The time series for each measure was collapsed to remove days with missing data as time series analyses are unable to process missing data. Missing values were not replaced for reasons outlined in Section 3.5.1. A similar procedure of collapsing the time series to remove missing values was employed by Woyshville et al (1999). Since Woyshville et al (1999) reported statistically significant differences between participants with no missing data compared to participants with missing data, the impact of collapsing the time series on the findings were also conducted. All participants in the present study displayed missing data for one or more daily measures across the monitoring period. Thus, the participant's time series, collapsed to remove missing values, was compared to the longest time period across which the participant had no missing data for that variable.

The variables subject to time series analyses were measures indicated to differ between the bipolar disorder and general population groups. Each participant's data for the measures were plotted across time, with the time series collapsed to remove any missing values. Firstly, autocorrelation analyses were conducted to assess whether an association existed

across days for each measure. Autocorrelation analyses are outlined in section 3.5.7.1. Secondly, cross-correlation analyses investigated associations across time between the measures. Cross-correlation analyses are outlined in section 3.5.7.2.

3.5.7.1 Autocorrelation analyses

The serial dependency of the data was investigated. A daily measurement may be more similar to the previous day's score than days further removed in time (West et al, 2000). Evidence has suggested stronger associations within measures across time may exist in bipolar disorder, compared to the general population. For instance, slower affect recovery following life stress has been reported in mood disorders (Goplerud & Depue, 1985; Peeters et al, 2003). These associations suggest stronger associations in the ratings of measures may be evident from day-to-day in bipolar disorder. Autocorrelation can detect whether data are serial dependent (Reis & Gable, 2000). For example, a lag one effect indicates dependency between adjacent days, a lag two effect indicates dependency between the data extends across two days. A partial autocorrelation function (PACF) was utilised in the present study. Partial autocorrelation provides a correlation coefficient for a time lag once the effects of smaller time lags have been removed (for instance, the time lag at day two has the effect of day one's time lag removed). If autocorrelation scores are within the 95% confidence limit, data can be regarded as independent. The PACF value is zero at all lags if there is no serial dependency in the time series (West & Hepworth, 1991).

A one day difference transformation was applied to control for autocorrelation; most of the significant autocorrelations were displayed at the one day lag (autocorrelation findings are provided in Section 4.11). Partial autocorrelation analyses were repeated with the one day difference transformed time series to check for significant autocorrelations. It was

necessary to remove the effect of autocorrelation prior to cross-correlation analyses as autocorrelations in the data may otherwise impact on findings.

3.5.7.2 Cross-correlation analyses

Simple correlation between two time series treats data as if it were cross-sectional; findings may be misleading if trends, cycles or serial dependency exist in the data (West & Hepworth, 1991). The relationship between variables was investigated by computing cross-correlation functions. Cross-correlations also need to control for serial dependence, otherwise findings may be erroneous. The autocorrelation analyses conducted identified the extent of serial dependency in each participant's time series for the measures. A one day difference transformation was applied to remove serial dependency. Concurrent cross-correlations were computed for each participant. Cross-correlation findings are outlined in Section 4.11.

Theoretical postulation (e.g. psychobiosocial models of bipolar disorder; Scott, 2001) has suggested variation in biological vulnerability, behaviour and cognition, within an ever changing environment, may lead to variation in affect. If interactions occur from day-to-day between these five systems, then associations across time may be measured to identify any direction of associations. Also, investigation of associations between measures across time could also indicate whether there a delayed or immediate interaction occurs between the systems. For instance, such analyses could suggest whether a decrease in self esteem had an immediate impact on affect levels or impacted over the following days.

3.5.8 Comparisons within the bipolar disorder group

The primary hypothesis of the current study was that greater variability would be observed in bipolar disorder compared to the general population. A second hypothesis was that

variability would also differ across participants with bipolar disorder. Participants with bipolar disorder who displayed greater variability were hypothesised to be more vulnerable to relapse. Inclusion criteria ensured participants were only included in the study if they had experienced a recent episode in the preceding two years. Most individuals with bipolar disorder remain vulnerable to relapse over time. It was not feasible to prospectively monitor participants until each individual had experienced an acute bipolar episode. Participants with bipolar disorder were relatively stable and regularly attended a lithium clinic during the study. However, evidence has reported relapse rates of 65% over two years (Silverstone et al, 1998) and 82% over seven years (Coryell et al, 1995). Thus most bipolar disorder participants were expected to subsequently experience relapse following study participation. A three year follow up was selected as a suitable time period to retrospectively assess each participant's vulnerability to relapse.

Relapse in bipolar disorder can be defined by several outcomes, such as an individual's recall of the first emergence of symptoms, clinician diagnosis, or hospitalisation. Furthermore, outcomes across a follow-up period could occur on numerous occasions. In particular, individuals with rapid cycling disorder by definition will experience several episodes across a year. Accordingly, first admission to hospital following study participation was selected as the follow-up outcome measure. The advantages of using first admission as the outcome measure included it being a dichotomous, well-defined measure, a marker of severity and provided a blind, independent measure of outcome. In April 2005, Forth Valley Primary Care NHS Trust Medical Records provided the date of first admission following study participation for the individuals with bipolar disorder. The follow up period ranged from a minimum 38 months to a maximum of 44 months since participants had been recruited to the study over a six month period.

3.5.8.1 Fisher's exact test

High and low variability group differences in admission to hospital were investigated with non-parametric analysis. Admission was analysed as a categorical variable with two values (admission to hospital; no admission). The hypothesis that greater vulnerability to admission would be observed in participants who displayed high variability was investigated. Contingency tables for admission and variability were produced, with participants divided into low and high variability subgroups for measures found to differ significantly between bipolar disorder and general population groups. A median split of variability scores divided participants into low and high variability groups. When sample size is less than 20 or when a cell in the 2x2 contingency table has an expected value less than five, it is recommended practice to use Fisher's exact test rather than the Chi-squared test (Norman & Streiner, 2000). Accordingly, Fisher's exact test investigated the difference in admissions over the follow up period in low and high variability subgroups of bipolar disorder participants.

3.5.8.2 Exploratory Kaplan-Meier survival analysis

Survival analysis investigated if tentative associations between variability measures and admission could be identified. Survival analyses may be considered exploratory due to the small sample size. Since participants had a variable length of follow-up, survival analysis may be a better method of analysing the patterns of admission between participant subgroups, than using contingency tables in isolation. Assumptions of survival analysis include identifiable start and end points. The date participants began daily monitoring was the selected start point; inclusion criteria meant participants with bipolar disorder were not experiencing an acute episode when they began study participation. The end point selected was first admission to hospital following each individual's start point. Since the exact date of first admission had been obtained from Medical Records, the Kaplan-Meier approach was

used instead of the actuarial approach which analyses survival over intervals of time. Admission dates provided the opportunity to calculate the number of days until admission. Furthermore, when sample size is small (N<50), the Kaplan-Meier is the recommended technique (Norman & Streiner, 2000). The cumulative probability of survival (i.e. not having an admission to hospital) across the follow up period was plotted in a survival curve.

The Kaplan-Meier approach was then used to investigate differences in time to first admission in participants with bipolar disorder who displayed high variability compared to individuals who displayed low variability across the monitoring period. The Kaplan-Meier analyses investigated differences in the variability measures found to differ between bipolar disorder and general population groups. Variability in measures were analysed as continuous measures. Subsequently, a median split was applied to group participants into low and high variability subgroups. Kaplan-Meier analyses were repeated with the categorical variability measures.

Admission to hospital was an outcome likely to differ across diagnostic subtypes. Clinical experience suggests individuals are more commonly admitted for mania than for depression, which would make individuals with bipolar I disorder more likely to have an admission compared to individuals with bipolar II disorder. Accordingly, further exploratory Kaplan-Meier analyses included diagnosis as a strata variable. The strata levels for diagnosis were: bipolar I disorder, bipolar II disorder, and rapid cycling disorder. The Mantel-Cox log-rank test investigated the equality of survival distributions for variability measures. The log-rank test is a non-parametric test that compares the occurrence of outcomes in each group across time. If no group differences exist, then at any time point, outcomes observed in each group (either variability or diagnosis) should be proportional to the

participants at risk of admission in each group. These subgroup analyses are provided in Appendix M.

3.5.8.3 Exploratory Cox regression

The current study prospectively monitored biological, behavioural, self esteem, and affect variability in bipolar disorder. Previous research has indicated several factors may interact to precipitate relapse in bipolar disorder. Accordingly, analyses of bipolar relapse may need to consider several variables in order to identify associations with relapse. Cox regression was thus used to investigate the effect of several variability measures in the prediction of time to first admission in bipolar disorder participants. Two blocks were entered into the Cox regression and a forward stepwise (conditional LR) method was used to identify variables that were significant predictors of time to admission.

The first block of the Cox regression looked at gender, diagnosis and age. Gender (male, female) and diagnosis (Bipolar I Disorder, Bipolar II Disorder, Rapid Cycling Disorder) were analysed as categorical variables. Age was analysed as a continuous variable. A limited number of covariates were included in the block due to the small sample size. With a larger sample, length of history and number of previous episodes would have been useful to include as both may influence relapse in bipolar disorder (Goodwin & Jamison, 1990). The three demographic variables selected were included because of their known impact on bipolar relapse. Furthermore, these demographic variables have also been reported to impact on the measures used in the current study. For instance, sleep disturbances have been associated with both age and gender (Breslau et al, 1996). Thus, it was important to control for the effect of these factors in order to identify if variability measures contributed any further predictive power.

Several covariates were included in the second block of the Cox regression. These covariates included variability in the four affect measures: positive affect variability; negative affect variability; elated variability; and depressed variability. In addition, the variability measures found to differ between bipolar disorder and general population groups were included as covariates. The covariates were analysed as continuous variables to identify associations with admission in bipolar disorder. Indicator parameter coding was used to identify whether high variability was associated with greater risk of admission.

The second block of covariates were subsequently reanalysed as categorical variables. A median split was applied to each measure to divide participants into high and low variability subgroups. The main advantage of these supplementary analyses was to assess the impact of any outliers as with a small sample size, an extreme variability score could skew the results. Repeating the analyses with categorical covariates was thus used as a checking device. The overall group median, high variability median and low variability median were produced for each covariate.

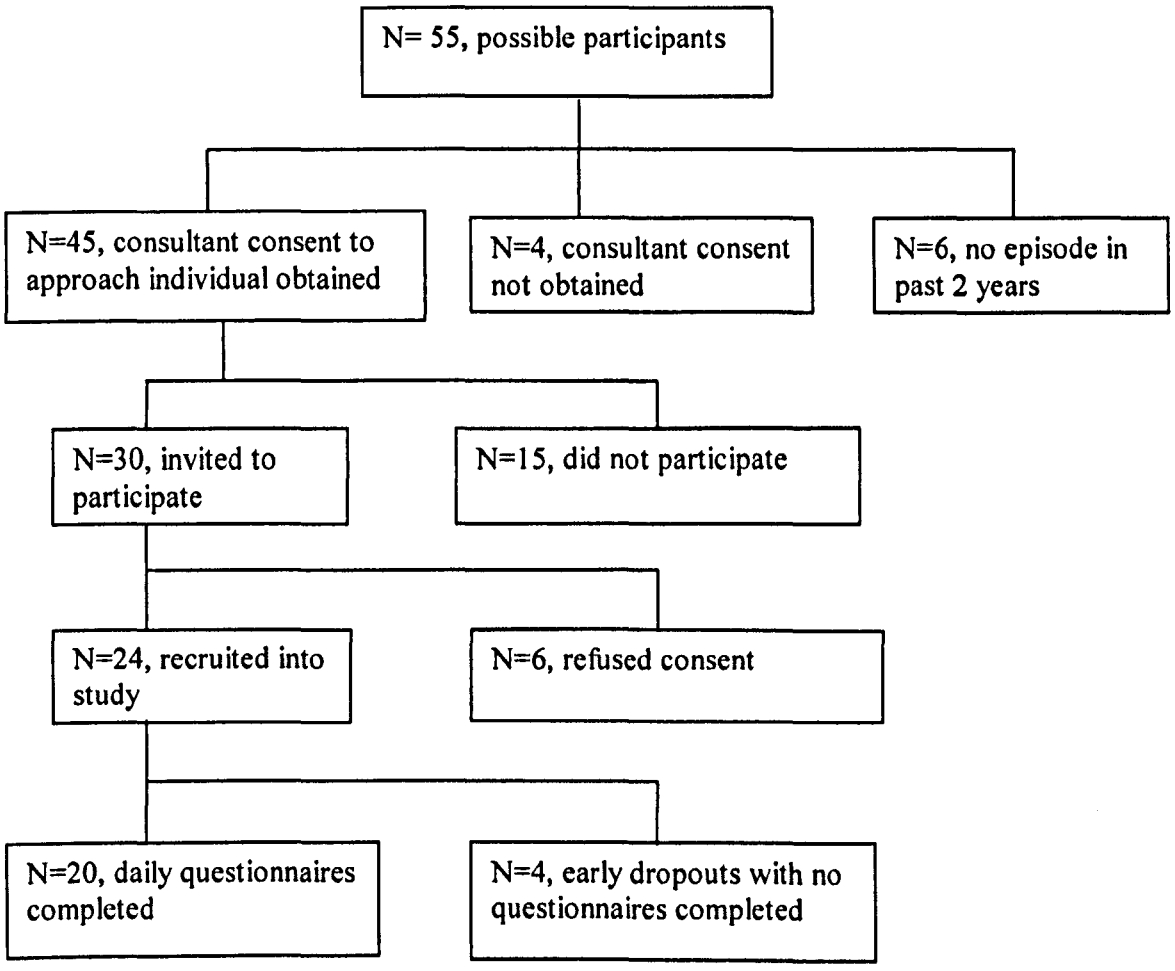
3.6 Summary of method

The aim of the present study was to investigate variability in bipolar disorders. The average level and variability of diathesis vulnerability, behaviour, self esteem and affect measures in bipolar disorder were compared to the general population. Prospective daily monitoring provided the average level and variability of measures for each participant. Group differences in the average level and variability of measures were investigated. Measures observed to differ between groups were subsequently subject to time series analyses for participants with bipolar disorder. Finally, a three year follow-up assessed the clinical importance of variability in bipolar disorder. The association between variability and subsequent hospital admission in bipolar disorder was investigated.

Chapter 4 Comparison of bipolar disorder and general population groups

The recruitment of bipolar disorder and general population participants and their respective demographic characteristics will be outlined briefly (Section 4.1). Secondly, the extent of missing data for each measure will be reported (Section 4.2). Thirdly, descriptive statistics for the mean level and variability of biological, behaviour, self esteem and affect measures will be provided for each participant group, with the inferential analyses that investigated group differences (Sections 4.3 to 4.10). Fourthly, time series analyses of variability within bipolar disorder participants will be produced (Section 4.11). Finally, associations between variability and subsequent hospital admission will be reported (Sections 4.12 to 4.14). The findings of the current study will then be summarised (Section 4.15).

Figure 4.1: Flowchart of bipolar disorder participants recruited to study



4.1 Recruitment of bipolar disorder participants

A total of 55 individuals with bipolar disorder were identified, although six had not relapsed in the previous two years, leaving 49 as suitable for inclusion. Consultant consent was obtained for 45 of these individuals (Figure 4.1). Fifteen individuals were unable to be asked to participate (Section 4.1.2 provides reasons for non-participation). Thirty individuals were invited to participate in the research project. Twenty-four individuals were recruited. Four early dropouts did not complete any questionnaires. The final sample comprised 20 participants with bipolar disorder (41% of individuals identified as suitable for inclusion).

4.1.1 Characteristics of bipolar disorder participants

Twenty individuals with bipolar disorder participated in the research project. Demographic information is provided in the table below (Table 4.1). Participants had an age range from 30 to 62 years and had a history of bipolar disorder ranging from one to 43 years. The number of previous episodes experienced ranged from two to 15 episodes. Eight participants were prescribed lithium only, and five participants received another mood stabiliser. The remainder (N=7) were prescribed a combination of lithium and other mood stabilising drugs. Duration of illness and number of previous episodes was unclear in casenotes for three participants. The number of previous episodes was also unclear for another four participants. Illness duration and number of prior episodes were not reported in cases where the participant was a poor historian, the history was complicated, or casenotes were incomplete. Medication and illness history of participants with bipolar disorder are provided in Table 4.2.

Table 4.1: Demographic characteristics of bipolar disorder participants

Values are numbers (percentages) of participants unless stated otherwise.

Variable	Participants (N=20)	Early Dropouts (N=4)	Refusers (N=6)
Mean (SD) age (years)	43 (11)	35 (8)	57 (6)
Females	10 (50%)	3 (75%)	3 (50%)
Type of bipolar illness:			
Bipolar I	8 (40%)	2 (50%)	3 (50%)
Bipolar II	4 (20%)	2 (50%)	2 (33%)
Rapid Cycling	8 (40%)	0	1 (17%)

Table 4.2: Medication and illness history of bipolar disorder participants

Values are numbers (percentages) of participants unless stated otherwise.

Variable	Participants (N=20)
Prescribed lithium	15 (75%)
Prescribed mood stabilising drugs	12 (60%)
Median duration of illness, in years (inter-quartile range)	10 (6-15)[1]
Median no. of bipolar episodes (inter-quartile range)	7 (4-10)[2]

[1] Median based on N=17 out of 20 for duration of illness

[2] Median based on N=13 out of 20 for number of episodes

4.1.2 Characteristics of non-participants

Six individuals with bipolar disorder refused to participate in the research project. Four early dropouts provided a signed consent form but did not complete any questionnaires. Demographic characteristics for these individuals (N=10) are provided in the table above (Table 4.1). Reasons for non-participation for the early dropouts included physical health problems (N=2); patient consent withdrawn (N=1); and work commitments (N=1). Reasons for refusal (N=6) were not provided. Fifteen individuals, identified as suitable for inclusion, were unable to be recruited for the study. Reasons for individuals not participating (N=15) included: time constraints of clinic, no time to ask for consent (N=11); inpatient (N=1); died (N=1); moved away from area (N=1); and physical illness (N=1).

4.1.3 Characteristics of general population participants

A control group was recruited from the general population. The general population participants had an age range from 26 to 59 years. The general population individuals were recruited by opportunity sampling from personal and occupational sources. Age and gender information for the general population participants are available in Table 4.3. An independent samples t test indicated the difference between bipolar disorder and general population participants in age was not significant (t= -0.401, df 28, p=0.691).

Table 4.3: Demographic characteristics of general population participants

Values are numbers (percentages) of participants unless stated otherwise.

Variable	Participants (N=10)
Mean (SD) age (years)	41 (14)
Females	5 (50%)

4.2 Missing data

The range of completed daily questionnaires for the twenty participants with bipolar disorder was two to 24 weeks. The ten general population participants completed two to four weeks of daily monitoring. Although a high proportion of questionnaires were completed by participants, missing data did occur. In particular, not all participants with bipolar disorder were willing or able to complete all of the questionnaires as well as undergo actigraph monitoring. Five participants with bipolar disorder did not agree to wear an actiwatch. Similar to a recent UK study where RSEQ completion had a self-reported depressive impact (N=32 professional participants, N=21 service users or lay people; Blount et al, 2002), two bipolar disorder participants were unwilling to complete the self esteem questionnaire as they reported completion was too distressing. Participants did not report any distress at completing the SRM, PANAS or BIS/BAS questionnaires.

Participant mean and variability scores were calculated for a 14 day monitoring period to compare the mean level and variability of measures between groups. The proportion of missing data that occurred within each group over these 14 day monitoring periods are provided in Table 4.4. Missing data also occurred with actigraph monitoring of the sleep-wake cycle. For participants who underwent actigraph monitoring, missing sleep data were evident for 15 nights (8%) for the bipolar disorder group and eight nights (6%) for the general population group. A larger percentage of missing data were evident in the bipolar disorder group compared to the general population group for self completion of SRM, RSEQ, and BIS/BAS questionnaires and actigraph monitoring.

Table 4.4: Frequency of questionnaires not completed over 14 days of monitoring

Values are numbers (percentages) of questionnaires not completed

Questionnaires	Bipolar Disorder (N=20)	General Population (N=10)
PANAS	16 (6%)	10 (7%)
BIS/BAS	11 (28%)	2 (10%)
RSEQ	33 (12%)	8 (6%)
SRM	2 (5%)	0 (0%)

4.3 Mean level and variability of diathesis vulnerability, behaviour, self esteem and affect measures

The bipolar disorder and general population groups were compared on average level and variability of diathesis vulnerability, behaviour, self esteem and affect measures. The mean level and variability for each measure was calculated for each participant across a 14 day monitoring period (Section 3.5.2 provides further information on this methodology). Group means for each measure's level and variability were then calculated from these participant means. Multivariate analyses of variance were conducted to investigate between-group differences in the mean level and variability of measures:

- Mean scores of sleep variables: time in bed, sleep duration, night waking time, sleep efficiency, sleep latency and fragmentation index
- Day-to-day variability of sleep variables: time in bed, sleep duration, night waking time, sleep efficiency, sleep latency and fragmentation index
- Mean scores of social and circadian rhythm variables: social rhythm regularity, daily activity level index (DALI), night time activity level (L5), day time activity level (M10), relative amplitude (RA), interdaily stability (IS) and intradaily variability (IV)

- Week-to-week variability of social and circadian rhythm variables: social rhythm regularity, DALI, L5, M10, relative amplitude, IS and IV
- Mean scores of behavioural inhibition and activation: BIS, BAS reward responsiveness, BAS drive and BAS fun seeking
- Week-to-week variability of behavioural inhibition and activation: BIS, BAS reward responsiveness, BAS drive and BAS fun seeking
- Mean scores of self esteem and affect variables: self esteem (SE), positive affect (PA), negative affect (NA), elated and depressed
- Day-to-day variability of self esteem and affect variables: SE, PA, NA, elated and depressed
- Mean scores and day-to-day variability of positive and negative self esteem subscales

The following sections will outline the descriptive and inferential statistics for each group of variables. When parametric assumptions were not met for a group of variables, non-parametric test results were selected as the preferred test for group differences. Inferential tests conducted but not presented in this chapter are provided in Appendix J. Analyses for sleep, social rhythms, and circadian rhythms, are provided in section 4.4 and behavioural activation/inhibition analyses are provided in section 4.5. The analyses for the self esteem and affect measures are provided in section 4.6.

4.4 Level and variability of diathesis vulnerability and behaviour measures

The circadian rhythm of the sleep-wake cycle and self-report assessment of behavioural activation/inhibition provided diathesis vulnerability measures for participants. Daily social rhythms were monitored to provide a measure of behaviour. The sleep-wake cycle was objectively estimated with actigraphy whilst self report completion of the Social Rhythm Metric (SRM) provided daily social rhythms. The average level and variability of sleep-wake measures will be outlined first, and then the occurrence and regularity of social and

circadian rhythms will be reported (circadian rhythms obtained from actigraph sleep-wake analysis). Thirdly, average level and variability of behavioural activation and inhibition will be reported.

4.4.1 Average levels of sleep measures

Time in bed was provided for most days of prospective monitoring since bed-time and get up times were recorded on the SRM questionnaire. The remaining five sleep variables (sleep duration; night waking time; sleep efficiency; sleep latency; and fragmentation index) were only available for nights when an actigraph device was worn by the participant. Table 4.5 provides the mean sleep measures for the bipolar disorder and general population groups. Six participants with bipolar disorder did not undergo actigraph monitoring, so the bipolar disorder group means are based on the remaining fourteen participants. A MANOVA was conducted for the mean level of six sleep variables: time in bed, sleep duration, night waking time, sleep efficiency, sleep latency and fragmentation index. The sample sizes were unequal (N=14 bipolar disorder; N=10 general population), but the significance of Box's M was greater than 0.001 (Box's M 54.688, F=1.778, df 21, 1377.759 p=0.016). This suggests the MANOVA will be robust to any deviation from homogeneity of covariance. However, Levene's test was significant for sleep duration (F=4.351, df 1, 22, p=0.049) indicating the error variance of this dependent variable was not equal across the two groups. Furthermore, five of the six mean sleep variables were not normally distributed (Appendix I). Since two parametric assumptions were not met, the results of the multivariate test were discarded (F=2.319, df 6, 17, p=0.081). Mann-Whitney test results for the mean level of six sleep variables are provided in Table 4.5. The rejected MANOVA results are provided in Appendix J. Large effect sizes were evident, with significant differences between groups observed for time in bed, night waking, sleep efficiency, and fragmentation index. Thus, differences in averaged sleep measures between

bipolar disorder and the general population over a 14 day period suggested sleep disturbances occur in bipolar disorder during inter-episode periods.

4.4.2 Night-to-night variability of sleep measures

A MANOVA was conducted for the variability of the six sleep variables. The sample sizes were unequal (N=14 bipolar disorder; N=10 general population), but the significance of Box's M was greater than 0.001 (Box's M 59.545, F=1.936, df 21, 1377.759 p=0.007) which suggests the MANOVA will be robust to any deviation from homogeneity of covariance. Levene's test was significant for sleep efficiency variability (F=6.926, df1, 22, p=0.015), sleep latency variability (F=5.203, df1, 22, p=0.033) and fragmentation index variability (F=6.622, df1, 22, p=0.017). This indicates the error variances of these three dependent variables were not equal across the groups. The six sleep variability variables were not normally distributed (Appendix I). Since two parametric assumptions were not met, the results of the multivariate test were discarded (F=1.515, df 6, 17, p=0.232). Mann-Whitney test results for the variability of sleep variables are displayed in Table 4.6. The rejected MANOVA results are provided in Appendix J. There were four significant differences in the variability of sleep measures between the bipolar disorder and general population groups. Greater variability in sleep duration, night waking, sleep efficiency, and fragmentation index measures were evident in bipolar disorder. Greater night-to-night variability in sleep measures in bipolar disorder suggested disturbances in the sleep-wake cycle.

Table 4.5: Averaged sleep measures comparison between bipolar disorder and general population groups

Sleep variable	Bipolar Disorder		General Population		Effect	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*		
Time in bed (min.)	543 (61)	508-578	499 (45)	467-530	0.8*	35	0.040*
Sleep duration (min.)	426 (84)	377-475	427 (33)	403-451	-0.01	65	0.770
Night waking time (min.)	77 (37)	56-98	47 (24)	30-64	0.9*	30	0.019*
Sleep efficiency (%)	78 (12)	71-84	86 (6)	82-90	-0.7	32	0.026*
Sleep latency (min.)	36 (26)	21-51	21 (17)	9-32	0.7	45	0.143
Fragmentation index	39 (17)	29-49	25 (11)	17-33	0.9*	28	0.014*

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table 4.6: Sleep variability comparison between bipolar disorder and general population groups

Sleep variable	Bipolar Disorder		General Population		Effect	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*		
Time in bed variability (min.)	77 (34)	57-97	59 (22)	43-75	0.6	38	0.061
Sleep duration variability (min.)	80 (37)	59-101	53 (21)	38-68	0.8*	30	0.019*
Night waking variability (min.)	33 (21)	22-45	14 (8)	9-19	1.0*	15	0.001*
Sleep efficiency variability (%)	9 (5)	6-12	4 (2)	3-6	1.0*	20	0.003*
Sleep latency variability (min.)	34 (24)	21-48	18 (10)	10-25	0.8*	42	0.101
Fragmentation index variability	13 (6)	9-17	8 (2)	6-9	0.8*	29	0.016*

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

4.4.3 Average levels of social and circadian rhythm measures

Daily completion of the SRM provided a habitual time for an activity over each weekly period. A weekly regularity score that indicated the variability of daily social rhythms from their habitual weekly time was calculated. In addition, the number of activities completed daily was calculated (DALI). Mean levels of SRM regularity and DALI are provided in Table 4.7 for each group. Circadian rhythm variables for the sleep-wake cycle were calculated for each week of actigraph monitoring. In particular, interdaily stability and intradaily variability measures provide an indication of rest-activity regulation over time. Table 4.7 also provides the mean circadian rhythm scores for the bipolar disorder and general population groups.

A MANOVA was conducted for the mean level of two social rhythm (regularity of social rhythms, number of daily activities performed) and five circadian rhythm variables (night time activity level, day time activity level, relative amplitude, interdaily stability, intradaily variability). The sample sizes were unequal (N=14 bipolar disorder; N=10 general population), but the significance of Box's M was greater than 0.001 (Box's M 74.451, F=1.670, df 28, 1309.218, p=0.016) which suggests the MANOVA will be robust to any deviation from homogeneity of covariance. Levene's test did not indicate any significant findings, suggesting the error variance of the seven dependent variables was equal across the participant groups. Four of the mean social rhythm and circadian rhythm variables did not display a normal distribution of scores (Appendix I). Two out of three parametric assumptions were met, so the parametric analysis was considered the preferred test for group differences. The multivariate tests did not indicate any significant difference between groups for mean levels of social and circadian rhythm variables (F=1.938, df 7, 16, p=0.129).

Table 4.7: Averaged social and circadian rhythm measures comparison between bipolar disorder and general population groups

Social/circadian rhythm variables	Bipolar Disorder		General Population		Effect Size*	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI				
Regularity score	4.00 (0.78)	3.55-4.45	3.88 (0.84)	3.28-4.47	0.2	23	0.142	0.710
DALI	12 (2)	11-13	13 (1)	12-14	-0.7	23	3.069	0.094
L5	1533 (1353)	752-2314	754 (715)	243-1266	0.7	23	2.742	0.112
M10	20628 (16281)	11228-30028	17853 (7580)	12431-23275	0.2	23	0.249	0.622
RA	0.85 (0.10)	0.79-0.90	0.91 (0.06)	0.87-0.96	-0.7	23	3.754	0.066
IS	0.50 (0.12)	0.43-0.57	0.52 (0.14)	0.42-0.62	-0.2	23	0.129	0.723
IV	0.81 (0.20)	0.69-0.92	0.88 (0.15)	0.78-0.99	-0.4	23	1.027	0.322

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Variables: DALI, Daily activity level index; L5, Night time activity level; M10, Day time activity level; RA, Relative amplitude; IS, Interdaily stability; IV, Intradaily variability

Disruption may also be observed in the timing of circadian rhythms. Thus, mean onset times of night time and day time activity levels were also calculated for each group (Table 4.8). Large skewness and kurtosis z scores (skewness 8.12, kurtosis 18.23) were evident for the distribution of scores for night time activity onset time suggesting non-parametric analysis would be appropriate. Mann-Whitney U analyses indicate no significant differences in onset times in either day time or night time activity levels. Circadian rhythm timing does therefore not appear to be disturbed in the bipolar disorder participants.

Table 4.8: Mean onset times for lowest night time activity and highest day time activity levels

Variable	Bipolar Disorder		General Population		U	p
	M (SD)[1]	95% CI	M (SD)[2]	95% CI		
L5 onset	2:27 (2:46)	0:51-4:04	1:42 (0:35)	1:16-2:07	66.5	0.841
M10 onset	9:47 (1:57)	8:39-10:54	10:21 (1:33)	9:13-11:28	52.5	0.312

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

Variables: L5 onset, Lowest five hour period of night time activity level onset time; M10 onset, Highest ten hour period of day time activity level onset time

4.4.4 Variability of social and circadian rhythm measures

Variability in social rhythm measures were investigated in terms of variability in the weekly regularity of social rhythms and in the number of daily activities. Variability in circadian rhythm measures was also investigated. Variability in social and circadian rhythm measures were calculated as the standard deviation across the 14 day period for each participant. Social and circadian rhythm variables were calculated for each seven day period; variability was therefore calculated from the two standard deviation values for the 14 day period. The

DALI was a daily measure of social rhythms, with the overall mean and standard deviation calculated across the 14 day period, as per the daily self-report questionnaires (Section 3.5.2 provides more information about the computation of group mean and variability levels). A MANOVA was conducted for the variability of the seven social and circadian rhythm variables (daily activity level index, social rhythm regularity, night time activity level, day time activity level, relative amplitude, interdaily stability, intradaily variability). Box's M was significant (Box's M=99.909, F=2.157, df 28, 1286.042, p=0.000) indicating the assumptions of homogeneity of covariance were not met. Unequal sample sizes (N=12 bipolar disorder; N=10 general population) in combination with a significant Box's M suggests the MANOVA results should be considered tentatively (Tabachnick & Fidell, 2001). Furthermore, Levene's test was significant for variability in three circadian rhythm variables: night time activity level (F=14.001, df 1, 20, p=0.001), relative amplitude (F=6.323, df 1, 20 p=0.021) and intradaily variability (F=5.269, df 1, 20, p=0.033). Furthermore, five of the variability in social and circadian rhythm variables were not normally distributed (Appendix I). The multivariate analysis was discounted (F=2.217; df 7, 14; p=0.097) since the parametric assumptions were not met. Mann-Whitney test results for variability of social and circadian rhythm variables are displayed in Table 4.9. The rejected MANOVA results are provided in Appendix J. Greater variability in relative amplitude in bipolar disorder was the only significant difference observed in the variability of social and circadian rhythms between groups. Variability in relative amplitude suggested individuals with bipolar disorder were less consistent in their waves of rest and activity over the monitoring period.

Table 4.9: Social and circadian rhythm variability comparison between bipolar disorder and general population groups

Social/circadian rhythm variable	Bipolar Disorder		General Population		Effect Size*	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI			
Regularity score variability	0.54 (0.47)	0.24-0.84	0.59 (0.33)	0.35-0.82	-0.2	85	0.645
DALI variability	1.26 (0.45)	0.98-1.55	1.15 (0.27)	0.96-1.35	0.3	87	0.567
L5 variability	382 (468)	84-679	102 (90)	38-167	0.8*	38	0.094
M10 variability	3872 (3433)	1691-6053	1752 (1632)	585-2920	0.7	40	0.121
RA variability	0.04 (0.03)	0.01-0.06	0.01 (0.02)	-0.001-0.02	1.0*	28.5	0.023*
IS variability	0.06 (0.06)	0.02-0.10	0.05 (0.04)	0.02-0.08	0.2	61	0.804
IV variability	0.09 (0.05)	0.05-0.12	0.19 (0.17)	0.06-0.31	-0.8*	43	0.172

[1] Based on participant mean scores over 14 days for N=12 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Variables: DALI, Daily activity level index; L5, Night time activity level; M10, Day time activity level; RA, Relative amplitude; IS, Interdaily stability; IV, Intradaily variability

4.5 Level and variability of behavioural activation/inhibition measures

Each participant's level of behavioural activation/inhibition was monitored weekly with the self-report BIS/BAS Scales. The variability of behavioural activation from week-to-week was of particular interest since bipolar disorder has been theoretically postulated to occur with behavioural activation dysregulation (Depue et al, 1987). Mutual inhibition has also been proposed to exist between the behavioural activation and inhibition systems (Pickering et al, 1999). Thus, level and variability of behavioural inhibition was also investigated.

4.5.1 Average level of behavioural activation/inhibition levels

Mean levels of behavioural activation and inhibition for the participant groups are available in Table 4.10. A MANOVA was conducted for the mean level of behavioural inhibition (BIS) and the three behavioural activation variables (BAS reward responsiveness, BAS drive, BAS fun seeking). The sample size was unequal between the groups (N=16 bipolar disorder; N=10 general population). Box's M results indicated the analysis would be robust to any deviation from homogeneity of covariance (Box's M=24.726, F=1.976, df 10, 1689.922, p=0.032). Levene's test of equality of error variances indicated the error variance of BAS reward responsiveness (F=4.953, df 1, 24, p=0.036) and BAS drive (F=4.124, df 1, 24, p=0.053) was not equal across groups. The mean BAS fun seeking variable was not distributed normally (Appendix I). Thus, the multivariate analysis (F=2.024, df 4, 21, p=0.128) was discarded since two of the parametric assumptions were not met. Mann-Whitney test results are provided in Table 4.10. The rejected MANOVA results are provided in Appendix J. No significant differences between the groups for behavioural inhibition or any of the three behavioural activation subscales were observed.

Table 4.10: Averaged behavioural activation/inhibition measures comparison between bipolar disorder and general population groups

BIS/BAS	Bipolar Disorder		General Population		Effect	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*		
BIS	23 (4)	20-25	20 (5)	16-23	0.7	49	0.101
BAS reward responsiveness	15 (3)	14-17	15 (2)	14-16	0.1	81.5	0.860
BAS drive	10 (4)	8-12	10 (2)	8-11	0.1	82	0.879
BAS fun seeking	10 (2)	9-11	9 (1)	9-10	0.5	67	0.362

[1] Based on participant mean scores over 14 days for N=16 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

4.5.2 Week-to-week variability of behavioural activation/inhibition measures

The variability of behavioural activation and inhibition over the 14 day period was also assessed since bipolar disorder is postulated to be characterised by dysregulation of the behavioural activation system. The results of Box's M test (Box's M=34.353, F=2.411, df 10, 1033.845, p=0.008) and almost equal sample groups (N=9 bipolar disorder, N=8 general population) indicated the analysis would be robust to any deviation from homogeneity of covariance. Smaller group sample size compared to the analysis of averaged behavioural activation/inhibition measures was due to fewer participants completing the BIS/BAS measure on two occasions over the 14 day period. Levene's test indicated the error variance for the four dependent variables was equal across the groups. Three of the variability of behavioural activation/inhibition variables were not distributed normally (Appendix I). Since two of the parametric assumptions were satisfied, MANOVA was retained as the preferred inferential test to investigate group differences. The findings of the multivariate analysis indicated no significant difference in behavioural activation and inhibition variability between the groups (F=0.323, df 4, 12, p=0.857). Group means for behavioural inhibition and activation variability are displayed in Table 4.11.

Table 4.11: Behavioural activation/inhibition variability comparison between bipolar disorder and general population groups

BIS/BAS	Bipolar Disorder		General Population		Effect	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*			
BIS variability	1.6 (1.2)	0.7-2.5	1.2 (1.0)	0.3-2.0	0.4	16	0.640	0.436
BAS reward responsiveness variability	1.4 (2.2)	-0.3-3.1	1.1 (0.9)	0.3-1.8	0.2	16	0.173	0.684
BAS drive variability	0.9 (1.5)	-0.2-2.1	0.8 (0.8)	0.1-1.5	0.1	16	0.059	0.812
BAS fun seeking variability	0.6 (0.6)	0.1-1.0	1.0 (1.1)	0.1-1.9	-0.4	16	1.057	0.320

[1] Based on participant mean scores over 14 days for N=9 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=8 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

4.6 Level and variability of self esteem and affect measures

Self esteem was monitored to provide a measure of cognition from day-to-day. The average level and variability of self esteem, as measured by the RSEQ, was calculated for each participant group. Positive and negative affect were measured to provide a general measure of affect, whilst measures of elation and depression were used to provide affect monitoring specific to bipolar disorder. Average levels and variability of the affect measures were also calculated for each participant group.

4.6.1 Average level of self esteem and affect measures

Table 4.12 provides the group mean levels of self esteem and affect measures. The unequal sample sizes (N=18 bipolar disorder; N=10 general population) combined with a significant Box's M test (Box's M=116.419, F=2.719, df 28, 1225.586, p=0.000) suggested the multivariate analysis should be considered tentatively. Levene's test was significant for the depressed rating (F=8.919, df 1, 26, p=0.006) and self esteem (F=8.850, df 1, 26, p=0.006), indicating that the error variance of these two dependent variables was not equal across the groups. Mean depression and negative affect variables were not distributed normally (Appendix I). Thus, with two parametric assumptions not being met, the results of the MANOVA were discounted (F=1.872; df 7, 20; p=0.128). Mann-Whitney test results for mean self esteem and affect measures are provided in Table 4.12. The rejected MANOVA results are provided in Appendix J. Significantly lower positive affect, lower self esteem, higher negative affect, and higher depressed ratings were evident for the bipolar disorder group. Although this suggests reduced self esteem and affect levels occur in bipolar disorder across inter-episode periods, such attenuation may have been due to higher depression levels. However, analyses using depression ratings as a covariate were not conducted to investigate this possibility.

Table 4.12: Averaged self esteem and affect measures comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder M (SD)[1]	95% CI	General Population M (SD)[2]	95% CI	Effect Size*	U	Significance
SE	41 (16)	34-49	56 (8)	50-62	-1.0*	39	0.014*
PA	21 (7)	17-24	29 (5)	25-33	-1.0*	27.5	0.001*
NA	17 (8)	13-21	13 (4)	10-16	0.6	45.5	0.016*
Elated	1.7 (0.8)	1.3-2.1	2.3 (0.7)	1.8-2.8	-0.8*	60.5	0.081
Depressed	2.1 (1.2)	1.5-2.7	1.2 (0.3)	0.9-1.4	0.9*	35.5	0.004*

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

4.6.2 Variability of self esteem and affect measures

The variability of self esteem and affect across the 14 day monitoring period were then considered. Although sample sizes were unequal (N=18 bipolar disorder; N=10 general population), Box's M test was not significant (Box's M=42.296, F=0.988, df 28, 1225.586, p=0.484), indicating multivariate analysis will be robust to any deviation from homogeneity of covariance. Levene's test was significant for SE variability (F=4.615, df 1, 26, p=0.041) suggesting the error variance of this dependent variable was not equal across groups. Variability in self esteem and negative affect variables were not distributed normally (Appendix I). The MANOVA results were discounted (F=2.278; df 7, 20; p=0.070) as two of the parametric assumptions were not met. The Mann-Whitney test results for variability of SE and affect variables are displayed in Table 4.13. The rejected MANOVA results are provided in Appendix J. Significantly greater SE and NA variability was observed in the bipolar disorder group.

4.6.3 Positive and negative self esteem subscales

A robust finding from the between group analyses was lower self esteem level and greater self esteem variability were observed in the bipolar disorder group. Self esteem, as assessed by the Rosenberg Self Esteem Questionnaire, provides positive and negative self esteem subscales which combine to form a total self esteem score. The average level and variability of the positive and negative self esteem subscales were also calculated (Table 4.14). Further analysis was conducted for self esteem to investigate whether positive or negative self esteem played a specific role in differentiating bipolar disorder and the general population.

Four self esteem dependent variables were entered into a multivariate analysis: positive SE level; negative SE level; positive SE variability; and negative SE variability. Unequal

sample sizes (N=18 bipolar disorder; N=10 general population) and a Box's M test greater than p=0.001 suggests the multivariate analysis will be robust to any deviation from homogeneity of covariance (Box's M=35.320, F=2.844, df 10, 1606.780, p=0.002). Levene's test was significant for positive SE level (F=21.725, df 1, 26, p=0.000), positive SE variability (F=7.367, df 1, 26, p=0.012) and negative SE variability (F=4.796, df 1, 26, p=0.038). Significant results for Levene's test indicate the error variance of these three dependent variables was not equal across the groups. Positive self esteem variability was not distributed normally (Appendix I). The results of the multivariate analysis were discarded (F=3.087, df 4, 23, p=0.036). The results of the Mann-Whitney tests for the self esteem subscales are provided in Table 4.14. Significant differences between groups for the four self esteem variables were observed. Lower positive and negative SE levels were observed in the bipolar disorder group; scores for positive SE items were reversed so that higher scores on either SE subscale indicate higher SE (Section 3.4.4.1 outlines scoring for the RSEQ). Furthermore, greater variability in positive and negative SE was observed in bipolar disorder compared to the general population group. Thus, these results suggest both the level and variability of positive and negative self esteem, as measured by the RSEQ, differentiate bipolar disorder and the general population.

Table 4.13: Self esteem and affect variability comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder		General Population		Effect	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*		
SE variability	4.5 (2.6)	3.2-5.8	1.8 (0.8)	1.2-2.4	1.1*	24	0.002*
PA variability	4.2 (2.2)	3.1-5.3	5.1 (2.2)	3.5-6.6	-0.4	74	0.253
NA variability	4.0 (2.7)	2.6-5.3	2.1 (2.3)	0.5-3.7	0.7	54	0.043*
Elated variability	0.5 (0.4)	0.3-0.7	0.8 (0.4)	0.5-1.1	-0.8*	60.5	0.081
Depressed variability	0.6 (0.5)	0.3-0.8	0.3 (0.3)	0.1-0.5	0.8*	58	0.061

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table 4.14: Average level and variability of positive and negative self esteem comparison between bipolar disorder and general population groups

Self esteem	Bipolar Disorder		General Population		Effect	U	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*		
Positive SE level	23 (8)	19-27	30 (2)	28-31	-1.0*	45	0.031*
Negative SE level	19 (8)	15-23	26 (6)	22-31	-0.9*	40	0.017*
Positive SE variability	2.3 (1.5)	1.6-3.1	0.7 (0.5)	0.3-1.1	1.1*	18.5	0.001*
Negative SE variability	2.7 (1.5)	1.9-3.4	1.6 (0.8)	1.0-2.2	0.9*	46	0.035*

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

4.7 Holm correction for univariate between group analyses

Across a 14 day period, the average level of eight variables (time in bed, night waking, sleep efficiency, fragmentation index, self esteem, positive affect, negative affect, depression) and the variability of seven variables (sleep duration, night waking, sleep efficiency, fragmentation index, relative amplitude, self esteem, negative affect) were observed to differ between bipolar disorder and general population groups. However, these significant findings may require interpretation with consideration of the impact of multiple univariate analysis comparisons. The Holm method was therefore applied to correct the alpha level to 0.05 for the number of comparisons conducted for each conceptual group of variables. Following this correction of the alpha level, significant differences in the average level of four variables (self esteem, positive affect, negative affect, depression) and the variability of three variables (night waking, sleep efficiency, self esteem) remained between groups. Thus, lower self esteem and positive affect, higher negative affect and depressed ratings, and greater variability in night waking time, sleep efficiency and self esteem were observed in the bipolar disorder group with conservative interpretation of non-parametric analyses.

4.8 Longer monitoring period for bipolar disorder participants

The experimental hypothesis was that greater variability would be observed in bipolar disorder compared to the general population. Although participants had completed varying monitoring periods (median 8 weeks for bipolar disorder, median 2 weeks for general population), each participant had the mean level and variability of measures calculated from a 14 day monitoring period. If the data had been aggregated over longer periods for participants with bipolar disorder, greater variability exhibited in the bipolar disorder group could merely be due to the artefact of the longer time frame. Alternatively longer prospective monitoring may be necessary to give a more accurate estimation of the mean level and variability of measures in bipolar disorder. Previous findings have indicated

identification of social rhythm 'traits' required seven weeks of monitoring in mood disorder samples, whereas two weeks were adequate for general population samples (Monk et al, 1991; Ashman et al, 1999). Parametric comparisons between groups were therefore repeated using the full prospective monitoring period of the participants with bipolar disorder.

The mean level and variability of measures in bipolar disorder participants over their full prospective monitoring period were compared to the mean level and variability of measures in general population participants over their two week monitoring period (Analyses provided in Appendix K). In brief, these multivariate analyses of variance observed similar results to the comparison of a 14 day monitoring period. Across a longer monitoring period for bipolar disorder, the average level of seven variables (night waking, sleep efficiency, fragmentation index, night time activity level, self esteem, positive affect, depression) and the variability of 11 variables (sleep duration, night waking, sleep efficiency, fragmentation index, daily activity level index, night time activity level, day time activity level, relative amplitude, self esteem, negative affect, depression) were observed to differ between bipolar disorder and general population groups. When alpha levels were corrected for multiple univariate comparisons, the average level of three variables (self esteem, positive affect, depression) and the variability of six variables (sleep efficiency, fragmentation index, relative amplitude, self esteem, negative affect, depression) remained significantly different between the groups. Lower self esteem, lower positive affect, higher depression and greater variability in sleep efficiency, fragmentation index, relative amplitude, self esteem, negative affect, and depression were evident in bipolar disorder.

4.9 Summary of group comparisons

Comparison of diathesis vulnerability, behaviour, self esteem and affect measures suggested differences existed between bipolar disorder and the general population across the average level and variability of several measures used in the current study. Parametric group comparisons were conducted over 14 days and repeated over longer time periods for bipolar disorder participants. Non-parametric comparisons were conducted over 14 days to check the impact of violating parametric assumptions. Although significant differences between groups changed across these statistical comparisons, consistencies emerged in the disturbances observed in the average level and variability of certain measures. Group comparisons over longer time periods in bipolar disorder should be considered tentative since differences observed may have been an artefact of using different monitoring periods across participant groups. Non-parametric analyses were considered more reliable for variables with extreme skewness and kurtosis scores for the sample distribution (level of negative affect and depression, variability in night waking and sleep efficiency). Thus to summarise, the more robust group differences observed with parametric and non-parametric analyses over 14 days, corrected for multiple comparisons, were lower self esteem and positive affect, higher negative affect and depressed ratings, and greater variability in night waking, sleep efficiency and self esteem in bipolar disorder.

4.10 Time series analyses of bipolar disorder participants

Time series analyses were conducted to further investigate variability in bipolar disorder in terms of how measures changed across time. Variables found to significantly differ between the bipolar disorder and general population groups were subjected to time series analyses: sleep efficiency; night waking time; self esteem; positive affect; negative affect; and depressed ratings. In addition, although elated ratings did not differ significantly between the groups over a 14 day period, it was considered important to investigate elated

ratings across time in a bipolar disorder sample. Time series analyses included plotting the data across time, conducting autocorrelation analyses and then cross-correlation analyses. Time series were collapsed to remove days with missing data; time series analyses cannot be conducted on series that have missing data points.

Example plots for one bipolar disorder participant's actigraph estimation of night waking and sleep efficiency over 24 weeks (a collapsed time series of alternate 2 week periods that comprised a total 82 nights with 2 missing nights removed) and self esteem ratings over 24 weeks (a collapsed time series of 161 days with 7 days with missing data removed) are displayed in Figures 4.2, 4.3 and 4.4. Greater variability in night waking, sleep efficiency and self esteem had been observed in bipolar disorder compared to the general population. Time series plots of these measures suggested frequent variation across time. Associations between night waking and sleep efficiency can be clearly observed in Figures 4.2 and 4.3 where this participant evidently had several days of disturbed sleep.

Time series analyses were repeated for each participant's longest consecutive time series to check the impact of collapsing the data set. Autocorrelation analyses assessed the association of ratings from one day to the next for each measure; a partial autocorrelation function (PACF) was used, with effects of smaller time lags removed. Cross-correlation analyses investigated associations across time between the measures. Difference transformations were applied to remove the serial dependency of measure before cross-correlations were computed. Further description of the time series analyses methodology is provided in section 3.5.7. The following sections provide the results of autocorrelations and cross-correlations of sleep, self esteem and affect measures.

Figure 4.2: Time series plot of night-to-night actigraph estimation of night waking in a participant with rapid cycling disorder

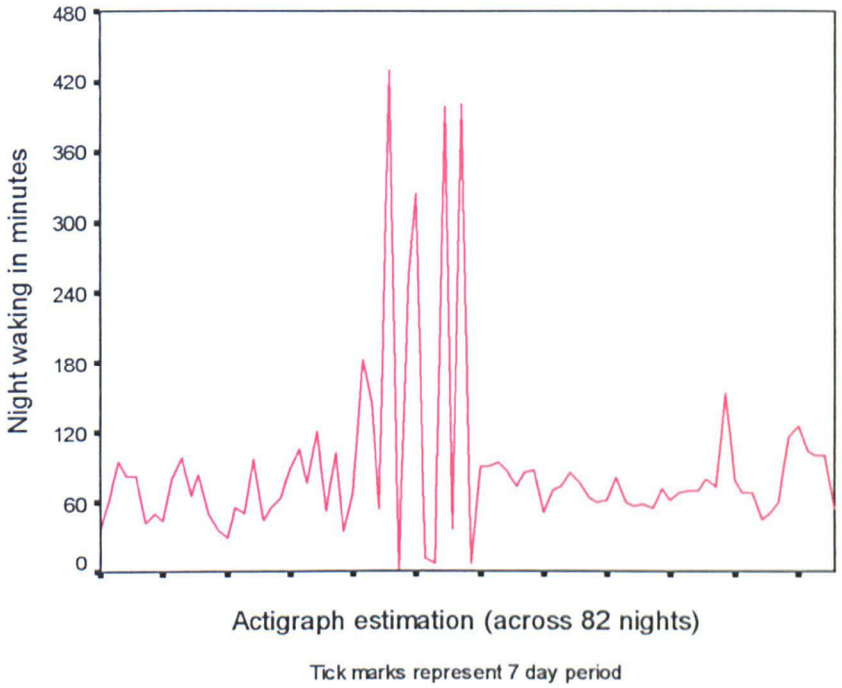


Figure 4.3: Time series plot of night-to-night actigraph estimation of sleep efficiency in a participant with rapid cycling disorder

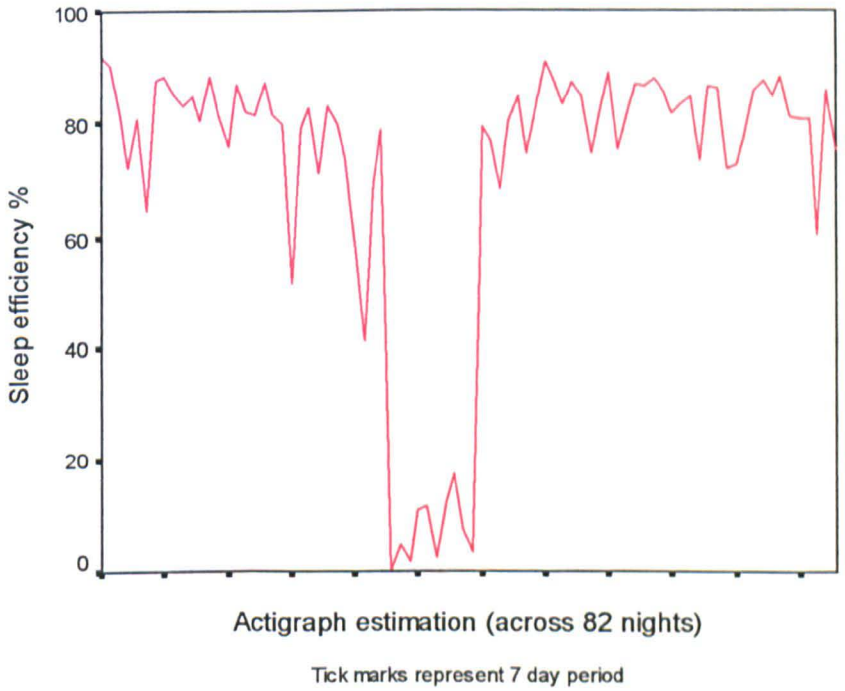
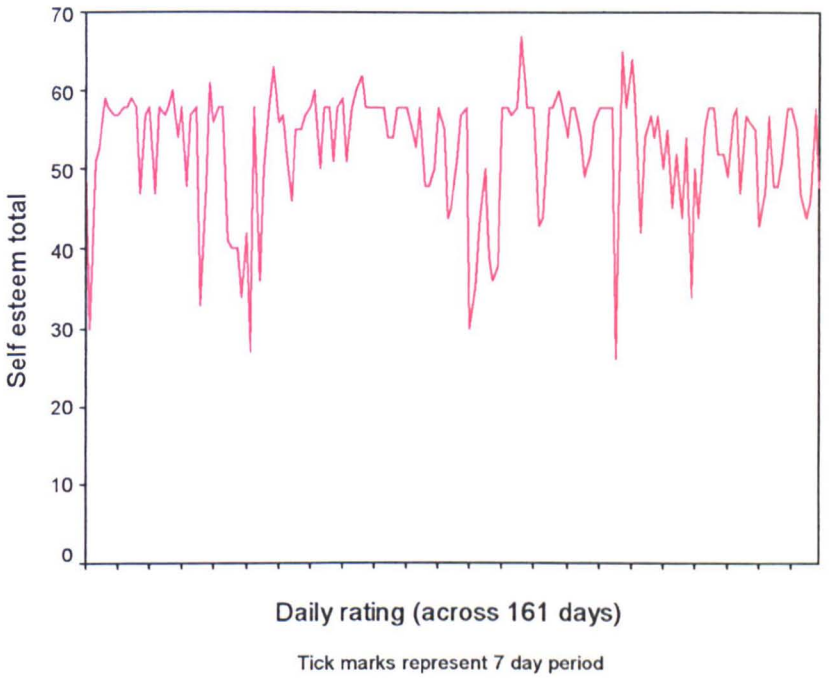


Figure 4.4: Time series plot of day-to-day self esteem ratings in a participant with rapid cycling disorder



4.10.1 Autocorrelations of sleep measures

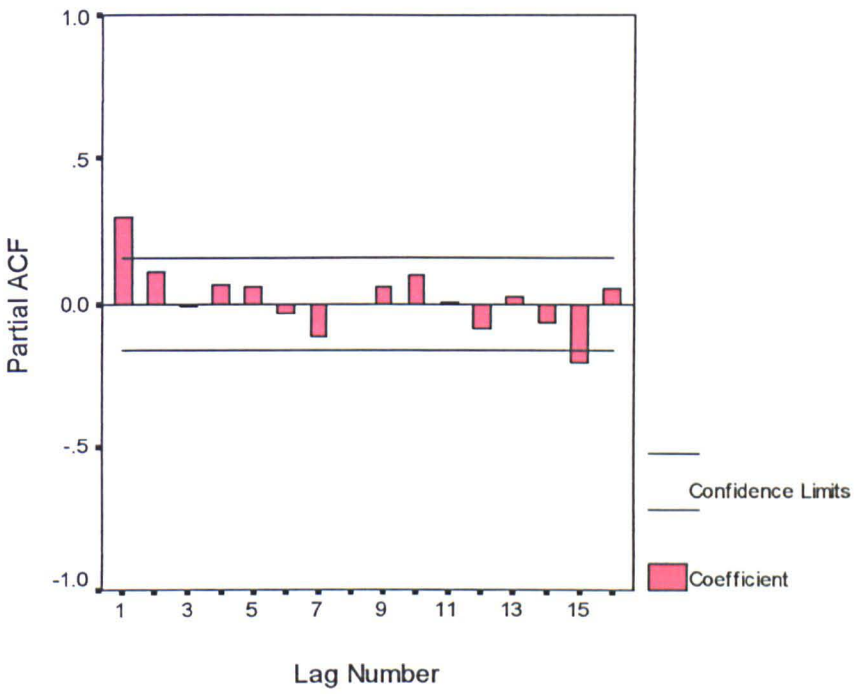
Partial autocorrelation plots for night-to-night sleep efficiency and night waking time were conducted for 15 participants with bipolar disorder; five remaining participants with bipolar disorder did not undergo actigraph monitoring of the sleep-wake cycle. The collapsed time series of these 15 participants was a median 27 days (range 7 to 82 days). The longest consecutive time series for sleep measures was a median 14 days (range 6 to 27 days). The PACF plots for sleep efficiency showed positive lags for six participants, three of these participants had also displayed positive lags for night waking time. Positive lags show dependency in the measure across days. For instance, a one day lag would suggest that night waking one night was influenced by night waking the previous night. When each participant's longest consecutive time series was subjected to PACF analysis, none of the participants displayed positive lags for sleep efficiency. The PACF plots for night waking time showed positive lags for six participants; 60% of participants displayed no significant night-to-night association for night waking time. When the longest consecutive time series

for each participant was subjected to PACF analysis, only one participant displayed a significant one day lag for night waking time. Thus, partial autocorrelations for night waking time and sleep efficiency for participants with bipolar disorder show no consistent serial dependency from one night to the next night. In other words, the time spent awake and the sleep efficiency for a specific night did not appear to impact on night waking or sleep efficiency for any following nights in most of the participants with bipolar disorder.

4.10.2 Autocorrelations of self esteem and affect measures

Partial autocorrelations were conducted for 19 participants for self esteem as one participant only completed the self esteem questionnaire on one occasion. The median collapsed time series was 30 days for self esteem (range 5 to 161 days). The longest consecutive time series for self esteem was a median 14 days (range 3 to 42 days). The self esteem PACF plots for the collapsed time series showed positive lags for five of the participants. An example of a participant's partial autocorrelation plot of self esteem is provided in Figure 4.5. A positive lag one effect was evident for one participant with a 42 day consecutive time series for self esteem ratings. No consistent association for the 19 participants was observed for self esteem ratings across days.

Figure 4.5: Partial autocorrelation function of self esteem in a participant with rapid cycling disorder



Partial autocorrelations were conducted for 20 participants for positive affect, negative affect, depressed, and elated ratings. The median collapsed time series was 35 days for affect (range 8 to 163 days). The longest consecutive time series for affect measures was a median 14 days (range 2 to 28 days). The positive affect PACF plots indicated nine participants had positive lags for their collapsed time series; a positive lag one effect was evident for one participant with a 70 day consecutive time series for positive affect ratings. The negative affect PACF plots for the collapsed time series showed positive lags for ten of the participants, whilst only two of these participants displayed a positive one day lag for the consecutive negative affect time series. Five participants had positive lags for elated ratings, with three participants having significant positive lags over the consecutive elated time series. Finally, ten participants showed positive lags for their collapsed time series for depressed ratings. Four participants also had positive lags for the consecutive time series

for depressed ratings. No consistent associations for the 20 participants were observed for the four affect measures across days.

In summary, most lags displayed in the PACF plots for self esteem and affect were within the 95% confidence limits. Although 25 to 50% of participants displayed significant partial autocorrelations, there was no consistent pattern to the autocorrelations observed. In particular, participants with longer time series did not appear any more likely to have positive lags across time. Since the majority of lags were within the 95% confidence limits for most participants, there did not appear to be any consistent serial dependency of self esteem or affect ratings from day-to-day. Stronger associations within measures across time had been hypothesised in bipolar disorder in line with previous findings. For instance, stronger associations of affect across days have been suggested by the observation of slower affect recovery following life stress in mood disorders (Goplerud & Depue, 1985; Peeters et al, 2003).

4.10.3 Cross-correlations of sleep and affect measures

Although no consistent serial dependency was identified by the autocorrelation plots for any variable, the autocorrelation values did differ from zero. This indicated the data were not completely independent across time. As such, one day difference transformations were conducted to remove any underlying serial dependency. Differencing also makes a time series stationary, an essential component of cross-correlation analysis. Following these transformations, the partial autocorrelation analyses were repeated to check the impact of transforming the data. A one day difference transformation was effective in removing positive lags for each variable, which then enabled cross-correlations to be computed.

Fifteen participants with bipolar disorder had completed actigraph monitoring and had sleep data available. However, cross-correlations were only able to be conducted for measures that varied across time. Five participants had constantly rated elation as 'very slightly or not at all.' Although two participants had constantly rated depression as 'very slightly or not at all,' one of these participants did not have sleep data available either. Consequently, cross-correlations of sleep measures that included elated ratings were conducted for 10 participants; cross-correlations that included depressed ratings were conducted for 14 participants.

Elated and depressed ratings were subject to cross-correlation analyses with night waking and sleep efficiency to investigate associations between these sleep measures and bipolar mood ratings. Associations between elation and sleep measures were not consistent across participants (N=10 participants with bipolar disorder). There was no significant cross-correlation between night waking and elation for five participants; the remaining five participants displayed significant cross-correlations with no distinct pattern. Six participants had no significant cross-correlation between sleep efficiency and elation; there was no pattern identified for the four participants with significant correlations. Similarly, no consistent associations between depression and sleep measures were identified across participants (N=14 participants with bipolar disorder). Eight participants displayed no significant cross-correlation between night waking and depressed ratings. Six participants had significant cross-correlations with no consistent pattern. Nine participants had no significant cross-correlations between sleep efficiency and depressed ratings, while the remaining five participants had a range of significant cross-correlations that were inconsistent. Thus evidence in this small sample of participants with bipolar disorder suggests there were no consistent associations between sleep measures and elated or depressed ratings across inter-episode periods.

4.10.4 Cross-correlations of self esteem and affect measures

Elated and depressed ratings were subject to cross-correlation analyses with positive affect, negative affect and self esteem. Self esteem was then cross-correlated with positive and negative affect. Finally, cross-correlations of positive and negative affects were conducted for participants. As with cross-correlations of sleep and affect measures, one day difference transformations were conducted to remove any underlying serial dependency. Partial autocorrelation analyses were then repeated to check the impact of transforming the data. One day difference transformations were effective in removing positive lags for the variables. Cross-correlations were conducted, for each participant, on the transformed time series for each measure. Twenty participants had daily ratings of affect whilst 19 participants had daily self esteem ratings. However, five participants had constantly rated elation as 'very slightly or not at all' and two participants had constantly rated depression as 'very slightly or not at all.' Consequently, the number of participants in cross-correlations of self esteem and affect varied from 14 to 20 participants, depending on scores available.

Associations between depression ratings and positive and negative affect were investigated with cross-correlation analyses (N= 18 participants with bipolar disorder). Ten participants (56%) displayed significant negative zero lag correlations between depression and positive affect. A significant zero lag cross-correlation indicates the level of one variable is associated with the level of the second variable on the same day. In addition, six participants showed depression/positive affect associations across time. Fifteen participants (83%) displayed significant positive zero lag correlations between depression and negative affect, with seven participants showing depression/negative affect associations across time. Over half the participants were observed to have depression ratings that were correlated with same day positive and negative affect ratings. Thus, whilst over half of the

participants rated depression and positive affect inversely on the same day, most participants rated same day depression and negative affect ratings consistently.

Associations between elation ratings and positive and negative affect were investigated with cross-correlation analyses (N= 15 participants with bipolar disorder). Seven participants (47%) displayed significant positive zero lag correlations between elation and positive affect; five participants showed elation/positive affect associations across time. Three participants displayed significant positive zero lag correlations between elation and negative affect, whilst one participant displayed a significant negative zero lag correlation. Lastly, six participants showed varying associations between elation and negative affect across time. Accordingly, associations between elated ratings and positive and negative affect ratings across time were not consistent across participants.

Daily positive and negative affects were cross-correlated concurrently to investigate their independence (N=20 participants with bipolar disorder). Research evidence has indicated conflicting positive affect-negative affect associations, with some reports indicating independence and others indicating a negative correlation. In the current study, eight participants (40%) displayed a significant negative zero lag correlation between PA and NA, whilst two participants (20%) displayed a significant positive zero lag correlation. Furthermore, six participants showed associations between NA and PA across time. Thus, whilst some participants showed PA-NA associations across the same day, no consistent association between positive and negative affect ratings was identified for the majority of participants.

Finally, the association between self esteem and affect variables was investigated. Self esteem was cross-correlated with positive affect, negative affect, and elation and depression

ratings. An example of a participant's cross-correlation plot for self esteem and depression ratings is displayed in Figure 4.6. Eight participants (42%) displayed significant positive zero lag correlations between self esteem and positive affect. Nine participants showed associations between self esteem and positive affect across time. Seven participants (37%) displayed significant negative zero lag correlations between self esteem and negative affect, whilst five participants showed associations between self esteem and negative affect across time. Significant positive zero lag correlations between self esteem and elated ratings were evident for four participants; a further participant displayed a significant negative zero lag correlation. Six participants displayed negative zero lag correlations for self esteem and depressed ratings. These findings suggest self esteem on a given day was not consistently associated with elated/depressed ratings across participants with bipolar disorder. Thus, cross-correlation evidence indicated whilst some participants showed associations between self esteem and affect for a given day and over time, others displayed no significant association. Cross-correlation observations are summarised in Table 4.15. In line with mood-state hypotheses that posit stronger cognition-mood associations in mood disorders, (e.g. Teasdale, 1988) and previous reports of self esteem associations with mania and depression (e.g. Lyon et al, 1999), self esteem-affect associations had been expected to occur across time in the current study. However, no consistent association between self esteem and affect was identified for a majority of participants with bipolar disorder.

Figure 4.6: Cross-correlation of self esteem and depressed ratings in a participant with rapid cycling disorder

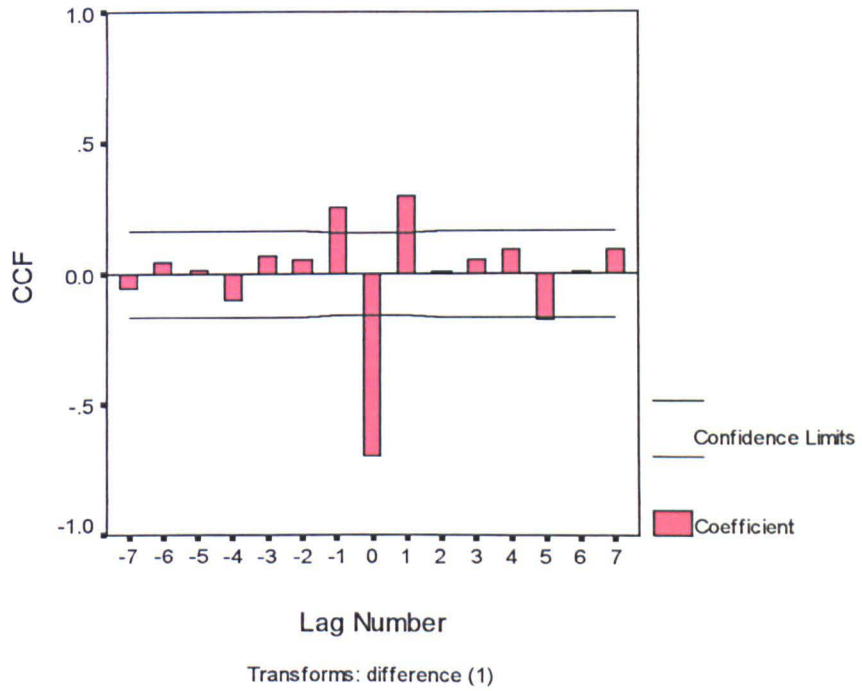


Table 4.15: Summary of cross-correlations between measures in bipolar disorder

Cross-correlation on same day	% of participants	Type of association
SE-PA	42%	Positive
SE-NA	37%	Negative
Depression-SE	32%	Negative
Depression-PA	56%	Negative
Depression-NA	83%	Positive
Elation-SE	21%	Positive
Elation-PA	47%	Positive
Elation-NA	20%	Positive

4.10.5 Summary of time series analyses in bipolar disorder

The daily scores for night waking, sleep efficiency, self esteem, positive affect, negative affect, elated, and depressed ratings were plotted across time for participants with bipolar disorder. Partial autocorrelations for each measure were conducted to identify associations across time. In particular, strong associations within measures across adjacent nights had been expected in line with theoretical postulation (e.g. Wehr, 1987) and previous observations of delayed affect recovery (e.g. Goplerud & Depue, 1987). Although some participants did display associations across time, no consistent serial dependency was observed across participants for the sleep, self esteem and affect measures. Furthermore, when measures were cross-correlated, few consistent associations were identified across most participants with bipolar disorder. Strong associations between affect and sleep and between affect and self esteem had been expected, in line with mood-state hypotheses (e.g. Teasdale, 1988).

4.11 Variability comparison of bipolar disorder participants

Variability may be considered a clinically useful measure if associated with vulnerability to relapse in bipolar disorder. The study hypothesis that greater variability would be associated with increased vulnerability to relapse was investigated through comparison of admission dates. The first admission dates following study participation of the twenty individuals with bipolar disorder were obtained in April 2005 from Forth Valley Primary Care NHS Trust Medical Records. The follow up period ranged from 38 to 44 months due to staggered start dates of study participation. Eight (40%) participants had a hospital admission across an approximate three year follow up period. The median time to first admission for these eight participants was 284 days (range 40 to 1240 days). Associations between admission and variability in measures that differed between the bipolar disorder and general population groups were investigated: variability in self esteem, night waking time

and sleep efficiency. Variability for each measure was calculated as the standard deviation of scores across the monitoring period for each participant. Low and high variability groups were categorised according to a median split of variability scores; participants with variability scores below the median score were categorised as low variability; participants above the median score were categorised as high variability.

Group differences in the number of admissions to hospital between high and low variability subgroups were investigated with non-parametric analyses (Appendix L). Nineteen participants were categorised into low SE and high SE groups; one participant with bipolar disorder had completed the self esteem questionnaire on only one occasion and thus had no SE variability data available. The difference in the number of admissions between SE variability groups was not statistically significant ($p= 0.570$, one tailed Fisher's exact test). Admission rates in high and low variability for night waking and sleep efficiency were then compared. Fifteen participants were categorised into low and high night waking or sleep efficiency groups according to a median split. Five participants with bipolar disorder had no sleep measures variability data available over their monitoring period. Differences in the number of admissions between low and high variability subgroups were not significant for night waking ($p= 0.405$, one tailed Fisher's exact test) or for sleep efficiency ($p= 0.214$, one tailed Fisher's exact test).

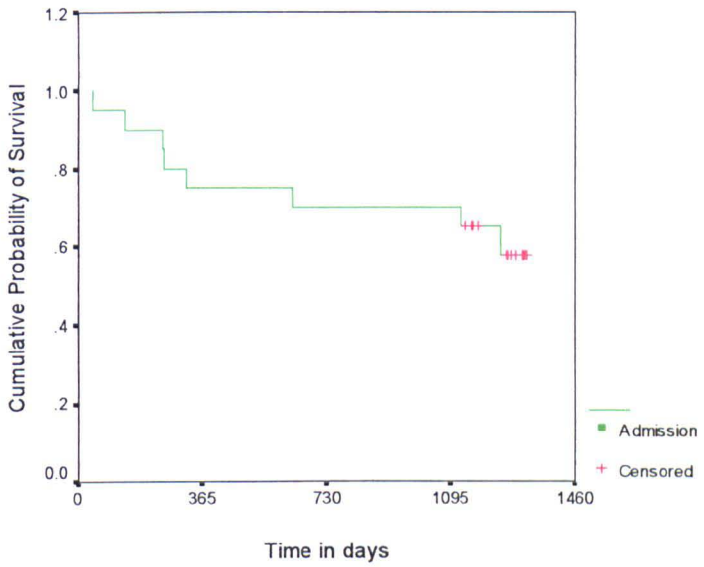
In summary, results suggested greater variability was not associated with increased vulnerability to relapse. The three measures (self esteem, night waking time, sleep efficiency) found to be significantly more variable in bipolar disorder compared to the general population were not associated with risk of subsequent admission to hospital. However, due to the small sample size and variable length of follow-up for bipolar disorder participants, contingency tables may not in themselves fully explore the significance of

variability in bipolar disorder. Instead of investigating the association between variability and the occurrence of relapse, it may be more clinically useful to investigate the association between variability and time to relapse in bipolar disorder. In order to address this issue, exploratory survival analysis was subsequently conducted for the present study.

4.12 Exploratory Kaplan-Meier survival analysis of variability in bipolar disorder

The Kaplan-Meier approach to survival analysis was used since the exact date of first admission to hospital over the follow up period was obtained from Medical Records for each participant. Eight of the twenty participants with bipolar disorder experienced an admission following study participation. The survival rate was calculated each time an admission occurred. Since participants were enrolled into the study across several months, participants had varying lengths of follow up. The follow up period for the twenty participants ranged from 1139 to 1319 days. There were four censored cases that occurred between the seventh admission at 1126 days and the last admission at 1240 days. The remaining eight participants were censored across 1258 to 1319 follow up days. A Kaplan-Meier survival curve for admission to hospital was subsequently plotted in Figure 4.7 (Cumulative survival rates for admission are provided in Appendix M). Censored cases were marked on the plot and were not included in the calculation of the cumulative survival rate. The observed 40% admission rate was lower than rates reported by previous research investigations of relapse rate in bipolar disorder. This suggests the sample of participants with bipolar disorder in the current study comprised individuals who experienced better outcome over a three year follow-up than outcomes more typically representative of this clinical population.

Figure 4.7: Kaplan-Meier survival curve for admission



Variability in bipolar disorder had been hypothesised to be associated with heightened risk for relapse. With consideration of the small sample size of bipolar disorder participants and the small number of outcomes (admissions) in the current study, it was decided not to investigate the association between outcome and the variability of each measure. Instead, the three measures (self esteem, night waking, and sleep efficiency) observed to vary to a greater extent in bipolar disorder across a 14 day period compared to the general population were selected. The significance of self esteem, night waking and sleep efficiency variability and subsequent admission to hospital were investigated with log-rank tests. The results are displayed in Appendix M. The Mantel-Cox log-rank tests suggested continuous measures of variability in self esteem, night waking and sleep efficiency predicted admission. When diagnostic strata were considered, high self esteem variability predicted admission specifically in bipolar I disorder. Participants were then categorised into low and high variability subgroups for self esteem, night waking and sleep efficiency. Log-rank tests were repeated with these categorical groups. Results suggested no significant association between variability and subsequent admission. When diagnostic strata were considered, no

significant associations between diagnosis and categorical variability groups emerged for prediction of admission. The cumulative probabilities of survival for self esteem, night waking and sleep efficiency variability subgroups were calculated and plotted (Appendix M). All Kaplan-Meier findings should be considered tentative due to the small sample size, particularly when analysed by diagnostic strata.

4.13 Exploratory Cox regression of variability in bipolar disorder

Cox regression analyses investigated the effect of several variability measures upon the time to first admission in bipolar disorder. Gender, diagnosis and age were entered into the first block of the Cox regression model. Given the small number of participants with bipolar disorder, it was decided not to enter all variables that may impact on relapse. The continuous covariates in the second block of the Cox regression included variability in the four affect measures: positive affect variability; negative affect variability; elated variability; and depressed variability. Variability measures found to differ between bipolar disorder and general population groups were also included as covariates: self esteem variability; night waking time variability; and sleep efficiency variability. Fourteen participants were included in this analysis (N=6 admissions, N=8 censored). A forward stepwise (conditional LR) method identified age and sleep efficiency variability as significant predictors of subsequent admission in bipolar disorder; increasing age and high variability in sleep efficiency predicted earlier admission. These results are displayed in Table 4.16.

Table 4.16: Cox regression significant predictor variables

Predictor variable	df	Exp(B)	95% CI for Exp(B)		p
			Lower	Upper	
Age	1	1.320	1.068	1.631	0.010
Sleep efficiency variability	1	1.385	1.038	1.849	0.027

Subsequently, the Cox regression analysis was repeated using categorical high and low variability participant subgroups for seven covariates: self esteem, night waking, sleep efficiency, positive affect, negative affect, elated, and depressed. This supplementary analysis was to check if any outliers had skewed the findings of the continuous covariate Cox regression. With Cox regression of categorical covariates, age was the only variable identified to predict admission in bipolar disorder (Exp(B) = 1.151, 95% CI 1.030-1.286, p=0.013). Cox regression analyses with such a small participant sample were exploratory, so inconsistent findings across continuous and categorical covariate analyses was perhaps not unexpected. A tentative finding was variability in sleep efficiency, measured continuously, predicted first admission in bipolar disorder across a three year follow up.

4.14 Summary of results for the present study

The aims of the current study were to investigate the average level and variability of diathesis vulnerability, behaviour, self esteem and affect measures in general population and bipolar disorder participants and to assess the clinical importance of variability in bipolar disorder. When average level and variability of measures across a 14 day period were compared between bipolar disorder and general population groups, significant differences emerged. After controlling for multiple comparisons, lower positive affect, higher negative affect, higher depressed ratings, lower self esteem, and greater variability in night waking time, sleep efficiency and self esteem were observed in bipolar disorder compared to the

general population. Overall, findings suggested averaged self esteem and affect measures differed between bipolar disorder and general population groups whilst averaged biological and behaviour measures did not differ over a 14 day period. Variability in self esteem, night waking time and sleep efficiency also differed between groups whilst variability in the other biological, behaviour and affect measures did not differ. Time series analyses indicated self esteem and affect measures were correlated for some participants with bipolar disorder across the same day, but no associations across time between measures were identified. Finally, a three year follow-up suggested variability in self esteem and sleep efficiency may predict first admission to hospital for participants with bipolar disorder.

Chapter 5 Discussion

The present study prospectively investigated whether an underlying dysregulation in diathesis vulnerability, behaviour, self esteem, and affect measures could be identified during inter-episode periods in bipolar disorder. Greater variability was hypothesised to occur in bipolar disorder, compared to general population participants, as variability was posited to reflect the underlying vulnerability of the disorder. Night waking, sleep efficiency and self esteem were observed to be more variable day-to-day in bipolar disorder across a prospective 14 day period. Furthermore, lower average levels of self esteem and positive affect, and higher average levels of negative affect and depressed ratings were observed in bipolar disorder across 14 days. These findings suggest that individuals with bipolar disorder differ from the general population across sleep, self esteem and affect measures, even during inter-episode periods.

The association between the observed dysregulation during inter-episode periods in bipolar disorder and relapse was then investigated by follow up of subsequent admission to hospital. The observed 40% admission rate at an approximate three year follow up was lower than expected. Previous research evidence had reported rates of relapse in bipolar disorder at 65% over two years (Silverstone et al, 1998) and 73% over five years (Gitlin et al, 1995). Reasons for this low admission rate in the current study may include the potential for early intervention with individuals who regularly attended a Lithium Clinic. Also, the admission rate in the current study does not take into account those individuals who experienced an acute episode that was managed without requiring admission. Variability in sleep efficiency and self esteem were suggested to predict earlier time to admission. Thus, a tentative conclusion from the current study's findings was that variability in bipolar disorder may play a role in determining relapse.

5.1 Average level and variability of sleep measures

The present study reported sleep disturbances occur in bipolar disorder during inter-episode periods. Consistent differences in the variability of sleep measures emerged between bipolar disorder and the general population. Trends towards sleep disturbance in bipolar disorder were suggested in terms of lower sleep efficiency, greater night waking and fragmented sleep. However, when multiple comparisons were considered, averaged sleep measures were not found to differ across a 14 day period or over longer monitoring periods for bipolar disorder. Differences between bipolar disorder and the general population in sleep variability, but not averaged sleep measures, may suggest chaotic dysregulation rather than an impoverished sleep-wake cycle in bipolar disorder. Sleep disturbance in bipolar disorder was suggested by the present study to involve greater variability from night-to-night rather than consistently poor sleep when compared to the general population.

No differences in average levels of sleep measures between bipolar disorder and the general population was a finding consistent with other research. Previous studies over five days using EEG measures (Knowles et al, 1986) and actigraph sleep measures (Millar et al, 2004) have also reported no differences in average sleep measures between individuals with bipolar disorder and the general population. Millar et al (2004) did report some trends towards lower sleep efficiency, greater sleep latency and sleep duration in bipolar disorder. Indeed, a more recent actigraph investigation over eight days reported increased time in bed and reduced sleep efficiency in bipolar disorder compared to the general population (Harvey et al, 2005). Since samples recruited by the present study and other actigraph studies (Millar et al, 2004; Harvey et al, 2005) were relatively small, trends towards objective sleep disturbance in bipolar disorder during inter-episode periods, measured by actigraphy, may warrant further investigation. Thus to date, preliminary evidence suggests average sleep measures over brief time periods may differ between bipolar disorder and general population

samples. In the current study, however, more robust differences were observed in the variability of sleep measures across time.

Greater night-to-night variability's of night waking and sleep efficiency were observed in bipolar disorder participants across 14 days. This suggested that individuals with bipolar disorder displayed sleep disturbance when compared to individuals from the general population. Furthermore, since individuals with bipolar disorder were not experiencing an acute manic episode, this may suggest ongoing biological dysregulation across inter-episode periods in bipolar disorder. Participants with bipolar disorder had been included in the study if they were not currently experiencing mania. When variability in sleep was measured across each bipolar disorder participant's full monitoring period, greater variability in sleep efficiency and the fragmentation index were observed in bipolar disorder compared to the general population. Trends towards greater variability in night waking and sleep duration were also suggested in bipolar disorder across a longer monitoring period. The observed greater variability in sleep measures may suggest a general dysregulation or instability in the sleep-wake cycle in bipolar disorder.

Greater night-to-night variability of night waking and sleep efficiency in bipolar disorder suggests sleep disturbance occurs during inter-episode periods as well as being symptomatic of acute bipolar episodes. Furthermore, the presence of ongoing sleep disturbance in bipolar disorder suggests a biologically vulnerable sleep-wake cycle that may be less able to withstand further disruption compared to the more stable cycle displayed in the general population. This vulnerability may explain why sleep disturbance can have a clinically significant impact on mood in bipolar disorder (e.g. the precipitation of bipolar relapse by long distance flights; Jauhar & Weller, 1982). The presence of sleep disturbance during

inter-episode periods is consistent with the circadian rhythm disruption diathesis-stress model of bipolar disorder.

Differences in the variability of sleep measures between bipolar disorder and the general population has also been suggested by previous research. A recent actigraph study over five days (Millar et al, 2004) observed differences in sleep variability between bipolar disorder and the general population. Millar et al (2004) observed greater variability in actigraph and subjective estimates of sleep duration in bipolar disorder whilst actigraph measurement of night waking time variability and subjective sleep latency and sleep efficiency variability's were significantly greater in bipolar disorder participants (N=19 bipolar disorder, in remission, N=19 general population; Millar et al, 2004). Thus, evidence from the current study and Millar et al (2004) suggests sleep disturbance, as indicated by night-to-night variability, may be observed in individuals with bipolar disorder during inter-episode periods. A tentative conclusion is that this sleep disturbance may be symptomatic of possible chronic circadian rhythm dysregulation in bipolar disorder.

The current study observed sleep disturbance was associated with subsequent relapse in bipolar disorder. Variability in sleep efficiency was suggested as a predictor of earlier time to admission. This is consistent with previous literature review findings that suggested sleep disturbance may be a risk factor for relapse in mood disorders (Gillin, 1998; Jackson et al, 2003). A small prospective study reported increased sleep disturbance occurred prior to relapse in major depression; individuals who relapsed were compared with individuals who did not relapse, matched for age, gender and time from last relapse, (N=14; Perlis et al, 1997). Further prospective investigation of the sleep-wake cycle and long term course may clarify which aspects of sleep disturbance may be associated with subsequent relapse in bipolar disorder.

5.2 Average level and variability of circadian and social rhythm measures

The current study observed no differences in either the level or variability of circadian rhythm measures over 14 days between bipolar disorder and general population participants. A trend towards greater variability in relative amplitude was observed in bipolar disorder, but did not remain significant after controlling for multiple comparisons. In line with theoretical postulation that circadian rhythm disruption may cause relapse in mood disorders (e.g. Healy and Williams, 1988, 1989), the present study had hypothesised that an underlying biological vulnerability to bipolar disorder may be present during inter-episode periods; disturbances in circadian rhythms were proposed to indicate biological dysregulation. Reasons for the ongoing sleep disruption observed in bipolar disorder may have included homeostatic regulation problems or faulty circadian timing. Indeed, when participants with bipolar disorder were considered over their full monitoring periods, greater variability in the relative amplitude of the sleep-wake cycle was observed after controlling for multiple comparisons. Relative amplitude describes the wave of the sleep-wake cycle across day and night in terms of activity levels. Greater variability may suggest that the waves of rest and activity in individuals with bipolar disorder were more unstable. Thus, some disturbance in circadian rhythms may be tentatively suggested to occur over longer time periods in bipolar disorder. Evidence, however, suggested no underlying circadian rhythm disturbance across a brief 14 day period in bipolar disorder, as measured by actigraphy.

There has been little actigraph research conducted to date that investigated circadian rhythm disruption in mood disorders. Two studies have observed circadian rhythm disturbances in seasonal affective disorder samples. A study by Teicher et al (1997) reported lower interdaily stability occurred over a three day period in seasonal affective disorder compared to the general population (N=25 unipolar or bipolar depression with seasonal pattern; N=20

general population). This suggests less regularity of the rest-activity rhythm to environmental zeitgebers from day-to-day in individuals with seasonal affective disorder. A more recent study (N=17 seasonal affective disorder, N=17 general population; Winkler et al, 2005) reported a lower level of relative amplitude in seasonal affective disorder; no differences were observed in either interdaily stability or intradaily variability between seasonal affective disorder and general population samples. Actigraph research has also observed circadian rhythm disruption in Alzheimer's disease; lower interdaily stability and higher intradaily variability occurred in individuals with Alzheimer's disease compared to general population individuals (Witting et al, 1990). Similar disturbances were expected to be observed in the current study. Actigraphy is a valid measure of circadian rhythms, so possible reasons for non-significant findings in the current study include the sample size and length of monitoring period, particularly since relative amplitude disturbance, but not attenuation, showed trends towards greater variability across 14 days whilst this greater variability was evident across a longer time period in bipolar disorder. It also remains possible that circadian rhythm disturbance of the rest-activity rhythm does not occur during inter-episode periods in bipolar disorder.

The timing of circadian rhythms may be maintained by several environmental and social zeitgebers, including light and social rhythm regularity. Disturbances in these zeitgebers may thus lead to disruption in circadian rhythms; zeitgeber disturbance may be an incipient indicator of future circadian rhythm disturbance. In the present study, the level and variability of circadian rhythm measures over 14 days were not observed to differ between bipolar disorder and the general population. The zeitgeber monitored in the present study was daily social rhythms. When the level and variability of social rhythm measures were compared, similar to circadian rhythm findings, no differences emerged between participant groups over a 14 day period. No evidence of social rhythm disruption was evident across

longer monitoring periods in bipolar disorder either, after controlling for multiple comparisons. Thus, the current study observed no disturbances in social rhythms during inter-episode periods in bipolar disorder.

Previous research evidence, with a similar sample size to the current study, has shown social rhythm disturbances in mood disorder samples over longer monitoring periods. A research study with a remitted depression sample suggested seven weeks of monitoring was required to obtain a representative estimate of an individual's level of social rhythm regularity, although two weeks monitoring was adequate for a general population sample (N=20 unipolar depression, N=15 general population; Monk et al, 1991). Although no disturbances in social rhythm regularity were evident across longer monitoring periods in bipolar disorder, ten of the twenty participants had completed less than seven weeks of social rhythms monitoring. This may have impacted on the results obtained. Therefore, perhaps longer monitoring periods across all participants would have provided a more accurate indication of whether social rhythm disturbance occurs in bipolar disorder over inter-episode periods.

Social rhythm regularity was not found to differ between bipolar disorder and the general population in the present study. Although research evidence has suggested lower social rhythm regularity in acute depression (Szuba et al, 1992; Brown et al, 1996), regularity has not been reported to significantly differ from the general population when depression is in remission (Monk et al, 1991). Since participants with bipolar disorder in the present study were monitored over a 14 day period during which no acute episodes occurred, it was consistent with these earlier findings that no group differences emerged. However, Ashman et al (1999) reported lower social rhythm regularity in rapid cycling bipolar disorder compared to the general population. Furthermore, Ashman et al found no variation in social

rhythm regularity for bipolar disorder participants across elated and depressed states suggesting lower regularity was not due to mood state. Thus, it remains unclear to what extent, if any, that social rhythms may change across euthymic, depressed and elated states in individuals with bipolar disorder. Findings from the present study add to the evidence that social rhythm regularity during inter-episode periods in mood disorders may not differ from the general population.

Similar regularity in social rhythms across bipolar disorder and general population groups suggested the participants with bipolar disorder maintained regular lifestyles. This was an interesting finding since bipolar disorder has been previously associated with reduced occupational functioning (Coryell et al, 1993; MacQueen et al, 2001). As work can be considered a regular zeitgeber, reduced occupational functioning could be expected to impact on social rhythm regularity in bipolar disorder. The Social Rhythm Metric recorded the activity time to 'start work, school, housework, volunteer activities, child or family care,' but no specific information on occupation activity was collected. However, only six (30%) of the bipolar disorder participants were known to be employed compared to eight (80%) of the general population participants. Moreover, some of the participants with bipolar disorder regularly attended structured group activities such as gardening and art classes at the Lithium Clinic. It is possible that this attendance had a positive effect on the regularity of social rhythms. This should be considered tentatively with further investigation necessary to investigate the potentially beneficial effect of attending structured activities at a Lithium Clinic on social rhythm regularity.

Greater variability of social rhythm regularity had been expected to occur in the bipolar disorder group. A previous study by Monk et al (1991) had reported greater variability in weekly social rhythm regularity in remitted depression compared to the general population.

In contrast, the present study found no differences in the variability of social rhythm regularity between bipolar disorder and the general population. Sample sizes from the current study and Monk et al's (1991) research were relatively small, suggesting more investigations into variability of social rhythms in mood disorders may be necessary to identify whether greater variability occurs across inter-episode periods, in comparison to the general population. Indeed, variability during inter-episode periods may differ between unipolar and bipolar disorders.

Investigation of the level and variability of daily activities suggested no group differences; number of daily activities completed was not found to differ between bipolar disorder and the general population in the present study. Previous research comparisons between general population and mood disorder samples have observed lower numbers of weekly activities performed in currently depressed (Brown et al, 1996) and rapid cycling bipolar disorder individuals (Ashman et al, 1999) but no differences in acutely depressed (Szuba et al, 1992) or remitted depressed individuals (Monk et al, 1991). Although the present study found no evidence that the number of daily activities completed differed between bipolar disorder and the general population, since ten participants with bipolar disorder had completed less than the seven weeks necessary to identify social rhythm 'traits' (Monk et al, 1991), longer monitoring periods across all participants may have been more effective in determining whether social rhythm disturbances exist during inter-episode periods in bipolar disorder.

5.3 Average level and variability of behavioural activation/inhibition measures

Although behavioural activation dysregulation theories (e.g. Depue et al, 1987) suggest the emotion systems of behavioural activation and inhibition would differ in bipolar disorder compared to the general population, no significant differences in either level or variability

were evident in the present study. Although behavioural activation and inhibition are posited to be biological systems, the systems were measured with a self report questionnaire about behaviour. The behavioural inhibition system (BIS) level and three behavioural activation system (BAS) subscale (reward responsiveness, drive, fun seeking) levels or their respective variability's across 14 days were not observed to differ between bipolar disorder and general population groups. Further investigation of behavioural activation and inhibition across longer monitoring periods in bipolar disorder also suggested the level and variability of these measures does not differ between bipolar disorder and the general population.

Earlier research evidence had suggested differences in behavioural activation and inhibition levels between mood disorder and general population individuals may exist. A study by Meyer et al (2001) reported higher cross-sectional levels of behavioural inhibition, BAS drive and BAS fun seeking in bipolar disorder participants compared to the general population; no significant group differences were observed in BAS reward responsiveness. However, it is possible that methodological factors, including the impact of cultural differences, may have contributed to the group differences reported; Meyer et al (2001) compared 59 American individuals with bipolar disorder with 729 Australians recruited from the general population by another study (Jorm et al, 1999). Furthermore, behaviour activation/inhibition measures were self-reported in individuals with bipolar disorder across a range of euthymic, depressive, mixed and manic states. The impact of grouping this spectrum of mood states on the level of behavioural activation/inhibition is uncertain. The directions of behavioural activation levels in mood disorders compared to the general population were contrary between Meyer et al (2001) and a more recent study (Kasch et al, 2002). Similarly to Meyer et al (2001), a study by Kasch et al (2002) observed higher cross-sectional levels of BIS in currently depressed participants compared to the general

population. In contrast, Kasch et al (2002) reported lower BAS reward responsiveness, BAS drive and BAS fun seeking. Thus, although preliminary cross-sectional evidence suggested differences in behavioural activation and inhibition may exist between mood disorders and the general population, direction of differences may be influenced by current mood symptoms. Indeed, the level of behavioural activation has been theoretically postulated to vary across mood states in bipolar disorder; high behavioural activation during mania and low behavioural activation during depression (Depue & Zald, 1993).

Three previous research studies addressed the associations between behavioural activation and inhibition with manic and depressive symptoms in mood disorder samples (Meyer et al, 1999, 2001; Kasch et al, 2002). Meyer et al's (1999) cross-sectional study reported the three BAS subscales were positively correlated with manic symptoms whilst negatively correlated with depressive symptoms in individuals at risk of developing a mood disorder. The BIS was also significantly correlated with depressive symptoms, but not manic symptoms. Meyer et al (2001) observed no significant cross-sectional correlations between BAS subscales and depressive/ manic symptom severity in bipolar disorder participants. However, a significant positive correlation was observed between BIS and depressive symptom severity; BIS level did not correlate significantly with manic symptom severity. Finally, Kasch et al (2002) reported significant negative cross-sectional correlations between depressive symptom severity and BAS subscale levels for the depressed participants; BIS level did not correlate significantly with depressive severity. Thus, evidence to date suggests higher behavioural activation may be associated with elation, lower behavioural activation with depression and higher behavioural inhibition with depression. However, findings across studies were not entirely consistent and generalisation may be limited by the diverse samples recruited.

If behavioural activation or inhibition does vary across different mood states in bipolar disorder, then greater variability would be evident in BIS and BAS across time. Variability across a 14 day period in behavioural activation or inhibition was not found to differ between bipolar disorder and general population groups in the present study. Two studies with mood disorder samples have also investigated associations between BIS/BAS and symptoms across time. Firstly, Kasch et al (2002) reported BIS and BAS were stable across initial and eight month follow up ratings in individuals with current major depression; changes in BIS/BAS ratings were not found to be associated with changes in depression severity. Secondly, Meyer et al's (2001) investigation of longitudinal associations between BIS/BAS and elation/depression observed no associations between behavioural activation and elation/depression across time. The level of behavioural inhibition was found to vary with depression, but not with mania. Thus, research to date has not provided compelling evidence that dysregulated behavioural activation exists in bipolar disorder.

If behavioural activation dysregulation does exist in bipolar disorder, then a possible methodological explanation for the lack of variability observed by research studies may be the measurement of behavioural activation. Since the BIS/BAS Scales is a trait measure that individuals rate how they feel generally and not for a specific time period, then it is perhaps unsurprising that variability across time has not been indicated. Furthermore, a recent theoretical proposal by Johnson et al suggested that it may not be the level of behavioural activation that differs over time but the occurrence of incentive cues that vary leading to symptoms of mania in bipolar disorder (Johnson et al, 2003). In particular, Johnson et al's (2000c) study observed increased symptoms of mania following goal attainment life events, which may be considered as reward responsiveness cues. Although a strong theoretical base led the hypothesised association between behavioural activation

and elation/depression in bipolar disorder, the present study did not provide any evidence to support the theory of behavioural activation system dysregulation in bipolar disorder.

5.4 Average level and variability of self esteem measures

The present study observed differences in the level and variability of self esteem between individuals with bipolar disorder during inter-episode periods and the general population. Participants with bipolar disorder reported lower levels of self esteem with higher day-to-day variability across a prospective 14 day period. These differences remained between groups when the level and variability of self esteem were considered for participants with bipolar disorder over their full prospective monitoring periods. Furthermore, when positive and negative self esteem subscales were investigated, both level and variability of the subscales differed between bipolar disorder and general population groups. This would suggest that general self esteem, rather than a specific dimension, differed in bipolar disorder during inter-episode periods compared to the general population.

The current finding of lower self esteem in bipolar disorder compared to the general population was consistent with previous research studies. Most investigations have reported lower self esteem levels in bipolar disorder, during inter-episode periods, compared to the general population (Shapira et al, 1999; Blairy et al, 2004; Serretti et al, 1999, 2005). A different level of self esteem in remitted bipolar disorder compared to the general population may suggest self esteem as an enduring cognitive vulnerability factor, with reduced self esteem associated with relapse in the disorder. A recent review reported the interaction between low self esteem and onset of depressive symptoms or episodes was not robust (Roberts & Monroe, 1999). However, since studies reviewed mainly comprised general population samples such findings may not necessarily reflect associations in clinical samples. A more recent study with a bipolar disorder sample, reported low self esteem

level was associated with onset of bipolar depression but not related to mania (Johnson et al, 2000b). Furthermore, preliminary evidence has suggested differences exist in self esteem levels across individuals categorised by bipolar mood state; self esteem was lowest in bipolar depression, highest in remission, whilst in hypomania, self esteem level occurred between the levels of depressed and remitted states (N=77 bipolar disorder; Scott & Pope, 2003). Thus, although low self esteem may occur across inter-episode periods in bipolar disorder, with few investigations of diathesis-stress associations, the clinical significance of low self esteem with regard to relapse in bipolar disorder is as yet unclear.

Research evidence has suggested that low self esteem may be a relative term which actually reflected intermediate responding. For instance, Baumeister et al (1989) reviewed self esteem sample distributions from 23 research studies with general population samples and observed a higher self esteem sample midpoint than the conceptual midpoint. Intermediate responding has also been observed in remitted bipolar disorder samples with higher mean self esteem levels than conceptual midpoints (Johnson et al, 2000b; Blairy et al, 2004; Serretti et al, 2005). The current study also observed an average self esteem level in bipolar disorder that was higher than the conceptual midpoint of Rosenberg's self esteem questionnaire. Self esteem levels higher than the conceptual midpoint suggest that although individuals do not have a high opinion of themselves, they do not necessarily have a negative view of themselves. When Likert response self esteem ratings were plotted for bipolar disorder and general population groups, descriptive differences between groups emerged. General population participants tended to 'agree' with positive self esteem statements and 'disagree' with negative self esteem statements. In contrast, participants with bipolar disorder had a wide range of responses to positive and negative self esteem statements, with no particular mode response (Appendix F provides distribution of rating

responses to self esteem. These findings may be usefully applied to targeted psychological interventions to improve self esteem levels, which may then reduce risk of relapse.

The current study observed group differences in both the level and variability of positive and negative self esteem measures. Lower levels of positive and negative self esteem were evident in bipolar disorder (higher scores indicated higher self esteem for both subscales due to application of reverse scoring). Moreover, higher variability's of positive and negative self esteem were evident in bipolar disorder. These findings suggested that general self esteem, rather than a specific dimension, was disturbed across inter-episode periods in bipolar disorder, compared to the general population. This was consistent with recent research that reported the Rosenberg self esteem questionnaire to be unidimensional with general population samples (Gray-Little et al, 1997; Greenberger et al, 2003). In particular, Greenberger et al (2003) reported the two-factor structure of the questionnaire was an artefact of positive and negative wording. Evidence from the current study may suggest that negative and positive self esteem may both be considered as cognitive vulnerability factors in bipolar disorder.

Greater variability in self esteem was observed in bipolar disorder compared to general population participants. Disturbances in self esteem occur during acute bipolar episodes, but this finding suggests that disturbances in self esteem may also exist during inter-episode periods in bipolar disorder. Greater variability in self esteem may be considered a cognitive vulnerability factor in the course of bipolar disorder, particularly if this instability could be associated with the course of the disorder. Indeed, self esteem variability across time was suggested to be of clinical importance in the current study. Greater self esteem variability predicted earlier admission in the subgroup of bipolar I disorder participants. Therefore,

tentative analyses suggest greater self esteem variability was associated with poorer outcome in bipolar disorder.

The current finding of greater self esteem variability in bipolar disorder compared to the general population is in line with previous research findings. Studies have reported self esteem variability as a predictor of depressive symptoms in general population samples (Roberts & Monroe, 1992; Kernis et al, 1998). Little research has been conducted into self esteem variability in bipolar disorder. The current study's findings that variability in self esteem was heightened in bipolar disorder and possibly associated with earlier relapse has indicated the importance of further investigations with clinical samples will be necessary to test the robustness of these findings.

5.5 Average level and variability of affect measures

The average affect levels of individuals from bipolar disorder across inter-episode periods differed from the general population. Lower positive affect and higher negative affect and depressed levels were evident in bipolar disorder across a 14 day period; elated levels were not found to differ. When participants with bipolar disorder were considered over their full monitoring period, group differences between positive affect and depression levels remained. Differences in the level of positive affect between bipolar disorder and the general population was consistent with the theoretical model of behavioural activation dysregulation in bipolar disorder. Behavioural activation has been theoretically related to positive and negative affects. Although behavioural activation disturbances were not evident in the current study, it is posited that the observed disturbances in affect may reflect chronic disturbance in an underlying affect regulation system.

Some investigations have suggested differences in affect between the working week and the weekend. Positive affect has been reported to be higher and negative affect lower, on weekends than weekdays (Stone et al, 1985; Clark & Watson, 1988; Kennedy-Moore et al, 1992). Observation of different levels of affect between groups in the present study may thus be limited if participant groups had different proportions of midweek days and weekend days. However, in the present study, when days of the week were considered, 71% of monitoring days were midweek days (Monday to Friday) and 29% were weekend days (Saturday and Sunday) for both bipolar disorder and general population groups. Consequently, a day of week effect was not responsible for the observation of different affect levels between groups.

The current study observed lower average levels of positive affect and higher levels of negative affect in bipolar disorder. A discrepancy with the findings of a prior prospective investigation of affect levels was noted. An experience sampling method study observed lower positive affect in bipolar disorder during inter-episode periods, but no difference in negative affect, compared to the general population (N=38 bipolar disorder, N=49 general population; Myin-Germeys et al, 2003). The inconsistency in observed negative affect level across the two studies would suggest further investigation is necessary to supplement this preliminary evidence. In particular, investigation of affect levels with consideration of bipolar mood state may provide a more comprehensive understanding. To date, evidence is beginning to accumulate to suggest that affect levels across inter-episode periods in bipolar disorder remain disturbed compared to the general population. The direction of these disturbances in positive and negative affects may require consideration of the presence of concurrent bipolar mood symptoms.

Higher levels of depression were evident in bipolar disorder across inter-episode periods compared to the general population. This finding suggests that individuals with bipolar disorder were experiencing ongoing bipolar mood disturbance. The observed lower levels of positive affect and higher negative levels may also suggest the presence of depressive affect. Higher depressed affect during inter-episode periods was consistent with a previous investigation by Millar et al (2004) who reported higher average depressed ratings over five nights in bipolar disorder compared to general population individuals. Furthermore, longitudinal studies (Judd et al, 2002, 2003b; Joffe et al, 2004) have reported subsyndromal symptoms commonly occur during inter-episode periods in bipolar disorder.

Mood variability was not suggested to differ between bipolar disorder and the general population in the current study. No differences in the variability of positive, negative, depressed or elated affect ratings over 14 days were observed between participant groups. However, when participants with bipolar disorder were monitored over longer time periods, greater variability in negative affect and depressed ratings emerged. Current findings were in conflict with the hypothesised greater variability in affect expected to occur in bipolar disorder. In particular, high intraindividual variability in affect had been posited to provide support for the diathesis-stress model of behavioural activation dysregulation. Therefore, results suggested that although dysregulation in affect, in terms of variability, did not occur in the present bipolar disorder sample, disturbances were evident in terms of affect levels.

Evidence has been inconsistent as to whether greater mood variability occurs in mood disorders compared to the general population. A recent study by Millar et al (2004) found no difference in mood variability, measured by a visual analogue scale ranging from most depressed to most manic, over five days between bipolar disorder and general population groups. In contrast, Lovejoy and Steuerwald (1995) reported greater positive and negative

affect variability's across 28 days in individuals with cyclothymia compared to the general population. Furthermore, high positive and negative affect variability across 30 days have been associated with depressive symptoms in a general population sample (McConville & Cooper, 1996). The combination of few studies that used different lengths of monitoring with small sample sizes of clinical and non-clinical participants limits generalisations. Since studies reporting differences in affect variability used longer monitoring periods, uncertainty remains as to whether observation of greater affect variability in mood disorders required a longer monitoring period than the 14 days used in the present study. To date, evidence from the current study and Millar et al (2004) suggested no disturbance in affect variability in bipolar disorder across relatively brief inter-episode periods.

5.6 Limitations of current study

The present study had several limitations that may have had an impact on the findings obtained. The sample size recruited, power of study, statistical analyses with small sample sizes, different sample sizes across groups, groups not matched, diagnostic interview not used to screen participants, the mixed diagnostic bipolar disorder sample, daily monitoring, no measurement of complexity, no measurement of ongoing clinical symptoms, correlation of Rosenberg self esteem questionnaire with depressive symptoms, and admission as an outcome measure were identified as possible methodological limitations. The limitations identified suggest that Type II errors, rather than Type I errors, may have been more likely to occur. Each limitation identified will be briefly discussed in turn.

The first limitation of the study was the sample size of participants with bipolar disorder recruited was smaller than anticipated. The small sample size had an impact on the obtained power of the study. Although 55 individuals with bipolar disorder had been initially identified for the study, only 20 individuals were recruited and successfully

completed a period of prospective daily monitoring. Recruitment from a Lithium Clinic depended on a staff psychiatrist discussing the project with potential participants before introducing the researcher (Alison Jackson) to those individuals interested in participating in the project. Time constraints of the clinic meant 11 potential participants had not been approached during the recruitment phase of the project. Multivariate analysis of six dependent variables with an estimated moderate effect size (d=0.75), α 0.05, β 0.20 and desired level of 80% statistical power would require a sample of at least 50 participants. Thus, limited power may have led to underestimation of differences in average level and variability of measures between general population and bipolar disorder groups.

The small sample recruited also had an impact on the robustness of conducting statistical analyses with smaller subgroups of the sample. When investigating the significance of variability in bipolar disorder, the small clinical sample was divided into smaller subgroups according to diagnostic subtype or variability type for exploratory survival analyses. The results of survival analyses must be considered extremely tentative due to the very small numbers in the subgroups. The effect size in survival analysis is calculated as the ratio of events at a given time-point (Norman & Streiner, 2000), which in the current study was the ratio of admissions at an approximate three year follow-up (range of follow-up from 38 to 44 months). To test differences in survival between low and high variability subgroups with a two tailed test using α level 0.05, β level 0.20 and with a large effect size of 2.0, then N=33 admissions per group would have been required for the desired 80% power. With the observed 40% admission rate, the required sample size should have been approximately 83 participants in each group, comprising a total of 166 participants with bipolar disorder. Compared to the actual sample of 20 participants with bipolar disorder recruited and followed-up at three years, survival analyses with such small sample numbers may not have

been appropriate. Therefore, limited power in the exploratory bipolar disorder subgroup comparisons must be noted.

The comparisons between bipolar disorder and general population groups may have been limited since groups were not matched. Firstly, matching groups on factors that may impact on the mean level and variability of measures would have been beneficial. Factors that may have been used to match participants across groups include gender, age, occupation, and alcohol/drug use. The equal gender proportion of 50% males and 50% females was the same in both participant groups and there was no significant difference in age between bipolar disorder and general population groups (Section 4.1.3 provides more information). No specific information on occupation was collected, although this could have had an impact on most of the measures. For instance, employment may influence the regularity of social rhythms and the sleep-wake cycle. Finally, alcohol and substance use could have influenced measures in the current study. Prescribed medications in bipolar disorder participants were recorded, although adherence to medication (e.g. by blood lithium levels) was not monitored. It was not recorded if any general population participants were taking prescribed medication. In addition to prescription medicine, alcohol and substance use may both impact on social and circadian rhythms, including the sleep-wake cycle. By not matching groups in the current study, it remains unclear if the groups differed due to the presence of bipolar disorder or due to other factors.

The comparisons between bipolar disorder and general population groups may also have been limited since different sample sizes were recruited across groups. Initially, the current study intended to replicate and extend a previous investigation by Ashman et al (1999). When a participant with bipolar disorder had completed a minimum eight week period of monitoring, an age and gender matched participant from the general population was

recruited (Section 3.2.2 provides further information). Between-group comparisons were intended to compare a two week period in general population participants compared to the full monitoring period in bipolar disorder participants (full bipolar disorder monitoring period comparisons provided in Section 4.8 and Appendix K). However, following statistician advice, between-group comparisons were altered to compare the same time period length. Since this decision was taken after data collection had been completed, further participants from the general population were unable to be recruited. Between-group comparisons subsequently analysed differences in twenty participants with bipolar disorder compared to ten participants from the general population; group sample sizes differed between analyses as participants were excluded if missing data occurred. Therefore, unequal sample sizes may have impacted on the robustness of the analyses.

A diagnostic interview was not used to screen participants for the research study. Inclusion criteria specified that participants with bipolar disorder had to meet DSM-IV criteria for bipolar I or bipolar II disorders. A staff psychiatrist confirmed case diagnosis from the casenotes of individuals who participated. Using the Structured Clinical Interview for DSM-IV (First et al, 1997) for diagnostic classification would have been more rigorous. Furthermore, using this structured clinical interview to screen participants from the general population for mental health disorders would also have been beneficial. The use of a diagnostic interview would have required additional training for the research assistant (Alison Jackson) but would have been an improvement on the methodology applied for the current study.

A further methodological limitation was analysis of a mixed diagnostic bipolar disorder sample. The present study recruited a mixed bipolar disorder sample that comprised individuals with bipolar I, bipolar II and rapid cycling disorders. Bipolar disorder subtypes

by definition differ in the expression of symptom intensity and frequency. It is therefore quite possible that variability across inter-episode periods may also differ between bipolar disorder subtypes. Since research into inter-episode variability in bipolar disorders is preliminary, future investigations may benefit from considering each subtype of bipolar disorder separately. Indeed, survival analyses in the present study suggested high self esteem variability specifically predicted admission in bipolar I disorder, but not in bipolar II or rapid cycling disorders. Thus, if variability differs across diagnostic subtypes, then recruitment of a relatively small bipolar disorder sample with three subtypes may have obscured differences between level and variability of measures across bipolar disorder and general population groups.

Another possible methodological limitation of the current study was the use of daily monitoring to measure affect. Self esteem was rated for the present moment, whilst end of day completion for the social rhythm has already been indicated as reliable (Monk et al, 1990). In contrast, participants completed daily self report affect ratings at the end of each day. This method was reliant on participants' accurate recall of the day to provide a generalised rating for the day that was not distorted. Both mood duration and intensity throughout the day requires consideration for a representative daily average mood (Hedges et al, 1985). Furthermore, there may also be recency effects where more recent mood states may be remembered better (Parkinson et al, 1995). Future research should perhaps consider momentary assessment of affect. Momentary sampling within days to provide daily mood may be useful, although using a single momentary measure for each day may not provide accurate representation of daily mood (Hedges et al, 1985). However, limitations of frequent momentary assessment include potential reactive effects as well as becoming an increasingly intrusive procedure in the participant's daily life as frequency of monitoring

increases (Parkinson et al, 1995). Investigation of daily versus momentary assessments of affect in clinical samples may elucidate which methodology would be most useful to apply.

The present study did not consider the role of self-complexity or affect complexity in influencing variability in self esteem and affect. Research with general population samples has reported associations between complexity and variability. Greater self-complexity has been associated with less variability in both cognition (Rhodewalt et al, 1998) and affect (Campbell et al, 1991; Brown & Mankowski, 1993), whilst greater affect complexity has been associated with less variability in affect (Wessman & Ricks, 1966; Larsen & Cutler, 1996). Future investigations may benefit from exploration of self- or affect complexity in clinical and general population samples, as it is thus possible that complexity may influence the extent of day-to-day variability. Differences in self-complexity and affect complexity between mood disorders and the general population are unclear. Cognitive vulnerability has been reported in bipolar disorder, in terms of poor problem solving and over-general memory (Scott et al, 2000). Such evidence leads the suggestion that self-complexity disturbances may be more likely to occur in bipolar disorder. If variability in self esteem is a robust difference between bipolar disorder and the general population, then consideration of self-complexity may provide a more comprehensive understanding of the role of self esteem variability in the course of bipolar disorder.

Although the current study aimed to investigate a clinical sample until relapse, no measurement of ongoing clinical symptoms was conducted during the daily prospective monitoring period. The PANAS had been altered to include ratings of elated and depressed affect, but these ratings did not provide a clinical rating of bipolar mood. Using an ordinal five point rating scale from not at all to extremely for bipolar mood was limited since it was unclear if the items measured the same intensity of elation and depression

across bipolar disorder and general population samples. It is possible that individuals with bipolar disorder may have responded differently to these items; prior experience of acute manic and depressive episodes may impact on the completion of daily elated and depressed ratings. Furthermore, recent evidence indicates that individuals with bipolar disorder commonly experience varying levels of symptomatology outwith acute episodes (Judd et al, 2002, 2003b; Joffe et al, 2004). Use of clinician ratings (e.g. Hamilton Depression Rating Scale, Hamilton, 1960; Young Mania Rating Scale, Young et al, 1978) or self-report scales (e.g. Internal State Scale, Bauer et al, 1991) may have provided more robust indications of ongoing bipolar mood symptoms. Thus, the current study would have benefited from using a clinical measure of ongoing symptoms for the participants with bipolar disorder.

The current study observed lower self esteem in bipolar disorder compared to general population participants. This was consistent with previous cross-sectional investigations of self esteem across inter-episode periods in bipolar disorder in the absence of subsyndromal symptoms (Serretti et al, 1999; Shapira et al, 1999; Blairy et al, 2004). However, self esteem level has been reported to predict depressive symptoms in bipolar disorder (Johnson et al, 2000b) and mood disorder (Roberts et al, 1999) samples. In particular, the Rosenberg self esteem questionnaire has been observed to correlate with depressive symptoms, with lower self esteem associated with higher levels of depression. The current study observed higher depressed ratings in bipolar disorder compared to general population participants. It is therefore possible that the observed difference in self esteem level between groups could have been due to the difference in self-rated depressed affect.

First admission to hospital following study participation was selected as the follow-up outcome measure for bipolar disorder participants. The advantage of using the first admission date was that it was a well-defined, dichotomous marker of severity. One

possible limitation was that the episode polarity for admission was not known. Evidence has accumulated to suggest variables that impact on mania do not have the same importance for bipolar depression and vice versa. For example, self esteem may play a role in precipitating bipolar depression (Johnson et al, 2000b), whilst behavioural activation, particularly reward responsiveness, may be more important in precipitating mania (Meyer et al, 2001). Thus, by not obtaining admissions for manic and depressive relapses separately, it was possible that some associations may have been obscured. In any case, the small sample size recruited in the current study limited the extent of potential subgroup analyses. A further limitation of using first admission as an outcome measure was that no information was gathered for acute episodes managed without admission to hospital. The potential to manage episodes in the community may differ across mania and depression; clinician knowledge suggests individuals tend to be more likely admitted for mania than for depression. Therefore, further research should endeavour to monitor the occurrence of episodes where admission does not occur as well as episode polarity.

5.7 Implications

The present study highlighted the importance that length of prospective monitoring may play in determining differences between groups. Three group differences (self esteem, night waking, and sleep efficiency) were observed between bipolar disorder and the general population when the variability of measures over a 14 day period was compared. When participants with bipolar disorder were measured over a longer monitoring period, greater variability emerged in six measures for bipolar disorder (sleep efficiency, fragmentation index, relative amplitude, self esteem, negative affect and depressed ratings). Participants with bipolar disorder were monitored for up to six months in contrast to the 14 day monitoring period for general population participants. This longer time period could have led to a sampling error whereby greater variability in bipolar disorder occurred merely due to

differences in monitoring periods. Although this error is possible, it is also as likely that as the length of the monitoring period increases, each participant's ratings would provide a more accurate 'trait' level and variability for each measure.

As individuals with bipolar disorder commonly experience inter-episode symptoms of varying intensity, perhaps a longer sampling period may be necessary to provide a reliable average level and variability of a prospective measure. Previous investigations have already highlighted that a longer time period is necessary for social rhythm 'traits' to be identified in mood disorders than in the general population (Monk et al, 1991; Ashman et al, 1999). A methodological implication from the current study was that if future investigations monitored variability over a longer time period (e.g. eight weeks) in both clinical and general population samples this could provide more reliable estimations of the level and variability of diathesis vulnerability, behavioural, self esteem and affect measures over time.

Disturbances in the average level and variability of several measures, such as self esteem, were identified in bipolar disorder relative to the general population in the current study. Future investigations over longer time periods will be necessary to further clarify associations between the level and variability of measures and relapse in bipolar disorder. Furthermore, although considerably more time consuming than cross-sectional investigations, it would be methodologically important for future studies to prospectively assess the level and variability of measures. Previous investigations have identified that individuals do not accurately report their average level and variability for a specified measure. For instance, weak associations have been reported between self-report general self esteem levels and self esteem average levels (Kernis et al, 1992; Greenier et al, 1999) and between self- report measures of self esteem variability and prospectively measured self esteem variability (Kernis, 1993; Kernis et al, 1989, 1992). Prospective assessment may

also provide further opportunities to investigate associations from day-to-day with time series analyses. The present study did not provide any consistent evidence of associations between measures across time in bipolar disorder. However, larger samples following participants across euthymic and acute periods may provide clarification of both inter-and intra-individual associations between diathesis vulnerability, behaviour, self esteem and affect measures from day-to-day. Thus, to obtain accurate estimations of the average level and variability of measures over time, prospective assessment is essential.

The level and variability of self esteem was disturbed in bipolar disorder. Reduced self esteem levels during inter-episode periods in bipolar disorder were evident compared to the general population. Cross-sectional studies, with large samples have also observed low self esteem in remitted bipolar disorder (Shapira et al, 1999; Blairy et al, 2004; Serretti et al, 1999, 2005). Greater variability in self esteem was also evident in the current study, suggesting a general dysregulation in self esteem may occur in bipolar disorder. Survival analyses tentatively associated self esteem variability with earlier admission to hospital for bipolar I disorder in the current study. Low self esteem has been reported to predict higher levels of depression, with no observed impact on mania (N=31 bipolar I disorder; Johnson et al, 2000b). Furthermore, a previous investigation with a sample that comprised individuals with seasonal affective disorder suggested low self esteem was associated with earlier relapse (N=45 seasonal affective disorder; McCarthy et al, 2002). Bipolar disorder although routinely treated with pharmacotherapy, has been recognised to benefit from adjunctive psychological interventions (Scott & Todd, 2002). As such, self esteem disturbances in bipolar disorder may be considered as a potential focus for psychological interventions that may improve outcome for the disorder.

Night-to-night variability in night waking and sleep efficiency across inter-episode periods in bipolar disorder was disturbed relative to variability observed in the general population over a brief 14 day prospective monitoring period. Furthermore, variability in sleep efficiency was tentatively associated with earlier admission in bipolar disorder. These findings have important clinical implications for prognosis in bipolar disorders. Sleep disturbance may be considered as a potentially modifiable variable, whilst other risks of relapse are not susceptible to change. Indeed, two case studies suggested the course of rapid cycling disorder was stabilised by regulating timing and duration of sleep (Wehr et al, 1998; Wirz-Justice et al, 1999). The present study has provided further evidence of the clinical importance of sleep in the course of bipolar disorder.

Identification of sleep disturbance as a predictor of relapse may be of clinical importance for bipolar disorder. Sleep disturbance, unlike other risk factors for relapse, could be amenable to change. Psychological therapies already promote the advantages of a good sleep-wake cycle (e.g. interpersonal and social rhythm therapy; Frank et al, 1999). Actigraphy, in addition to being a research tool, could theoretically be applied in routine care as an early symptom monitoring tool to prevent relapse in bipolar disorder. Early symptom monitoring has been identified to be an effective strategy to prevent manic relapse in bipolar disorder (Perry et al, 1999). Furthermore, a systematic review of bipolar prodromes identified sleep disturbance was reported as an early symptom of mania by 77% of individuals and as an early symptom of bipolar depression by 24% of individuals (Jackson et al, 2003). However, one potential limitation of using actigraphy as an early monitoring strategy is that concordance from a significant proportion of individuals with bipolar disorder may not be obtained. In the current study, 25% (N=5/20 bipolar disorder participants) did not agree to wear an actiwatch, which is similar to the 30% observed in a previous study (N=6/20 bipolar disorder participants; Harvey et al, 2005). The application of actigraph monitoring in

clinical practice may be a useful strategy to modify sleep disturbance during inter-episode periods and reduce risk of relapse in bipolar disorder.

Self monitoring may be usefully applied to prevent relapse in bipolar disorder. A core strategy in recent psychological interventions for bipolar disorder has been the identification and monitoring of early symptoms of relapse (e.g. Perry et al, 1999). Individuals with bipolar disorder have been indicated to be willing to engage in self monitoring strategies to prevent relapse, within routine care as well as during research studies. Furthermore, voluntary organisations such as the Manic Depression Fellowship also promote identification and self-management of early symptoms. Paper and pencil monitoring systems have been usefully applied, but electronic monitoring has started to gain prominence. The current study observed the utility of actigraph monitoring as well as paper systems of monitoring changes in behaviour, self esteem and affect. More recent prospective monitoring studies have applied electronic systems. For instance, Bauer et al (2004) reported high acceptance of Chronorecord, a home computer-based system of self-report ratings. Eighty-three per cent of Bauer et al's (2004) sample completed three months of daily mood, sleep, menstrual cycle, medication and life events monitoring (N=96 bipolar disorder). Therefore, evidence suggests both electronic and paper systems of monitoring early symptoms of relapse in bipolar disorder may be usefully applied in future research investigations as well as routine care.

5.8 Conclusions

The reported differences in average level and variability of certain diathesis vulnerability, self esteem and affect measures between general population and bipolar disorder participants was consistent with recent studies using bipolar disorder samples. Three prospective, longitudinal studies over average follow-up periods of three years (N=138 bipolar disorder; Joffe et al, 2004) and thirteen years (N=146 bipolar I disorder, Judd et al, 2002; N= 86 bipolar II disorder, Judd et al, 2003b) reported individuals with bipolar disorder spend approximately half of their time euthymic. Consequently, the remaining half of their time is spent experiencing varying subsyndromal to acute symptomatic mood states. Thus, evidence is accumulating that bipolar disorder has a chronic, pervading presence consisting of ongoing dysregulation during inter-episode periods as well as recurrent acute episodes.

The current study observed individuals with bipolar disorder display disturbances in affect, self esteem and sleep measures during inter-episode periods. In comparison to the general population, lower positive affect, lower self esteem, higher negative affect, and higher depression levels were reported for participants with bipolar disorder. Greater variability in sleep efficiency, night waking and self esteem measures were also reported in bipolar disorder. High intraindividual variability was consistent with theoretical diathesis-stress models that posit weak regulation in underlying systems characterise bipolar disorder. These findings suggest underlying dysregulation across affect, self esteem and sleep occurs during inter-episode periods in bipolar disorder.

Variability in bipolar disorder across inter-episode periods was identified to have clinical importance. Variability in sleep efficiency was associated with earlier admission in bipolar disorder across a three year follow up. Furthermore, there was some suggestion that self

esteem variability specifically predicted admission in bipolar I disorder. Findings from survival analyses must be considered as exploratory due to small sample sizes. However, observations occurred in the expected directions, with greater variability associated with increased vulnerability to relapse. These findings were of clinical importance since sleep and self esteem disturbances may both be considered as potentially modifiable in reducing risk of relapse in bipolar disorder. Therefore, to conclude, the current study provided evidence that heightened variability in bipolar disorders across inter-episode periods may represent an underlying dysregulation.

References

Akiskal, H.S., Bourgeois, M.L., Angst, J., Post, R., Moller, H., & Hirshfield, R. (2000) Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *Journal of Affective Disorders* **59** supplement 5-30.

Alloy, L.B., Reilly-Harrington, N.A., Fresco, D.M., Whitehouse, W.G., & Zechmeister, J.G. (1999) Cognitive styles and life events in subsyndromal unipolar and bipolar disorders: stability and prospective prediction of depressive and hypomanic mood swings. *Journal of Cognitive Psychotherapy* **13** 21-40.

Altman, E.S., Rea, M.M., Mintz, J., Miklowitz, D.J., Goldstein, M.J., & Hwang, S. (1992) Prodromal symptoms and signs of bipolar relapse: a report based on prospectively collected data. *Psychiatry Research* **41** 1-8.

Ambelas, A. (1987) Life events and mania, a special relationship? *British Journal of Psychiatry* **150** 235-240.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV.* Washington, DC: APA.

American Sleep Disorders Association (1995) Practice parameters for the use of actigraphy in the clinical assessment of sleep disorders. *Sleep* **18** 285-287.

Aronson, T.A. & Shukla, S. (1987) Life events and relapse in bipolar disorder: the impact of a catastrophic event. *Acta Psychiatrica Scandinavica* **75** 571-576.

Ashman, S.B., Monk, T.H., Kupfer, D.J., Clark, C.H., Myers, F.S., Frank, E., & Leibenluft, E. (1999) Relationship between social rhythms and mood in patients with rapid cycling bipolar disorder. *Psychiatry Research* **86** 1-8.

Ball, J.R. Mitchell, P.B. Corry, J.C. Skillecorn, A. Smith, M. & Malhi, G.S. (2006) A randomised controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. *Journal of Clinical Psychiatry* **67** 277-286.

Barbini, B., Colombo, C., Benedetti, F., Campori, E., Bellodi, L., & Smeraldi, E. (1998) The unipolar bipolar dichotomy and the response to sleep deprivation. *Psychiatry Research* **79** 43-50.

Barbini, B., Bertelli, S., Colombo, C., & Smeraldi, E. (1996) Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Research* **65** 121-125.

Batson, C.D., Shaw, L.L., & Oleson, K.C. (1992) Differentiating affect, mood and emotion: toward functionally based conceptual distinctions. *Review of Personality and Social Psychology* **13** 294-326.

Bauer, M. Grof, P. Gyulai, L. Rasgon, N. Glenn, T. & Whybrow, P.C. (2004) Using technology to improve longitudinal studies: self-reporting with ChronoRecord in bipolar disorder. *Bipolar Disorders* **6** 67-74.

Bauer, M.S. Crits-Christoph, P. Ball, W.A. Dewees, E. McAllister, T. Alahi, P. Cacciola, J., & Whybrow, P.C. (1991) Independent assessment of manic and depressive symptoms by self-rating. *Archives of General Psychiatry* **48** 807-812.

Baumeister, R.F., Tice, D.M., & Hutton, D.G. (1989) Self-presentational motivations and personality differences in self esteem. *Journal of Personality* **57** 547-579.

Bebbington, P. & Ramana, R. (1995) The epidemiology of bipolar affective disorder. *Social Psychiatry and Psychiatric Epidemiology* **30** 279-292.

Beck, A.T. (1987) Cognitive models of depression. *Journal of Cognitive Psychotherapy* **1** 5-37.

Beck, A.T. Epstein, N. Harrison, R.P. & Emery, G. (1983) *Development of the Sociotropy-Autonomy Scale: A measure of personality factors in psychopathology.* Unpublished manuscript, University of Pennsylvania, Philadelphia.

Beevers, C.G. & Meyer, B. (2002) Lack of positive experiences and positive expectancies mediate the relationship between BAS responsiveness and depression. *Cognition and Emotion* **16** 549-564.

Berger, M., Vollmann, J., Hohagen, F., Konig, A., Lohner, H., Voderholzer, U., & Riemann, D. (1997) Sleep deprivation combined with consecutive sleep phase advance as a fast acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *American Journal of Psychiatry* **154** 870-872.

Bieling, P.J. Beck, A.T. & Brown, G.K. (2000) The Sociotropy-Autonomy Scale: structure and implications. *Cognitive Therapy and Research* **24** 763-780.

Blairy, S., Linotte, S., Souery, D., Papadimitriou, G.N., Dikeos, D., Lerer, B., Kaneva, R., Milanova, V., Serretti, A., Macciardi, F., & Mendlewicz, J. (2004) Social adjustment and

self-esteem of bipolar patients: a multicentric study. *Journal of Affective Disorders* **79** 97-103.

Blood, M.L., Sack, R.L., Percy, D.C., & Pen, J.C. (1997) A comparison of sleep detection by wrist actigraphy, behavioural response, and polysomnography. *Sleep* **20** 388-395.

Blount, C., Evans, C., Birch, S., Warren, F., & Norton, K. (2002) The properties of self report research measures: beyond psychometrics. *Psychology and Psychotherapy: Theory, Research and Practice* **75** 151-164.

Boivin, D.B., Czeisler, C.A., Dijk, D., Duffy, J.F., Folkard, S., Minors, D.S., Totterdell, P., & Waterhouse, J.M. (1997) Complex interaction of the sleep wake cycle and circadian phase modulates mood in healthy subjects. *Archives of General Psychiatry* **54** 145-152.

Bolger, N., Davis, A., & Rafaeli, E. (2003) Diary methods: capturing life as it is lived. *Annual Review of Psychology* **54** 579-616.

Bolger, N., DeLongis, A., Kessler, R.C., & Schilling, E.A. (1989) Effects of daily stress on negative mood. *Journal of Personality and Social Psychology* **57** 808-818.

Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996) Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biological Psychiatry* **39** 411-418.

Brown, J.D. & Mankowski, T.A. (1993) Self esteem, mood and self-evaluation: changes in mood and the way you see you. *Journal of Personality and Social Psychology* **64** 421-430.

Brown, L.F., Reynolds, C.F., Monk, T.H., Prigerson, H.G., Dew, M.A., Houck, P.R., Mazumdar, S., Buysse, D.J., Hoch, C.C., & Kupfer, D.J. (1996) Social rhythm stability following late life spousal bereavement: associations with depression and sleep impairment. *Psychiatry Research* **62** 161-169.

Brugha, T.S. & Cragg, D. (1990) The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica* **82** 77-81.

Bryman, A. & Cramer, D. (1997) Multivariate analysis, exploring differences among three or more variables. In: Bryman, A. and Cramer, D. (Ed.) *Quantitative data analysis with SPSS for windows, a guide for social scientists.* 203-236. Routledge.

Bunney, W.E., Murphy, D.L., Goodwin, F.K., & Borge, G.F. (1972) The "switch process" in manic depressive illness, I: A systematic study of sequential behavioural changes. *Archives of General Psychiatry* **27** 295-302.

Butler, A.C., Hokanson, J.E., & Flynn, H.A. (1994) A comparison of self esteem lability and low trait self esteem as vulnerability factors for depression. *Journal of Personality and Social Psychology* **66** 166-177.

Cambridge Neurotechnology Ltd. (2000) *The actiwatch activity monitoring system, instructions for use and software manual.*

Campbell, J.D., Chew, B., & Scratchley, L.S. (1991) Cognitive and emotional reactions to daily events: the effects of self-esteem and self-complexity. *Journal of Personality* **59** 473-505.

Carver, C.S., Meyer, B., & Antoni, M.H. (2000) Responsiveness to threats and incentives, expectancy of recurrence, and distress and disengagement: moderator effects in women with early stage breast cancer. *Journal of Consulting and Clinical Psychology* **68** 965-975.

Carver, C.S. & White, T.L. (1994) Behavioural inhibition, behavioural activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. *Journal of Personality and Social Psychology* **67** 319-333.

Cassano, G.B., Dell'Osso, L., Frank, E., Miniati, M., Fagiolini, A., Shear, K., Pini, S., & Maser, J. (1999) The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology. *Journal of Affective Disorders* **54** 319-328.

Cassidy, F., Murry, E., Forest, K., & Carroll, B.J. (1998) Signs and symptoms of mania in pure and mixed episodes. *Journal of Affective Disorders* **50** 187-201.

Clark, D.A. & Beck, A.T. (1991) Personality factors in dysphoria: a psychometric refinement of Beck's sociotropy autonomy scale. *Journal of Psychopathology and Behavioural Assessment* **13** 369-388.

Clark, L.A. & Watson, D. (1991) Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology* **100** 316-336.

Clark, L.A. & Watson, D. (1988) Mood and the mundane: relations between daily life events and self reported mood. *Journal of Personality and Social Psychology* **54** 296-308.

Cochran, S.D. (1984) Preventing medical non-compliance in the outpatient treatment of bipolar affective disorders. *Journal of Consulting and Clinical Psychology* **52** 873-878.

Cohen, B.H. (2001) *Explaining psychological statistics.* John Wiley and Sons.

Cohen, J. (1988) *Statistical power analysis for the behavioural sciences.* Hillsdale: NJ: Lawrence Erlbaum.

Cole, M.G. & Dendukuri, N. (2003) Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry* **160** 1147-1156.

Cole, R.J., Kripke, D.F., Gruen, W., Mullaney, D.J., & Gillin, J.C. (1992) Automatic sleep/wake identification from wrist activity. *Sleep* **15** 461-469.

Collins, L.M. & Sayer, A.G. (2000) Modeling growth and change processes, design, measurement, and analysis for research in social psychology. In: Reis, H.T. and Judd, C.M. (Ed.) *Handbook of research methods in social and personality psychology.* 478-495. Cambridge University Press.

Colom, F. Vieta, E. Reinares, M. Martinez-Aran, A. Torrent, C. Goikolea, J.M. & Gasto, C. (2003b) Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. *Journal of Clinical Psychiatry* **64** 1101-1105.

Colom, F. Vieta, E. Martinez-Aran, A. Reinares, M. Goikolea, J.M. Benabarre, A. Torrent, C. Comes, M. Corbella, B. Parramon, G. & Corominas, J. (2003a) *Archives of General Psychiatry* **60** 402-407.

Cooper, C. & McConville, C. (1990) Interpreting mood scores: clinical implications of individual differences in mood variability. *British Journal of Medical Psychology* **63** 215-225.

Corr, P.J. (2002a) Gray's reinforcement sensitivity theory: tests of the joint subsystems hypothesis of anxiety and impulsivity. *Personality and Individual Differences* **33** 511-532.

Corr, P.J. (2002b) J.A. Gray's reinforcement sensitivity theory and frustrative nonreward: a theoretical note on expectancies in reactions to rewarding stimuli. *Personality and Individual Differences* **32** 1247-1253.

Corr, P.J. (2001) Testing problems in J.A. Gray's personality theory: a commentary on Mathews and Gilliland (1999). *Personality and Individual Differences* **30** 333-352.

Coryell, W., Winokur, G., Solomon, D., Shea, T., Leon, A., & Keller, M. (1997) Lithium and recurrence in a long term follow up of bipolar affective disorder. *Psychological Medicine* **27** 281-289.

Coryell, W., Endicott, J., Maser, J.D., Mueller, T., Lavori, P., & Keller, M. (1995) The likelihood of recurrence in bipolar affective disorder: the importance of episode recency. *Journal of Affective Disorders* **33** 201-206.

Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G.L. (1993) The enduring psychosocial consequences of mania and depression. *American Journal of Psychiatry* **150** 720-727.

Craddock, N. and Jones, I. (2001) Molecular genetics of bipolar disorder. *British Journal of Psychiatry* **178** s128-s133.

Craddock, N. and Jones, I. (1999) Genetics of bipolar disorder. *Journal of Medical Genetics* **36** 585-594.

Czeisler, C.A. & Dijk, D. (2001) Human circadian physiology and sleep-wake regulation. In: Takahashi, F.W., Turek, F.W., and Monroe, R.Y. (Ed.) *Handbook of behavioural neurobiology: circadian clocks.* 531-569. Kluwer Academic/Plenum Publishers.

DasGupta, R. & Guest, J.F. (2002) Annual cost of bipolar disorder to UK society. *British Journal of Psychiatry* **180** 227-233.

David, J.P., Green, P.J., Martin, R., & Suls, J. (1997) Differential roles of neuroticism, extraversion and event desirability for mood in daily life: an integrative model of top-down and bottom-up influences. *Journal of Personality and Social Psychology* **73** 149-159.

Denicoff, K.D., Smith-Jackson, E.E., Disney, E.R., Suddath, R.L., Leverich, G.S., & Post, R.M. (1997) Preliminary evidence of the reliability and validity of the prospective life-chart methodology (LCM-p). *Journal of Psychiatry Research* **31** 593-603.

Depue, D.A. & Zald, D.H. (1993) Biological and environmental processes in nonpsychotic psychopathology: a neurobehavioural perspective. In: Costello, C.G. (Ed.) *Basic issues in psychopathology.* 127-237. Guilford Press.

Depue, R.A. & Iacono, W.G. (1989) Neurobehavioural aspects of affective disorders. *Annual Review of Psychology* **40** 457-492.

Depue, R.A., Krauss, S.P., & Spoont, M.R. (1987) A two dimensional threshold model of seasonal bipolar affective disorder. In: Magnusson, D. and Ohman, A. (Ed.) *Psychopathology: an interactionist perspective.* 95-123. Academic Press.

Eckblad, M. & Chapman, L.J. (1986) Development and validation of a scale for hypomanic personality. *Journal of Abnormal Psychology* **95** 214-222.

Egloff, B., Tausch, A., Kohlmann, C., & Krohne, H.W. (1995) Relationships between time of day, day of the week, and positive mood: exploring the role of the mood measure. *Motivation and Emotion* **19** 99-110.

Ehlers, C.L., Kupfer, D.J., Frank, E., & Monk, T.H. (1993) Biological rhythms and depression: the role of zeitgebers and zeitstorers. *Depression* **1** 285-293.

Ehlers, C.L., Frank, E., & Kupfer, D.J. (1988) Social zeitgebers and biological rhythms, a unified approach to understanding the etiology of depression. *Archives of General Psychiatry* **45** 948-952.

Ellicott, A., Hammen, C., Gitlin, M., Brown, G., & Jamison, K. (1990) Life events and the course of bipolar disorder. *American Journal of Psychiatry* **147** 1194-1198.

Emilien, G. & Maloteaux, J. (1999) Circadian system and sleep anomaly in depression. *Irish Journal of Psychological Medicine* **16** 18-23.

Epstein, S. (1984) The stability of behaviour across time and situations. In: Zucker, R.A., Aronoff, J., and Rabin, A.I. (Ed.) *Personality and the prediction of behaviour.* 209-268. Academic Press.

Fava, G.A. (1999) Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychological Medicine* **29** 47-61.

Feldman-Naim, S., Turner, E.H., & Leibenluft, E. (1997) Diurnal variation in the direction of mood switches in patients with rapid cycling bipolar disorder. *Journal of Clinical Psychiatry* **58** 79-84.

First, M.B. Gibbon, M. Spitzer, R.L. Williams, J.B.W. & Benjamin, L.S. (1997) *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition.* Washington, DC, American Psychiatric Press.

Frank, E. (1999) Interpersonal and social rhythm therapy prevents depressive symptomatology in bipolar I patients. *Bipolar Disorders* **1** 13-13.

Frank, E. Kupfer, D.J. Thase, M.E. Mallinger, A.G. Swartz, H.A. Fagiolini, A.M. Grochocinski, V. Houck, P. Scott, J. Thompson, W. & Monk, T. (2005) Two-year

outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry* **62** 996-1004.

Frank, E., Swartz, H.A., & Kupfer, D.J. (2000) Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biological Psychiatry* **48** 593-604.

Frank, E., Swartz, H.A., Mallinger, A.G., Thase, M.E., Weaver, E.V., & Kupfer, D.J. (1999) Adjunctive psychotherapy for bipolar disorder: effects of changing treatment modality. *Journal of Abnormal Psychology* **108** 579-587.

Frank, E., Kupfer, D.J., Ehlers, C.L., Monk, T.H., Cornes, C., Carter, S., & Frankel, D. (1994) Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behavioural approaches. *The Behaviour Therapist* **17** 143-149.

Gable, S.L., Reis, H.T., & Elliot, A.J. (2000) Behavioural activation and inhibition in everyday life. *Journal of Personality and Social Psychology* **78** 1135-1149.

Gable, S.L. & Nezlek, J.B. (1998) Level and instability of day-to-day psychological well-being and risk for depression. *Journal of Personality and Social Psychology* **74** 129-138.

Gencoz, T. (2002) Discriminant validity of low positive affect: is it specific to depression? *Personality and Individual Differences* **32** 991-999.

Gershon, S. & Soares, J.C. (1997) Current therapeutic profile of lithium. *Archives of General Psychiatry* **54** 16-20.

Gibbons, R.D., Hedeker, D., Elkin, I., Waternaux, C., Kraemer, H.C., Greenhouse, J.B., Shea, M., Tracie, I., Stanley, D., Sotsky, S.M., & Watkins, J.T. (1993) Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH treatment of depression collaborative research program dataset. *Archives of General Psychiatry* **50** 739-750.

Gillin, J.C. (1998) Are sleep disturbances risk factors for anxiety, depressive and addictive disorders? *Acta Psychiatrica Scandinavica* **98** s39-s43.

Gillin, J.C., Sitaram, N., Wehr, T., Duncan, W., Post, R., Murphy, D.L., Mendelson, W.B., Wyatt, R.J., & Bunney, W.E. (1984) Sleep and affective illness. In: Post, R.M. and Ballenger, J.C. (Ed.) *Neurobiology of mood disorders.* 157-189. Baltimore: Williams and Williams.

Gitlin, M.J., Swendsen, J., Heller, T.L., & Hammen, C. (1995) Relapse and impairment in bipolar disorder. *American Journal of Psychiatry* **152** 1635-1640.

Goodwin, F. & Jamison, K. (1990) *Manic-depressive illness.* Oxford University Press: Oxford.

Goplerud, E. & Depue, R.A. (1985) Behavioural response to naturally occurring stress in cyclothymia and dysthymia. *Journal of Abnormal Psychology* **94** 128-139.

Gotlib, I.H., Ranganath, C., & Rosenfeld, J.P. (1998) Frontal EEG alpha asymmetry, depression and cognitive functioning. *Cognition and Emotion* **12** 449-478.

Gray, J.A. (1994) Three fundamental emotion systems. In: Ekman, P. and Davidson, R.J. (Ed.) *The nature of emotion, fundamental questions.* 243-247. Oxford University Press.

Gray, J.A. (1990) Brain systems that mediate both emotion and cognition. *Cognition and Emotion* **4** 269-288.

Gray, J.A. (1989) Fundamental systems of emotion in the mammalian brain. In: Palermo, D.S. (Ed.) *Coping with uncertainty: behavioural and developmental perspectives.* 173-195. Hillsdale, N.J.: Lawrence Erlbaum Associates.

Gray-Little, B., Williams, V.S., & Hancock, T.D. (1997) An item-response theory analysis of the Rosenberg self esteem scale. *Personality and Social Psychology Bulletin* **23** 443-451.

Greenberger, D. & Padesky, C.A. (1995) *Mind over mood, a cognitive therapy treatment manual for clients.* The Guilford Press.

Greenberger, E., Chen, C., Dmitrieva, J., & Farruggia, S.P. (2003) Item-wording and the dimensionality of the Rosenberg self-esteem scale: do they matter? *Personality and Individual Differences* **35** 1241-1254.

Greenier, K.D., Kernis, M.H., McNamara, C.W., Waschull, S.B., Berry, A.J., Herlocker, C.E., & Abend, T.A. (1999) Individual differences in reactivity to daily events: examining the roles of stability and level of self esteem. *Journal of Personality* **67** 185-208.

Gruber, R., Sadeh, A.D., & Raviv, A. (2000) Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **39** 495-501.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology and Neurosurgery Psychiatry* **23** 56-62.

Hammen, C. & Gitlin, M. (1997) Stress reactivity in bipolar patients and its relation to prior history of disorder. *American Journal of Psychiatry* **154** 856-857.

Hammen, C., Ellicott, A., & Gitlin, M. (1992) Stressors and sociotropy/autonomy: a longitudinal study of their relationship to the course of bipolar disorder. *Cognitive Therapy and Research* **16** 409-418.

Hammen, C. Ellicott, A. Gitlin, M. & Jamison, K.R. (1989) Sociotropy/autonomy and vulnerability to specific life events in patients with unipolar depression and bipolar disorders. *Journal of Abnormal Psychology* **98** 154-160.

Harmon-Jones, E. (2003) Anger and the behavioural approach system. *Personality and Individual Differences* **35** 995-1005.

Harmon-Jones, E. Abramson, L.Y. Sigelman, J. Bohlig, A. Hogan, M.E. & Harmon-Jones, C. (2002) Proneness to hypomania/mania symptoms or depression symptoms and asymmetrical frontal cortical responses to an anger-evoking event. *Journal of Personality and Social Psychology* **82** 610-618.

Harmon-Jones, E. & Allen, J.J.B. (1997) Behavioural activation sensitivity and resting frontal EEG asymmetry: covariation of putative indicators related to risk for mood disorders. *Journal of Abnormal Psychology* **106** 159-163.

Harvey, A.G. Schmidt, D.A. Scarna, A. Semler, C.N. & Goodwin, G.M. (2005) Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry* **162** 50-57.

Haug, H.J. (1992) Prediction of sleep deprivation outcome by diurnal variation of mood. *Biological Psychiatry* **31** 271-278.

Hays, J.C., Krishnan, K.R., George, L.K., & Blazer, D.G. (1998) Age of first onset of bipolar disorder: demographic, family history, and psychosocial correlates. *Depression and Anxiety* 7 76-82.

Healy, D. & Williams, J.M.G. (1989) Moods, misattributions and mania: an interaction of biological and psychological factors in the pathogenesis of mania. *Psychiatric Developments* **1** 49-70.

Healy, D. & Williams, J.M.G. (1988) Dysrhythmia, dysphoria, and depression: the interaction of learned helplessness and circadian dysrhythmia in the pathogenesis of depression. *Psychological Bulletin* **103** 163-178.

Hedges, S.M., Jandorf, L., & Stone, A.A. (1985) Meaning of daily mood assessments. *Journal of Personality and Social Psychology* **48** 428-434.

Hennen, J. (2003) Statistical methods for longitudinal research on bipolar disorders. *Bipolar Disorders* **5** 156-168.

Hepburn, L. & Eysenck, M.W. (1989) Personality, average mood and mood variability. *Personality and Individual Differences* **10** 975-983.

Heubeck, B.G., Wilkinson, R.B., & Cologon, J. (1998) A second look at Carver and White's (1994) BIS/BAS scales. *Personality and Individual Differences* **25** 785-800.

Hewitt, P.L. & Flett, G.L. (1991) Perfectionism in the self and social contexts: conceptualisation, assessment, and association with psychopathology. *Journal of Personality and Social Psychology* **60** 456-470.

Hlastala, S.A., Frank, E., Kowalski, J., Sherrill, J.T., Tu, X.M., & Anderson, B. (2000) Stressful life events, bipolar disorder, and the "kindling model." *Journal of Abnormal Psychology* **109** 777-786.

Holm, S.A. (1979) A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* **6** 65-70.

Hopko, D.R., Armento, M.E., Cantu, M.S., Chambers, L.L., & Lejuez, C.W. (2003) The use of daily diaries to assess the relations among mood state, overt behaviour, and reward value of activities. *Behaviour Research and Therapy* **41** 1137-1148.

Hudson, J.I., Lipinski, J.F., Keck, P.E., Aizley, H.G., Lukas, S.E., Rothschild, A.J., Waternaux, C.M., & Kupfer, D.J. (1992) Polysomnographic characteristics of young manic

patients, comparison with unipolar depressed patients and normal control subjects. *Archives of General Psychiatry* **49** 378-383.

Hudson, J.I., Lipinski, J.F., Frankenburg, F.R., Grochocinski, V.J., & Kupfer, D.J. (1988) Electroencephalographic sleep in mania. *Archives of General Psychiatry* **45** 267-273.

Hunt, N., Bruce-Jones, W., & Silverstone, T. (1992) Life events and relapse in bipolar affective disorder. *Journal of Affective Disorders* **25** 13-20.

Jackson, A., Cavanagh, J., & Scott, J. (2003) A systematic review of manic and depressive prodromes. *Journal of Affective Disorders* **74** 209-217.

Jauhar, P. & Weller, M.P.I. (1982) Psychiatric morbidity and time zone changes: a study of patients from Heathrow Airport. *British Journal of Psychiatry* **140** 231-235.

Joffe, R.T., MacQueen, G.M., Marriott, M., & Young, L.T. (2004) A prospective longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disorders* **6** 62-66.

Joffe, R.T., Macdonald, C., & Kutcher, S.P. (1989) Life events and mania: a case-controlled study. *Psychiatry Research* **30** 213-216.

John, O.P. & Benet-Martinez, V. (2000) Measurement: reliability, construct validation, and scale construction. In: Reis, H.T. and Judd, C.M. (Ed.) *Handbook of research methods in social and personality psychology.* 339-369. Cambridge University Press.

Johnson, S.L. (2005) Life events in bipolar disorder: towards more specific models. *Clinical Psychology Review* **25** 1008-1027.

Johnson, S.L. Meyer, B. Winters, R.W. Sandrow, D. & Goodnick, P. (2003) The behavioural activation system and the course of mania. In: Scrimali, T. & Grimaldi, L. (Ed.) *Cognitive psychotherapy towards a new millennium.* New York: Kluwer Academic/Plenum Publishers.

Johnson, S.L., Greenhouse, W., & Bauer, M. (2000a) Psychosocial approaches to the treatment of bipolar disorder. *Current Opinion in Psychiatry* **13** 69-72.

Johnson, S.L., Meyer, B., Winett, C., & Small, J. (2000b) Social support and self esteem predict changes in bipolar depression but not mania. *Journal of Affective Disorders* **58** 79-86.

Johnson, S.L., Sandrow, D., Meyer, B., Winters, R., Miller, I., Solomon, D., & Keitner, G. (2000c) Increases in manic symptoms after life events involving goal attainment. *Journal of Abnormal Psychology* **109** 721-727.

Johnson, S.L. & Roberts, J.E. (1995) Life events and bipolar disorder: implications from biological theories. *Psychological Bulletin* **117** 434-449.

Jones, S.H. Hare, D.J. & Evershed, K. (2005) Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disorders* 7 176-186.

Jones, S.H. (2004) Psychotherapy of bipolar disorder: a review. *Journal of Affective Disorders* **80** 101-114.

Jones, S.H. (2001) Circadian rhythms, multilevel models of emotion and bipolar disorder - an initial step towards integration? *Clinical Psychology Review* **21** 1193-1209.

Jorm, A.F., Christensen, H., Henderson, A.S., Jacomb, P.A., Korten, A.E., & Rodgers, B. (1999) Using the BIS/BAS scales to measure behavioural inhibition and behavioural activation: factor structure, validity and norms in a large community sample. *Personality and Individual Differences* **26** 49-58.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Coryell, W., Maser, J., Rice, J.A., Solomon, D.A., & Keller, M.B. (2003a) The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *Journal of Affective Disorders* **73** 19-32.

Judd, L.L. Akiskal, H.S. Schettler, P.J. Coryell, W. Endicott, J. Maser, J.D. Solomon, D.A. Leon, A.C. & Keller, M.B. (2003b) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Archives of General Psychiatry* **60** 261-269.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., & Keller, M.B. (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry* **59** 530-537.

Kasch, K.L., Rottenberg, J., Arnow, B.A., & Gotlib, I.H. (2002) Behavioural activation and inhibition systems and the severity and course of depression. *Journal of Abnormal Psychology* **111** 589-597.

Keck, P.E., Mendlwicz, J., Calabrese, J.R., Fawcett, J., Suppes, T., Vestergaard, P.A., & Carbonell, C. (2000) A review of randomised controlled clinical trials in acute mania. *Journal of Affective Disorders* **59** 31-37.

Keck, P.E. & McElroy, S.L. (1996) Outcome in the pharmacologic treatment of bipolar disorder. *Journal of Clinical Psychopharmacology* **16** 15-23.

Keitner, G.I., Solomon, D.A., Ryan, C.A., Miller, I.W., Mallinger, A., Kupfer, D.J., & Frank, E. (1996) Prodromal and residual symptoms in bipolar I disorder. *Comprehensive Psychiatry* **37** 362-367.

Keller, M.B., Lavori, P.W., Kane, J.M., Gelenberg, A.J., Rosenbaum, J.F., Walzer, E.A., & Baker, L.A. (1992) Subsyndromal symptoms in bipolar disorder, a comparison of standard and low serum levels of lithium. *Archives of General Psychiatry* **49** 371-376.

Kennedy, S., Thompson, R., Stancer, H.C., Roy, A., & Persad, E. (1983) Life events precipitating mania. *British Journal of Psychiatry* **142** 398-403.

Kennedy-Moore, E., Greenberg, M.A., Newman, M.G., & Stone, A.A. (1992) The relationship between daily events and mood: the mood measure may matter. *Motivation and Emotion* **16** 143-155.

Kernis, M.H. (1993) The roles of stability and level of self esteem in psychological functioning. In: Baumeister, R.F. (Ed.) *Self esteem: the puzzle of low self regard.* 167-182. Plenum Press.

Kernis, M.H., Whisenhunt, C.R., Waschull, S.B., Greenier, K.D., Berry, A.J., Herlocker, C.E., & Anderson, C.A. (1998) Multiple facets of self-esteem and their relations to depressive symptoms. *Personality and Social Psychology Bulletin* **24** 657-668.

Kernis, M.H., Greenier, K.D., Herlocker, C.E., Whisenhunt, C.R., & Abend, T.A. (1997) Self perceptions of reactions to doing well or poorly: the roles of stability and level of self esteem. *Personality and Individual Differences* **22** 845-854.

Kernis, M.H. & Waschull, S.B. (1995) The interactive roles of stability and level of self esteem: research and theory. In: Zanna, M.P. (Ed.) *Advances in experimental social psychology.* 93-141. Academic Press.

Kernis, M.H., Cornell, D.P., Sun, C., Berry, A., & Harlow, T. (1993a) There's more to self esteem than whether it is high or low: the importance of stability of self esteem. *Journal of Personality and Social Psychology* **65** 1190-1204.

Kernis, M.H. Greenier, K. Whisenhunt, C. Waschull, S.B. & Berry, A.J. (1993b) Stability of self esteem and ego involvement: initial considerations. *Paper presented at the Nags Head Self and Society Conference, Highland Beach, FL.*

Kernis, M.H., Grannemann, B.D., & Barclay, L.C. (1992) Stability of self esteem: assessment, correlates, and excuse making. *Journal of Personality* **60** 621-644.

Kernis, M.H., Grannemann, B.D., & Mathis, L.C. (1991) Stability of self esteem as a moderator of the relation between level of self esteem and depression. *Journal of Personality and Social Psychology* **61** 80-84.

Kernis, M.H., Grannemann, B.D., & Barclay, L.C. (1989) Stability and level of self esteem as predictors of anger arousal and hostility. *Journal of Personality and Social Psychology* **56** 1013-1022.

Kerr, A.W., Hall, H.K., & Kozub, S.A. (2002) *Doing statistics with SPSS.* London: Sage.

Kessing, L.V., Andersen, P.K., Mortensen, P.B., & Bolwig, T.G. (1998) Recurrence in affective disorder: I. Case register study. *British Journal of Psychiatry* **172** 23-28.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H., & Kendler, K.S. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry* **51** 8-19.

Kilzieh, N. & Akiskal, H.S. (1999) Rapid cycling bipolar disorder: an overview of research and clinical experience. *Psychiatric Clinics of North America* **22** 585-607.

King, B.M. & Minium, E.M. (2003) Interpreting the results of hypothesis testing: effect size, type I and type II errors, and power. In: King, B.M. and Minium, E.M. (Ed.) *Statistical reasoning in psychology and education.* 263-286. John Wiley and Sons.

Knowles, J.B., Cairns, J., Maclean, A.W., Delva, N., Prowse, A., Waldron, J., & Letemendia, F.J. (1986) The sleep of remitted bipolar depressives: comparison with sex and age matched controls. *Canadian Journal of Psychiatry* **31** 295-298.

Koukopoulos, A., Reginaldi, D., Minnai, G., Serra, G., Pani, L., & Johnson, F.N. (1995) The long term prophylaxis of affective disorders. In: Gessa, G., Fratta, W., Pani, L., and Serra, G. (Ed.) *Depression and mania: from neurobiology to treatment.* 127-147. Raven Press, New York.

Kushida, C.A., Chang, A., Gadkary, C., Guilleminault, C., Carrillo, O., & Dement, W.C. (2001) Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep disordered patients. *Sleep Medicine* **2** 389-396.

Lam, D.H. Hayward, P. Watkins, E.R. Wright, K. & Sham, P. (2005) Relapse prevention in patients with bipolar disorder: cognitive therapy outcomes after two years. *American Journal of Psychiatry* **162** 324-329.

Lam, D.H., Bright, J., Jones, S., Hayward, P., Schuck, N., Chisholm, D., & Sham, P. (2000) Cognitive therapy for bipolar illness- a pilot study of relapse prevention. *Cognitive Therapy and Research* **24** 503-520.

Lam, D.H., Watkins, E.R., Hayward, P., Bright, J., Wright, K., Kerr, N., Parr-Davis, G., & Sham, P. (2003) A randomised controlled study of cognitive therapy for relapse prevention for bipolar affective disorder. *Archives of General Psychiatry* **60** 145-152.

Lam, D., Jones, S.H., Hayward, P., & Bright, J.A. (1999) *Cognitive therapy for bipolar disorder, a therapist's guide to concepts, methods and practice.* Wiley.

Lam, D. & Wong, G. (1997) Prodromes, coping strategies, insight and social functioning in bipolar affective disorders. *Psychological Medicine* **27** 1091-1100.

Larsen, R.J. (1990) Spectral analysis of psychological data. In: Von Eye, A. (Ed.) *Statistical methods in longitudinal research. Volume II, Time series and categorical longitudinal data.* 319-349. Academic Press.

Larsen, R.J. (1987) The stability of mood variability: a spectral analytic approach to daily mood assessments. *Journal of Personality and Social Psychology* **52** 1195-1204.

Larsen, R.J. & Cutler, S.E. (1996) The complexity of individual emotional lives: a within-subject analysis of affect structure. *Journal of Social and Clinical Psychology* **15** 206-230.

Larsen, R.J. & Ketelaar, T. (1991) Personality and susceptibility to positive and negative emotional states. *Journal of Personality and Social Psychology* **61** 132-140.

Leibenluft, E. & Frank, E. (2001) Circadian rhythms in affective disorders. In: Takahashi, F.W., Turek, F.W., and Monroe, R.Y. (Ed.) *Handbook of behavioural neurobiology: circadian clocks.* 625-644. Kluwer Academic/Plenum Publishers.

Leibenluft, E. & Suppes, T. (1999) Treating bipolar illness: focus on treatment algorithms and management of the sleep wake cycle. *American Journal of Psychiatry* **156** 1976-1981.

Leibenluft, E., Albert, P.S., Rosenthal, N.E., & Wehr, T.A. (1996) Relationship between sleep and mood in patients with rapid cycling bipolar disorder. *Psychiatry Research* **63** 161-168.

Leibenluft, E. & Wehr, T.A. (1992) Is sleep deprivation useful in the treatment of depression? *American Journal of Psychiatry* **149** 159-168.

Leone, L., Perugini, M., Bagozzi, R.P., Pierro, A., & Mannetti, L. (2001) Construct validity and generalisability of the Carver-White behavioural inhibition system/behavioural activation system scales. *European Journal of Personality* **15** 373-390.

Lockley, S.W., Skene, D.J., & Arendt, J. (1999) Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *Journal of Sleep Research* **8** 175-183.

Lonigan, C.J., Hooe, E.S., David, C.F., & Kistner, J.A. (1999) Positive and negative affectivity in children: confirmatory factor analysis of a two factor model and its relation to symptoms of anxiety and depression. *Journal of Consulting and Clinical Psychology* **67** 374-386.

Lovejoy, M.C. & Steuerwald, B.L. (1995) Subsyndromal unipolar and bipolar disorders: comparisons on positive and negative affect. *Journal of Abnormal Psychology* **104** 381-384.

Lovejoy, M.C. & Steuerwald, B.L. (1992) Psychological characteristics associated with subsyndromal affective disorder. *Personality and Individual Differences* **13** 303-308.

Lyon, H.M., Startup, M., & Bentall, R.P. (1999) Social cognition and the manic defence: attributions, selective attention and self schema in bipolar affective disorder. *Journal of Abnormal Psychology* **108** 273-282.

MacAndrew, C. & Steele, T. (1991) Grays' behavioural inhibition system: a psychometric examination. *Personality and Individual Differences* **12** 157-171.

MacQueen, G.M., Young, L.T., & Joffe, R.T. (2001) A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatrica Scandinavica* **103** 163-170.

Maj, M. (2000) The impact of lithium prophylaxis on the course of bipolar disorder: a review of the research evidence. *Bipolar Disorders* **2** 93-101.

Maj, M., Pirozzi, R., Magliano, L., & Bartoli, L. (1998) Long term outcome of lithium prophylaxis in bipolar disorder: a 5 year prospective study of 402 patients at a lithium clinic. *American Journal of Psychiatry* **155** 30-35.

Malkoff-Schwartz, S., Frank, E., Anderson, B.P., Hlastala, S.A., Luther, J.F., Sherrill, J.T., Houck, P.R., & Kupfer, D.J. (2000) Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychological Medicine* **30** 1005-1016.

Malkoff-Schwartz, S., Frank, E., Anderson, B., Sherrill, J.T., Siegel, L., Patterson, D., & Kupfer, D.J. (1998) Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes. *Archives of General Psychiatry* **55** 702-707.

McCarthy, E., Tarrier, N., & Gregg, L. (2002) The nature and timing of seasonal affective symptoms and the influence of self-esteem and social support: a longitudinal prospective study. *Psychological Medicine* **32** 1425-1434.

McConville, C. & Cooper, C. (1997) The temporal stability of mood variability. *Personality and Individual Differences* **23** 161-164.

McConville, C. & Cooper, C. (1996) Mood variability and the intensity of depressive states. *Current Psychology* **14** 329-338.

McConville, C. & Cooper, C. (1995) Is emotional intensity a general construct? *Personality and Individual Differences* **18** 425-427.

McGuffin, P. Rijsdijk, F. Andrew, M. Sham, P. Katz, R. & Cardno, A. (2003) The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry* **60** 497-502.

McPherson, H., Herbison, P., & Romans, S. (1993) Life events and relapse in established bipolar affective disorder. *British Journal of Psychiatry* **163** 381-385.

Mendlewicz, J. & Kerkhofs, M. (1991) Sleep electroencephalography in depressive illness, a collaborative study by the World Health Organisation. *British Journal of Psychiatry* **159** 505-509.

Mendlowicz, M.V., Jean-Louis, G., Von Gizycki, H., Zizi, F., & Nunes, J. (1999) Actigraphic predictors of depressed mood in a cohort of non-psychiatric adults. *Australian and New Zealand Journal of Psychiatry* **33** 553-558.

Meyer, B., Johnson, S.L., & Winters, R. (2001) Responsiveness to threat and incentive in bipolar disorder: relations of the BIS/BAS Scales with symptoms. *Journal of Psychopathology and Behavioural Assessment* **23** 133-143.

Meyer, B., Johnson, S.L., & Carver, C.S. (1999) Exploring behavioural activation and inhibition sensitivities among college students at risk for bipolar spectrum sensitivities. *Journal of Psychopathology and Behavioural Assessment* **21** 275-292.

Miklowitz, D.J. George, E.L. Richards, J.A. Simoneau, T.L. & Suddath, R.L. (2003) A randomised study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Archives of General Psychiatry* **60** 904-912.

Miklowitz, D.J., Simoneau, T.L., George, E.L., Richards, J.A., Kalbag, A., Sachs-Ericsson, N., & Suddath, R. (2000) Family focused treatment of bipolar disorder: one year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biological Psychiatry* **48** 582-592.

Miklowitz, D.J., Frank, E., & George, E.L. (1996) New psychosocial treatments for the outpatient management of bipolar disorder. *Psychopharmacology Bulletin* **32** 613-621.

Millar, A., Espie, C., & Scott, J. (2004) The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *Journal of Affective Disorders* **80** 145-153.

Molnar, G., Feeney, M.G., & Fava, G.A. (1988) Duration and symptoms of bipolar prodromes. *American Journal of Psychiatry* **145** 1576-1578.

Monk, T.H., Frank, E., Potts, J.M., & Kupfer, D.J. (2002) A simple way to measure daily lifestyle regularity. *Journal of Sleep Research* **11** 183-190.

Monk, T.H., Reynolds, C.F., Kupfer, D.J., Hoch, C.C., Carrier, J., & Houck, P.R. (1997) Differences over the life span in daily life-style regularity. *Chronobiology International* **14** 295-306.

Monk, T.H., Petrie, S.R., Hayes, A.J., & Kupfer, D.J. (1994) Regularity of daily life in relation to personality, age, gender, sleep quality and circadian rhythms. *Journal of Sleep Research* **3** 196-205.

Monk, T.H., Kupfer, D.J., Frank, E., & Ritenour, A.M. (1991) The social rhythm metric (SRM): measuring daily social rhythms over 12 weeks. *Psychiatry Research* **36** 195-207.

Monk, T.H., Flaherty, J.F., Frank, E., Hoskinson, K., & Kupfer, D.J. (1990) The social rhythm metric, an instrument to quantify the daily rhythms of life. *Journal of Nervous and Mental Disease* **178** 120-126.

Monroe, S.M. & Simons, A.D. (1991) Diathesis stress theories in the context of life stress research: implications for the depressive disorders. *Psychological Bulletin* **110** 406-425.

Morriss, R. (2002) Clinical importance of inter-episode symptoms in patients with bipolar affective disorder. *Journal of Affective Disorders* **72** 3-13.

Muller-Oerlinghausen, B., Berghofer, A., & Bauer, M. (2002) Bipolar disorder. *The Lancet* **359** 241-247.

Myin-Germeys, I., Peeters, F., Havermans, R., Nicolson, N., Devries, M.W., Delespaul, P., & Van Os, J. (2003) Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatrica Scandinavica* **107** 124-131.

Neale, J.M. (1988) Defensive functions of manic episodes. In: Maher, B.A. and Oltmanns, T.F. (Ed.) *Delusional beliefs.* 138-156. Wiley.

Norman, G.R. & Streiner, D.L. (2000) *Biostatistics, the bare essentials.* B.C. Decker Inc.

Nurnberger, J.I., Adkins, S., Lahiri, D.K., Mayeda, A., Hu, K., Lewy, A., Miller, A., Bowman, E., Miller, M.J., Rau, N.L., Smiley, C., & Davis-Singh, D. (2000) Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archives of General Psychiatry* **57** 572-579.

Pardoen, D., Bauwens, F., Dramaix, M., Tracy, A., Genevrois, G., Staner, L., & Mendlewicz, J. (1996) Life events and primary affective disorders: a one year prospective study. *British Journal of Psychiatry* **169** 160-166.

Pardoen, D., Bauwens, F., Tracy, A., Martin, F., & Mendlewicz, J. (1993) Self esteem in recovered bipolar and unipolar out-patients. *British Journal of Psychiatry* **163** 755-762.

Parkinson, B., Briner, R.B., Reynolds, S., & Totterdell, P. (1995) Time frames for mood: relations between momentary and generalised ratings of affect. *Personality and Social Psychology Bulletin* **21** 331-339.

Patterson, S.M., Krantz, D.S., Montgomery, L.C., Deuster, P.A., Hedges, S.M., & Nebel, L.E. (1993) Automated physical activity monitoring: validation and comparison with physiological and self report measures. *Psychophysiology* **30** 296-305.

Peeters, F., Nicolson, N.A., Berkhof, J., Delespaul, P., & Deuries, M. (2003) Effects of daily events on mood states in major depressive disorders. *Journal of Abnormal Psychology* **112** 203-211.

Penner, L.A., Shiffman, S., Paty, J.A., & Fritzsche, B.A. (1994) Individual differences in intraperson variability in mood. *Journal of Personality and Social Psychology* **66** 712-721.

Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X., & Kupfer, D.J. (1997) Self reported sleep disturbance as a prodromal symptom in recurrent depression. *Journal of Affective Disorders* **42** 209-212.

Perry, A., Tarrier, N., Morriss, R., McCarthy, E., & Limb, K. (1999) Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *British Medical Journal* **318** 149-153.

Petrie, A. & Sabin, C. (2000) *Medical statistics at a glance*. Blackwell Science.

Pickering, A.D., Corr, P.J., & Gray, J.A. (1999) Interactions and reinforcement sensitivity theory: a theoretical analysis of Rusting & Larsen (1997). *Personality and Individual Differences* **26** 357-365.

Pollak, C.P., Tryon, W.W., Nagaraja, H., & Dzwonczk, R. (2001) How accurately does wrist actigraphy identify the states of sleep and wakefulness? *Sleep* **24** 957-965.

Post, R.M. (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry* **149** 999-1010.

Post, R.M. & Weiss, S.R. (1995) The neurobiology of treatment-resistant mood disorders. In: Bloom, F.E. and Kupfer, D.J. (Ed.) *Psychopharmacology: the fourth generation of progress.* 1155-1170. Raven Press.

Post, R.M., Rubinow, D.R., & Ballenger, J.C. (1986) Conditioning and sensitisation in the longitudinal course of affective illness. *British Journal of Psychiatry* **149** 191-201.

Post, R.M., Ballenger, J.C., Rey, A.C., & Bunney, W.E. (1981) Slow and rapid onset of manic episodes: implications for underlying biology. *Psychiatry Research* **4** 229-237.

Power, M.J. Katz, R. McGuffin, P. Duggan, C.F. Lam, D. & Beck, A.T. (1994) The Dysfunctional Attitude Scale (DAS): A comparison of Forms A and B and proposals for a new subscaled version. *Journal of Research in Personality* **28** 263-276.

Prien, R.F. & Potter, W.Z. (1990) NIMH workshop report on treatment of bipolar disorder. *Psychopharmacology Bulletin* **26** 409-427.

Rea, M.M., Tompson, M.C., Miklowitz, D.J., Goldstein, M.J., Hwang, S., & Mintz, J. (2003) Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized controlled trial. *Journal of Consulting and Clinical Psychology* **71** 482-492.

Reilly-Harrington, N.A., Alloy, L.B., Fresco, D.M., & Whitehouse, W.G. (1999) Cognitive styles and life events interact to predict bipolar and unipolar symptomatology. *Journal of Abnormal Psychology* **108** 567-578.

Reis, H.T. & Gable, S.L. (2000) Event-sampling and other methods for studying everyday experience. In: Reis, H.T. and Judd, C.M. (Ed.) *Handbook of research methods in social and personality psychology.* 190-222. Cambridge University Press.

Rhodewalt, F., Madrian, J.C., & Cheney, S. (1998) Narcissism, self-knowledge organisation, and emotional reactivity: the effect of daily experiences on self-esteem and affect. *Personality and Social Psychology Bulletin* **24** 75-87.

Riemann, D. & Voderholzer, U. (2003) Primary insomnia: a risk factor to develop depression? *Journal of Affective Disorders* **76** 255-259.

Riemann, D. & Berger, M. (1998) Sleep disorders and mental disorders. *Current Opinion in Psychiatry* **11** 327-331.

Riemann, D., Wiegand, M., Lauer, C.J., & Berger, M. (1993) Naps after total sleep deprivation in depressed patients: are they depressiogenic? *Psychiatry Research* **49** 109-120.

Roberts, J.E. & Gamble, S.A. (2001) Current mood state and past depression as predictors of self esteem and dysfunctional attitudes among adolescents. *Personality and Individual Differences* **30** 1023-1037.

Roberts, J.E. Shapiro, A.M. & Gamble, S.A. (1999) Level and perceived stability of self esteem prospectively predict depressive symptoms during psychoeducational group treatment. *British Journal of Clinical Psychology* **38** 425-429.

Roberts, J.E. & Monroe, S.M. (1999) Vulnerable self esteem and social processes in depression: toward an interpersonal model of self esteem regulation. In: Joiner, T.E. and Coyne, J.C. (Ed.) *The interactional nature of depression: advances in interpersonal approaches.* 149-187. American Psychological Association.

Roberts, J.E. & Gotlib, I.H. (1997) Temporal variability in global self esteem and specific self evaluation as prospective predictors of emotional distress: specificity in predictors and outcome. *Journal of Abnormal Psychology* **106** 521-529.

Roberts, J.E. & Kassel, J.D. (1997) Labile self esteem, life stress, and depressive symptoms: prospective data testing a model of vulnerability. *Cognitive Therapy and Research* **21** 569-589.

Roberts, J.E. & Kassel, J.D. (1996) Mood-state dependence in cognitive vulnerability to depression: the roles of positive and negative affect. *Cognitive Therapy and Research* **20** 1-12.

Roberts, J.E., Kassel, J.D., & Gotlib, I.H. (1995) Level and stability of self esteem as predictors of depressive symptoms. *Personality and Individual Differences* **19** 217-224.

Roberts, J.E. & Monroe, S.M. (1994) A multidimensional model of self-esteem in depression. *Clinical Psychology Review* **14** 161-181.

Roberts, J.E. & Monroe, S.M. (1992) Vulnerable self esteem and depressive symptoms: prospective findings comparing three alternative conceptualisations. *Journal of Personality and Social Psychology* **62** 804-812.

Robins, C.J. (1990) Congruence of personality and life events in depression. *Journal of Abnormal Psychology* **99** 393-397.

Robins, C.J. & Block, P. (1988) Personal vulnerability, life events, and depressive symptoms: a test of a specific interactional model. *Journal of Personality and Social Psychology* **54** 847-852.

Rosenberg, M. (1979) *Conceiving the self.* 128-148. Basic Books Inc.

Rosenberg, M. (1965) *Society and the adolescent self image.* 16-36. Princeton University Press.

Ross, S.R., Millis, S.R., Bonebright, T.L., & Bailley, S.E. (2002) Confirmatory factor analysis of the Behavioural Inhibition and Activation Scales. *Personality and Individual Differences* **33** 861-865.

Roy-Byrne, P.P., Uhde, T.W., & Post, R.M. (1984) Antidepressant effects of one night's sleep deprivation: clinical and theoretical implications. In: Post, R.M. and Ballenger, J.C. (Ed.) *Neurobiology of mood disorders.* 817-835. Baltimore: Williams and Williams.

Royant-Parola, S., Borbely, A.A., Tobler, I., Benoit, O., & Widlocher, D. (1986) Monitoring of long term motor activity in depressed patients. *British Journal of Psychiatry* **149** 288-293.

Sachs, G.S., Koslow, C.L., & Ghaemi, S.N. (2000) The treatment of bipolar depression. *Bipolar Disorders* **2** 256-260.

Sadeh, A., Hauri, P.J., Kripke, D.F., & Lavie, P. (1995) The role of actigraphy in the evaluation of sleep disorders. *Sleep* **18** 288-302.

Sadeh, A., Sharkey, K.M., & Carskadon, M.A. (1994) Activity based sleep-wake identification: an empirical test of methodological issues. *Sleep* **17** 201-207.

Schou, M. (1997) Forty years of lithium treatment. *Archives of General Psychiatry* **54** 9-13.

Sclare, P. & Creed, F. (1990) Life events and the onset of mania. *British Journal of Psychiatry* **156** 508-514.

Scott, J. (2001) Cognitive therapy as an adjunct to medication in bipolar disorder. *British Journal of Psychiatry* **178** 164-168.

Scott, J. (1995) Psychotherapy for bipolar disorder. *British Journal of Psychiatry* **167** 581-588.

Scott, J. Paykel, E. Morriss, R. Bentall, R. Kinderman, P. Johnson, T. Abbott, R. & Hayhurst, H. (2006) Cognitive-behavioural therapy for severe and recurrent bipolar disorders. *British Journal of Psychiatry* **188** 313-320.

Scott, J. & Gutierrez, M.J. (2004) The current status of psychological treatments in bipolar disorders: a systematic review of relapse prevention. *Bipolar Disorders* **6** 498-503.

Scott, J. & Pope, M. (2003) Cognitive styles in individuals with bipolar disorders. *Psychological Medicine* **33** 1081-1088.

Scott, J. & Todd, G. (2002) Is there a role for psychotherapy in bipolar disorders? *Clinical Approaches in Bipolar Disorders* **1** 22-30.

Scott, J., Garland, A., & Moorhead, S. (2001) A pilot study of cognitive therapy in bipolar disorders. *Psychological Medicine* **31** 459-467.

Scott, J. Stanton, B. Garland, A. & Ferrier, I.N. (2000) Cognitive vulnerability in patients with bipolar disorder. *Psychological Medicine* **30** 467-472.

Scott-Killgore, W.D. (2000) Evidence for a third factor on the Positive and Negative Affect Schedule in a college student sample. *Perceptual and Motor Skills* **90** 147-152.

Serretti, A. & Olgiati, P. (2005) Profiles of "manic" symptoms in bipolar I, bipolar II and major depressive disorders. *Journal of Affective Disorders* **84** 159-166.

Serretti, A., Olgiati, P., & Colombo, C. (2005) Components of self-esteem in affective patients and non-psychiatric controls. *Journal of Affective Disorders* **88** 93-98.

Serretti, A., Cavallini, M.C., Macciardo, F., Namia, C., Franchini, L., Souery, D., Lipp, O., Bauwens, F., Smeraldi, E., & Mendlewicz, J. (1999) Social adjustment and self-esteem in remitted patients with mood disorders. *European Psychiatry* **14** 137-142.

Shapira, B., Zislin, J., Gelfin, Y., Osher, Y., Gorfine, M., Sovery, D., Mendlewicz, J., & Lerer, B. (1999) Social adjustment and self-esteem in remitted patients with unipolar and bipolar affective disorder: a case-control study. *Comprehensive Psychiatry* **40** 24-30.

Shumway, R.H. & Stoffer, D.S. (2000) *Time series analysis and its applications.* Springer.

Siever, L.J. & Davis, K.L. (1985) Overview: toward a dysregulation hypothesis of depression. *American Journal of Psychiatry* **142** 1017-1031.

Silverstone, T., McPherson, H., Hunt, N., & Romans, S. (1998) How effective is lithium in the prevention of relapse in bipolar disorder? A prospective follow up study. *Australian and New Zealand Journal of Psychiatry* **32** 61-66.

Simons, A.D., Gordon, J.S., Monroe, S.M., & Thase, M.E. (1995) Toward an integration of psychologic, social, and biologic factors in depression: effects on outcome and course of cognitive therapy. *Journal of Consulting and Clinical Psychology* **63** 369-377.

Smith, J.A. & Tarrier, N. (1992) Prodromal symptoms in manic depressive psychosis. *Social Psychiatry and Psychiatric Epidemiology* **27** 245-248.

Stone, A.A., Hedges, S.M., Neale, J.M., & Satin, M.S. (1985) Prospective and cross-sectional mood reports offer no evidence of a "blue Monday" phenomenon. *Journal of Personality and Social Psychology* **49** 129-134.

Streiner, D.L. (2002) The case of the missing data: methods of dealing with dropouts and other research vagaries. *Canadian Journal of Psychiatry* **47** 68-75.

Suls, J., Green, P., & Hillis, S. (1998) Emotional reactivity to everyday problems, affective inertia and neuroticism. *Personality and Social Psychology Bulletin* **24** 127-136.

Sutton, S.K. & Davidson, R.J. (1997) Prefrontal brain asymmetry: a biological substrate of the behavioural approach and inhibition systems. *Psychological Science* **8** 204-210.

Swendsen, J., Hammen, C., Heller, T., & Gitlin, M. (1995) Correlates of stress reactivity in patients with bipolar disorder. *American Journal of Psychiatry* **152** 795-797.

Szuba, M.P., Baxter, L.R., Altshuler, L.L., Allen, E.M., Guze, B.H., Schwartz, J.M., & Liston, E.H. (1994) Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. *Psychiatry Research* **51** 283-295.

Szuba, M.P., Yager, A., Guze, B.H., Allen, E.M., & Baxter, L.R. (1992) Disruption of social circadian rhythms in major depression: a preliminary report. *Psychiatry Research* **42** 221-230.

Szuba, M.P., Baxter, L.R., Fairbanks, L.A., Guze, B.H., & Schwartz, J.M. (1991) Effects of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. *Biological Psychiatry* **30** 817-829.

Tabachnick, B.G. & Fidell, L.S. (2001) *Using multivariate statistics.* 322-390. 4th edition, Allyn and Bacon.

Teasdale, J.D. (1988) Cognitive vulnerability to persistent depression. *Cognition and Emotion* **2** 247-274.

Teicher, M.H. (1995) Actigraphy and motion analysis: new tools for psychiatry. *Harvard Review of Psychiatry* **3** 18-35.

Teicher, M.H., Glod, C.A., Magnus, E., Harper, D., Benson, G., Krueger, K., & McGreenery, C.E. (1997) Circadian rest-activity disturbances in seasonal affective disorder. *Archives of General Psychiatry* **54** 124-130.

Thompson, C. (1984) Circadian rhythms and psychiatry. *British Journal of Psychiatry* **145** 204-206.

Tondo, L. & Baldessarini, R.J. (1998) Rapid cycling in women and men with bipolar manic-depressive disorders. *American Journal of Psychiatry* **155** 1434-1436.

Van den Hoofdakker, R.H. (1997) Total sleep deprivation: clinical and theoretical aspects. In: Honig, A. and Van Praag, H.M. (Ed.) *Depression: neurobiological, psychopathological and therapeutic advances.* 563-589. John Wiley and Sons Ltd.

Van Eck, M., Nicolson, N.A., & Berkhof, J. (1998) Effects of stressful daily events on mood states: relationship to global perceived stress. *Journal of Personality and Social Psychology* **75** 1572-1585.

Van Someren, E.J., Swaab, D.F., Colenda, C.C., Cohen, W., McCall, W.V., & Rosenquist, P.B. (1999) Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiology International* **16** 505-518.

Van Someren, E.J., Lijzenga, C., Mirmiran, M., & Swaab, D.F. (1997) Long term fitness training improves the circadian rest-activity rhythm in healthy elderly males. *Journal of Biological Rhythms* **12** 146-156.

Van Someren, E.J., Hagebeuk, E.E., Lijzenga, C., Scheltens, P., De Rooij, S.E., Jonker, C., Pot, A., Mirmiran, M., & Swaab, D.F. (1996) Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biological Psychiatry* **40** 259-270.

Verbeek, I., Klip, E.C., & Declerck, A.C. (2001) The use of actigraphy revisited: the value for clinical practice in insomnia. *Perceptual and Motor Skills* **92** 852-856.

Watson, D. (1988) The vicissitudes of mood measurement: effects of varying descriptors, time frames, and response formats on measures of positive and negative affect. *Journal of Personality and Social Psychology* **55** 128-141.

Watson, D., Clark, L.A., & Carey, G. (1988a) Positive and negative affectivity and their relation to anxiety and depressive disorders. *Journal of Abnormal Psychology* **97** 346-353.

Watson, D., Clark, L.A., & Tellegen, A. (1988b) Development and validation of brief measures of positive and negative affect: The PANAS Scales. *Journal of Personality and Social Psychology* **54** 1063-1070.

Watson, D. & Tellegen, A. (1985) Towards a consensual structure of mood. *Psychological Bulletin* **98** 219-235.

Watson, D. & Clark, L.A. (1984) Negative affectivity: the disposition to experience aversive emotional states. *Psychological Bulletin* **96** 465-490.

Wehr, T.A. (1992) Improvement of depression and triggering of mania by sleep deprivation. *JAMA* **267** 548-551.

Wehr, T.A. (1991) Sleep loss as a possible mediator of diverse causes of mania. *British Journal of Psychiatry* **159** 576-578.

Wehr, T.A. (1990) Effects of wakefulness and sleep on depression and mania. In: Montplaisir, J. and Godbout, R. (Ed.) *Sleep and biological rhythms.* 42-86. Oxford University Press.

Wehr, T.A. (1989) Sleep loss: a preventable cause of mania and other excited states. *Journal of Clinical Psychiatry* **50** 8-16.

Wehr, T.A. (1984) Biological rhythms and manic depressive illness. In: Post, R.M. and Ballenger, J.C. (Ed.) *Neurobiology of mood disorders.* 190-206. Baltimore: Williams and Williams.

Wehr, T.A., Turner, E.H., Shimada, J.M., Lowe, C.H., Barker, C., & Leibenluft, E. (1998) Treatment of a rapidly cycling bipolar patient by using extended bed rest and darkness to stabilise the timing and duration of sleep. *Biological Psychiatry* **43** 822-828.

Wehr, T.A., Sack, D.A., & Rosenthal, N.E. (1987) Sleep reduction as a final common pathway in the genesis of mania. *American Journal of Psychiatry* **144** 201-204.

Wehr, T.A. & Goodwin, F.K. (1983) *Circadian rhythms in psychiatry.* 129-184. Boxwood Press.

Wehr, T.A., Goodwin, F.K., Wirz-Justice, A., Breitmaier, J., & Craig, C. (1982) 48-hour sleep-wake cycles in manic depressive illness. *Archives of General Psychiatry* **39** 559-565.

Wehr, T.A., Muscettola, G., & Goodwin, F.K. (1980) Urinary 3-methoxy-4-hydroxyphenylglycol circadian rhythm. *Archives of General Psychiatry* **37** 257-263.

Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H., Joyce, P.R., Karam, E.G., Lee, C., Lellouch, J., Lepine, J., Newman, S.C., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H., & Yeh, E. (1996) Cross-national epidemiology of major depression and bipolar disorder. *JAMA* **276** 293-299.

Wessman, A.E. & Ricks, D.F. (1966) *Mood and personality.* Holt, Rinehart and Winston, Inc.

West, S.G., Biesanz, J.C., & Pitts, S.C. (2000) Causal inference and generalisation in field settings, experimental and quasi-experimental designs. In: Reis, H.T. and Judd, C.M. (Ed.)

Handbook of research methods in social and personality psychology. 40-84. Cambridge University Press.

West, S.G. & Hepworth, J.T. (1991) Statistical issues in the study of temporal data: daily experiences. *Journal of Personality* **59** 609-662.

Wicklow, A. & Espie, C.A. (2000) Intrusive thoughts and their relationship to actigraphic measurement of sleep: towards a cognitive model of insomnia. *Behaviour Research and Therapy* **38** 679-693.

Williams, C. (2001) *Overcoming depression, a five areas approach.* Arnold Publishers.

Winkler, D., Pjrek, E., Praschak-Rieder, N., Willett, M., Pezawas, L., Konstantinidis, A., Stastny, J., & Kasper, S. (2005) Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biological Psychiatry* **58** 331-336.

Winokur, G., Coryell, W., Akiskal, H.S., Endicott, J., Keller, M., & Mueller, T. (1994) Manic depressive (bipolar) disorder: the course in light of a prospective ten year follow up of 131 patients. *Acta Psychiatrica Scandinavica* **89** 102-110.

Winters, K.C. & Neale, J.M. (1985) Mania and low self esteem. *Journal of Abnormal Psychology* **94** 282-290.

Wirz-Justice, A. (1995) Biological rhythms in mood disorders. In: Bloom, F.E. and Kupfer, D.J. (Ed.) *Psychopharmacology: the fourth generation of progress.* 999-1017. Raven Press.

Wirz-Justice, A., Quinto, C., Cajochen, C., Werth, E., & Hock, C. (1999) A rapid cycling bipolar patient treated with long nights, bedrest, and light. *Biological Psychiatry* **45** 1075-1077.

Witting, W., Kwa, I.H., Eikelenboom, P., Mirmiran, M., & Swaab, D.F. (1990) Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biological Psychiatry* **27** 563-572.

Wong, G. & Lam, D. (1999) The development and validation of the coping inventory for prodromes of mania. *Journal of Affective Disorders* **53** 57-65.

Woyshville, M.J., Lackamp, J.M., Eisengart, J.A., & Gilliland, J.A. (1999) On the meaning and measurement of affective instability: clues from chaos theory. *Biological Psychiatry* **45** 261-269.

Wu, J.C. & Bunney, W.E. (1990) The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *American Journal of Psychiatry* **147** 14-21.

Wylie, R.C. (1989) *Measures of self-concept.* 24-35. University of Nebraska Press.

Young, R.C. Biggs, J.T. Ziegler, V.E. & Meyer, D.A. (1978) A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133** 429-435.

Zaretsky, A.E. Segal, Z.V. & Gemar, M. (1999) Cognitive therapy for bipolar depression: a pilot study. *Canadian Journal of Psychiatry* **44** 491-494.

Appendix A. Ethics of Research Committee and management approval

The research protocol was submitted to the Forth Valley Primary Care NHS Trust Ethics Committee in April 2001. A letter from the Ethics Committee, dated 1st May 2001, granted ethical approval to the study. Subsequently, it was necessary to obtain management approval from the Clinical Director and Chief Executive of Forth Valley Primary Care NHS Trust. Management approval was provided by the Chief Executive on the 5th June 2001 and from the Clinical Director on the 20th June 2001.

FORTH VALLEY HEALTH BOARD

AJH/ksh/0988ta

1st May 2001

Ms Alison Tait
Research Assistant
Department of Psychological Medicine
University of Glasgow
Gartnavel Hospital
1055 Great Western Road
GLASGOW G12 OXH

Dear Ms Tait

RE: A study of psychobiosocial functioning in bipolar disorders

Thank you for your application for the above study which was reviewed by Forth Valley Ethics of Research Committee at the meeting on 26th April 2001.

I am pleased to inform you that the FVERC grants ethical approval to the study.

The Committee asked why 40 people were chosen for the study and commented that there were a large number of forms for participants to complete – is there any way these could be reduced without detriment to the study?

The project must be started within three years of obtaining notification of ethical approval. You should follow the protocol agreed and advise this committee of any changes made. Any alterations or amendments to the study protocol will require prior approval from Forth Valley Ethics of Research Committee. You should also provide the committee with an annual progress report each year on the anniversary of approval of your project

Please ensure that the Committee are advised when the study has been completed, with if appropriate, any notification for publication of results.

33 Spittal Street, Stirling, FK8 1DX
Telephone: 01786 –457251
Facsimile: 01786 - 451474

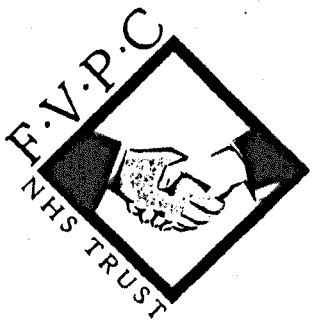
You will no doubt realise that whilst the Committee has given approval for your project on ethical grounds, it is still necessary for you to obtain management approval, if you have not already done so, from the relevant Clinical Director and/or Chief Executives of the Trusts in which the work will be carried out.

Yours sincerely

[redacted]

Dr A J Holliday
Secretary to Ethics of Research Committee

33 Spittal Street, Stirling, FK8 1DX
Telephone: 01786 -457251
Facsimile: 01786 - 451474



05 June 2001

EAH/FEK

Alison Tait
Research Assistant
Department of Psychological Medicine
University of Glasgow
Academic Centre
Gartnavel Royal Hospital
1055 Great Western Road
GLASGOW
G12 0XH

[redacted]

A Study of Psychobiosocial Functioning in Bipolar Disorders

Thank you for your letter of 25 May 2001 regarding the proposed study to be undertaken collaboratively between the Department of Psychological Medicine at the University of Glasgow and Dr McCabe of Westbank Day Unit. I am happy to approve your request for this study and look forward to hearing the outcome in due course.

Yours sincerely

[redacted]

E Anne Hawkins
Chief Executive

c.c. Dr Elaine McCabe, Westbank Day Unit

Forth Valley Primary Care NHS Trust
Old Denny Road, Larbert, FK5 4SD
Telephone : 01324 570 700 Facsimile : 01324 562 367

GJD/ed

20 June, 2001

Ms Alison Tait
Department of Psychological Medicine
University of Glasgow
Academic Centre, Gartnavel Royal Hospital
1055 Great Western Road
GLASGOW
G12 0XH

Dear Ms Tait

Project Title: A study of psychobiosocial functioning in bipolar disorders

Thank you for writing to me giving details of your excellent research proposal. I am pleased that you have considered asking my permission. I am delighted to grant it a look forward to the outcome of your work.

Kind regards.

Yours sincerely

[redacted]

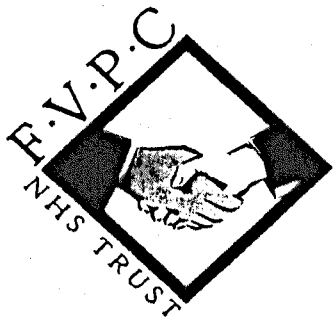
Dr Gareth Davies
Medical Director

cc: Professor Jan Scott, Head of Psychiatry, University of Glasgow
Dr Elaine McCabe, Staff Psychiatrist, FVPCT

Forth Valley Primary Care NHS Trust
Old Denny Road, Larbert, FK5 4SD
Telephone : 01324 570 700 Facsimile : 01324 562 367

Appendix B. Information sheets and consent forms

A staff psychiatrist identified individuals with bipolar disorder who attended a Lithium Clinic. Approval to approach each individual to participate was requested from the treating consultant psychiatrist. A consultant information sheet describing the research project was provided. Consultant approval was recorded for each individual on a consultant consent form. Individuals with bipolar disorder were approached to participate in the study by a staff psychiatrist, during routine appointments at a Lithium Clinic. Individuals received a patient information sheet, which outlined the purpose of the study and described what participating would involve. A patient consent form was completed by individuals who agreed to participate and a copy was provided for their own records.



Joan Searle Legacy Research Project: Information Sheet

Research Project: A study of psychobiosocial functioning in bipolar disorders

This research project aims to investigate the factors which may cause individuals with bipolar disorder to relapse. Ultimately, the research aims to investigate the antecedents, concomitants and consequences of relapse in bipolar disorder/manic depression. Goodwin and Jamison's (1990) three inter-related pathways to relapse in bipolar disorder (medication non-adherence, stressful life events, sleep disruption) will be monitored in combination with relevant personality vulnerability factors.

Individuals who have bipolar disorder, and have experienced a recent episode in the past two years are being asked to participate.

Inclusion criteria

1. Clinical diagnosis of Bipolar I or Bipolar II disorder
2. Currently in contact with general adult psychiatry services
3. Willingness to provide informed consent
4. Informed consent from the individual's consultant psychiatrist

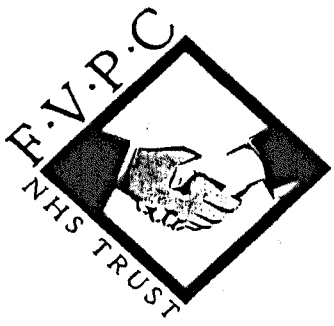
Exclusion criteria

1. Unable to give written informed consent
2. Current or recent involvement in other research projects

Research Team

Professor Jan Scott, Head of Psychiatry
Ms Alison Tait, Research Assistant
Dr Elaine McCabe, Staff Psychiatrist

For further information, please contact Alison Tait, Research Assistant on (0141) 211 3933, or in writing: Joan Searle Legacy Research Project, Department of Psychological Medicine, Garnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH.



Joan Searle Legacy Research Project: Consultant Psychiatrist Consent Form

I have received a copy of the information sheet regarding the research project in addition to a copy of the patient information sheet.

I have had an opportunity to discuss the research project with the research assistant and to address any concerns regarding the project.

I provide my consent for the individual named below to participate in the project.

Confidentiality regarding all information collected for this research project is assured. Access to the data will only be provided to individuals working on the project.

Name of patient (in capitals): .....

Name of consultant psychiatrist (in capitals): .....
Signature: .....
Date: .....

Joan Searle Legacy Research Project: Patient Information Sheet

Research project title: Symptoms of relapse in bipolar disorder

You are being invited to participate in a research project. It is important for you to understand the purpose of the research, and what participating will involve. Please read the following information carefully, and take time to decide whether or not you would like to take part.

What is the purpose of the study?

This research project aims to investigate the factors which may cause individuals who suffer from mood episodes to relapse. Research has indicated that, in addition to taking medication, individuals may be able to help prevent relapse by detecting early symptoms. Individuals may become vulnerable to relapse when their daily routine is disrupted or when a stressful life event occurs. If the factors which can cause individuals to relapse can be identified, it may be possible to prevent relapse occurring in some instances.

Why have I been chosen?

Individuals with a manic depressive disorder, who have experienced a recent episode, of either mania or depression, in the past two years are being asked to participate. The aim is to ask about 40 individuals to participate in the project.

Do I have to take part?

If you do decide to take part in the project, you will be given this information sheet to keep, and will be asked to sign a consent form. You will also receive a signed consent form to keep.

It is your decision to take part in the research, and if you change your mind at any point, you are free to withdraw, and you do not have to give any reason why you want to withdraw.

If you decide to withdraw from the research, your usual treatment will not be affected in any way.

Similarly, if you are not interested in initially consenting to participate in the research, your usual treatment will remain unaffected.

What will happen to me if I take part?

Whether you agree or not to take part in the research, the project will not interfere with your usual treatment. At the start of the research project, you will meet with the research assistant for an initial interview which will involve completing some questionnaires. Completion of questionnaires will take around one hour. If individuals do not like completing any of the questionnaires or individual items in an assessment, they need not do so.

We hope to meet every 8 weeks to discuss how the project is progressing for an individual and to address any questions or problems. At this appointment, we would also ask for some questionnaires to be completed. Individuals who do not like completing all questionnaires or individual items in the assessment need not do so. The length of this interview is estimated to be around one hour, which includes the completion of questionnaires.

What do I have to do?

Individuals are asked to provide daily information on how their day has been in the form of a daily monitoring package which is completed at the end of each day. Individuals, if they prefer, do not have to answer all the proposed questions. This daily package is estimated to take around 10 to 20 minutes to complete, and should take less time once an individual is familiar with the layout of the daily package. Individuals are also being asked to wear a acti-watch to monitor their sleep-wake cycle. This device is around the same size as an average wristwatch, and it is hoped that individuals will not find the device intrusive. The daily package and acti-watch will be collected at the end of each week by the research assistant, at a time convenient for the individual.

Each individual will be asked to participate in the research for 12 months. At the end of participating in the research, if you are interested, you can be provided with information regarding the questionnaires you completed. Some individuals might find it useful to view how certain factors vary over time and what effect this might have on manic depression.

We would also appreciate feedback on the research, and any suggestions which you feel could make monitoring easier.

Will taking part in the study help me?

The research aims to find out more about why individuals relapse, which may help us learn more about preventing relapse.

Will taking part in the study cost me anything?

There will be no cost to individuals taking part in the study. Any travelling expenses that are incurred will be reimbursed.

Will my taking part in the study be kept confidential?

The professionals involved in your care, including your GP, will be informed if you decide to take part. Your consultant psychiatrist will also be asked if the research will be beneficial for you.
It is your decision whether you tell family and friends about your involvement in the research.

All information which is collected about you during the course of the research will be kept strictly confidential, and will be kept secure at Gartnaval Royal Hospital. Only the individuals working on the project will have access to the information. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results are likely to be published approximately 1 year after the end of the project. Individuals who participate in the project will not be identified in any report or publication.

Who is organising and funding the research?

The Joan Searle Legacy is funding the research project. The funds are administered through the University of Glasgow.

Who has reviewed the study?

Greater Glasgow Primary Care NHS Trust Ethics Committee and Forth Valley Ethics of Research Committee have reviewed the study.

What if I have any questions

Any questions regarding the research project can be answered by Alison Tait, who is the Research Assistant on the project. Alison can be contacted by telephone on (0141) 211 3933.
If you prefer, you can also write to the following address: Joan Searle Legacy Research Project, Department of Psychological Medicine, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH.

What happens now?

If you are interested in taking part in the research project, please sign the following consent form.
The next stage will be to arrange a convenient time for the initial interview, where any further questions you may have can be addressed.

Joan Searle Legacy Research Project: Consent Form

Research Project copy of consent

Title of project: Symptoms of relapse in bipolar disorder
Name of researcher:

I have read and understood the information sheet, dated April 2001 (version 1) and have received a copy of the information sheet to keep.

I have had an opportunity to discuss the research project with the research assistant and to ask questions.

I understand that my participation is voluntary and I am aware that I am free to withdraw from the research at any time, without having to give a reason. I understand that my care and treatment will not be affected in any way.

Confidentiality regarding all information collected for this research project is assured. Access to the data will only be provided to individuals working on the project.

I agree to take part in the above study

Name (in capitals): ..... Date: .....
Signature: .....

Name of person taking consent (if different from researcher):
Name (in capitals): ..... Date: .....
Signature: .....

Researcher:
Name (in capitals): ..... Date: .....
Signature: .....

Appendix C. Actigraph monitoring

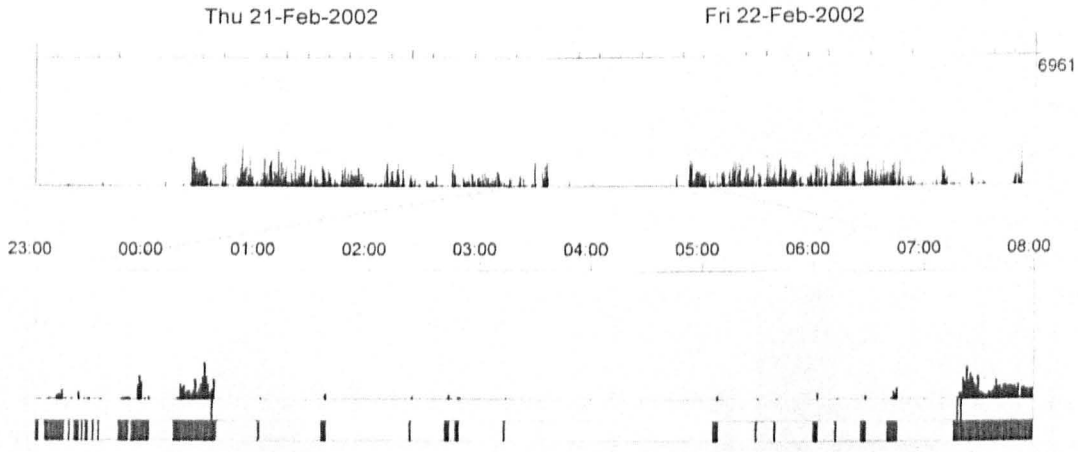
Sleep variables were calculated for each night of actiwatch monitoring. Bedtime and Get up time were manually inputted according to the SRM daily time. The "Actiwatch software" (Cambridge Neurotechnology Ltd.) uses a sleep-wake scoring algorithm to then calculate a large number of variables.

Non-parametric circadian rhythm analyses were calculated for each week of actigraph monitoring. A seven day analysis period provided mean values for circadian rhythm variables across that given week.

SLEEP WATCH
Daily Sleep printout

User identification CONTROL 1

Start date	20-Feb-2002	Start time	12:30	
Subject age	00	Subject sex	F	Epoch length 1.0 (Mins)
Day number	2			
Actogram Scale	6961			Sensitivity : MED



Bedtime	00:35	Get up time	07:20	Time in bed	06:45
Sleep start	00:35	Sleep end	07:18	Assumed sleep	06:43
Sleep efficiency	91.1 %	Sleep latency	00:00 mins		

Actual sleep time	06:09	(91.6 %)	Actual Wake time	00:34	(8.4 %)
No of sleep bouts	14		Mean length of sleep bouts	00:26:21	
No of wake bouts	14		Mean length of wake bouts	00:02:26	
No of mins moving	28.0	(6.9 %)	No of mins immobile	375.0	(93.1 %)
No of immobile phases	20		Mean length of immobility	18.8	

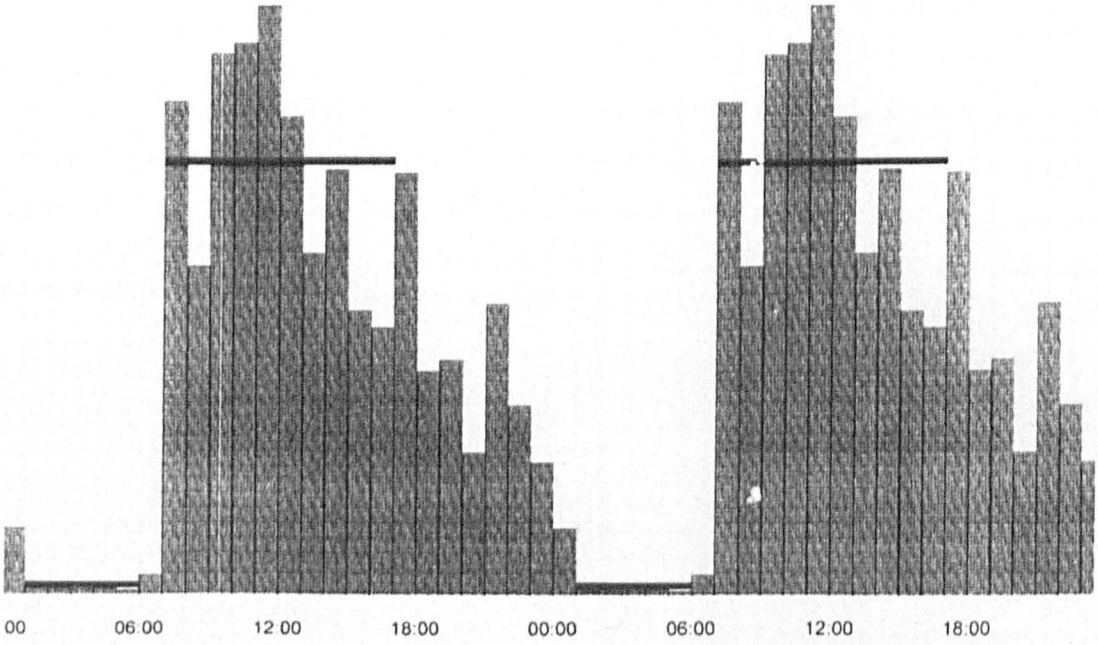
Immobility phases of 1 min	1	(5.0 %)

Total activity score	5290
Mean activity score	13.13
Mean score in active periods	188.93
Movement & fragmentation index	11.9
Wake movement	310.9

Watch S/N:V622282 Date File:26-Mar-2002

Non parametric circadian rhythm analysis

Identity:	control 1	Age: 56	Sex: F
Data start date:	20-Feb-2002 (Wed)		
Data start time:	12:30		
Analysis start:	Wed 20-Feb-2002	00:00	
Analysis length:	7days		
Intradaily stability:	0.744		
Intradaily variability:	0.921		
Lowest 5 hour count:	354	L5 Onset:	01:00
Max 10 hour count:	22055	M10 Onset:	07:00
Amplitude (M10-L5):	21701	Relative amp:	0.968



Watch S/N:V622282 Date File:26-Mar-2002 Cambridge Neurotechnology

Appendix D. Behavioural Inhibition System and Behavioural Activation Systems Scales

The Behavioural Inhibition System and Behavioural Activation Systems (BIS/BAS) Scales was developed by Carver and White (1994). The BIS/BAS Scales consists of one BIS subscale and three BAS subscales. The ♦ symbol denotes the seven BIS subscale items. The ▲ symbol denotes the five BAS Reward Responsiveness subscale items. The ● symbol denotes the four BAS Drive subscale items and the ♥ symbol denotes the four BAS Fun Seeking subscale items. Items were rated on a four point Likert scale (1=strong agreement, 4=strong disagreement). Scores for the two items phrased positively for the BIS subscale were reversed (items five and seven).

This scale lists different statements concerned with individual's feelings and behaviour. Please read each statement carefully and indicate how much you agree with what it says by placing a cross (X) under the appropriate column.

Statement	strong agreement	agreement	disagreement	strong disagreement
1. If I think something unpleasant is going to happen I usually get pretty "worked up." ♦				
2. I worry about making mistakes. ♦				
3. Criticism or scolding hurts me quite a bit. ♦				
4. I feel pretty worried or upset when I think or know somebody is angry at me. ♦				
5. Even if something bad is about to happen to me, I rarely experience fear or nervousness. ♦				

Statement	strong agreement	agreement	disagreement	strong disagreement
6. I feel worried when I think I have done poorly at something. ♦				
7. I have very few fears compared to my friends. ♦				
8. When I get something I want, I feel excited and energised. ▲				
9. When I'm doing well at something, I love to keep at it. ▲				
10. When good things happen to me, it affects me strongly. ▲				
11. It would excite me to win a contest. ▲				
12. When I see an opportunity for something I like, I get excited right away. ▲				
13. When I want something, I usually go all-out to get it. ●				

Statement	strong agreement	agreement	disagreement	strong disagreement
14. I go out of my way to get things I want. ●				
15. If I see a chance to get something I want, I move on it right away. ●				
16. When I go after something I use a "no holds barred" approach. ●				
17. I will often do things for no other reason than that they might be fun. ♥				
18. I crave excitement and new sensations. ♥				
19. I'm always willing to try something new if I think it will be fun. ♥				
20. I often act on the spur of the moment. ♥				

Appendix E. Social Rhythm Metric

The Social Rhythm Metric (SRM) was developed by Monk et al (1990, 1991). The SRM consists of 17 daily activities, of which 15 are specified and two are idiosyncratic to the individual. The SRM requires the individual to record the time at which an activity occurs and the number of people present. The SRM yields several variables calculated with an outlier elimination algorithm provided by Monk et al (1991). A Microsoft Excel (version 1997) spreadsheet was developed to facilitate algorithm calculations. An example algorithm calculation is provided for the activity 'get out of bed.'

Social Rhythm Metric

This diary-like sheet consists of a number of events and activities that individuals are likely to carry out on most days. Please complete the sheet at the end of the day, indicating the exact time at which the event was done (if done on that day) and with whom it was done (if done in the presence of another person).
Please use Activity A and Activity B to indicate activities that you carry out on most days (e.g. walking a dog, reading, having a bath)

Activity	Cross if did not do activity	Time	Cross to indicate the number of people present when activity was done			
			0	1	2	3 or more people
1. Get out of bed						
2. First contact (in person or by phone) with another person						
3. Have morning beverage						
4. Have breakfast						
5. Go outside for the first time						
6. Start work, school, housework, volunteer activities, child or family care						
7. Have lunch						
8. Take an afternoon nap						
9. Have dinner						
10. Physical exercise						
11. Have an evening snack/drink						
12. Watch evening TV news program						
13. Watch another TV program						
14. Activity A:						
15. Activity B:						
16. Return home (last time)						
17. Go to bed						

Algorithm for calculating scores on the Social Rhythm Metric

1. Compute the average time and standard deviation each activity was performed over the week.
2. Compute the minimum and maximum time range to determine outliers (Outliers are activity times that fall outside of 1.5 SD from the mean). Formulas are: MINTIME = AVERAGE TIME – (1.5 * SD) MAXTIME = AVERAGE TIME + (1.5 *SD) Therefore, non-outlier data fall within this range: MINTIME < TIME < MAXTIME
3. Re-compute the mean using only non-outlier data; this is the habitual time.
4. Recombine the non-outlier data and the outlier data to determine "hits." A "hit" is an activity time that occurs within 45 minutes of the habitual time. Formulas are: MINIMUM TIME FOR HIT = NEW MEAN – 45 MIN MAXIMUM TIME FOR HIT = NEW MEAN + 45 MIN Therefore, a time is considered a "hit" if it falls between this range: MINHIT < TIME < MAXHIT
5. Using all the 17 activities, select activities that occurred at least 3 times per week.
6. Calculate the number of activities occurring at least 3 times per week and the total number of hits for those activities.
7. Calculate SRM score = total number of hits for activities that occurred 3 or more times per week / number of activities occurring at least 3 times per week.
8. Calculate Activity Level Index (ALI) = total of all activities which occur over week Calculate Daily Activity Level Index (DALI) = total of all activities which occur that day
9. Calculate solitude ratio = total number of activities done alone / total number of all activities performed that week

Example Social Rhythm Metric get out of bed algorithm calculation

SRM:	*Get out of Bed*								
Date	**Time**	**Results**		**Non Outlier Range, N=6 days**			**Hit Times**		
19/09/01	07:45	**Mean**	**07:45**	07:45	**Habitual time**	**08:07**	07:45		
20/09/01	07:50	**SD**	**1:10**	07:50			07:50		
21/09/01	07:50			07:50			07:50		
22/09/01	09:30			09:30					
23/09/01	07:55			07:55			07:55		
24/09/01	07:55	**Min**	**05:30**	07:55	**Min Hit**	**07:22**	07:55	**No of Hits**	**5**
25/09/01	05:30	**Max**	**09:30**		**Max Hit**	**08:52**		**No of Misses**	**2**

Appendix F. Rosenberg Self Esteem Questionnaire

The Rosenberg Self Esteem Questionnaire (RSEQ) was developed by Rosenberg (1965). The RSEQ consists of ten items, with five negatively worded and five positively worded items to measure negative and positive self esteem subscales. The total score for both subscales measures global self esteem. Items were rated on a seven point Likert scale (1=strongly agree, 7=strongly disagree). The scoring for the five positively worded items was reversed. The + symbol denotes positive self esteem items.

Likert response ratings for positive and negative self esteem statements were plotted for bipolar disorder and general population groups. General population participants tended to 'agree' with positive self esteem statements and 'disagree' with negative self esteem statements. Participants with bipolar disorder had a wide range of responses to positive and negative self esteem statements, with no particular mode of response.

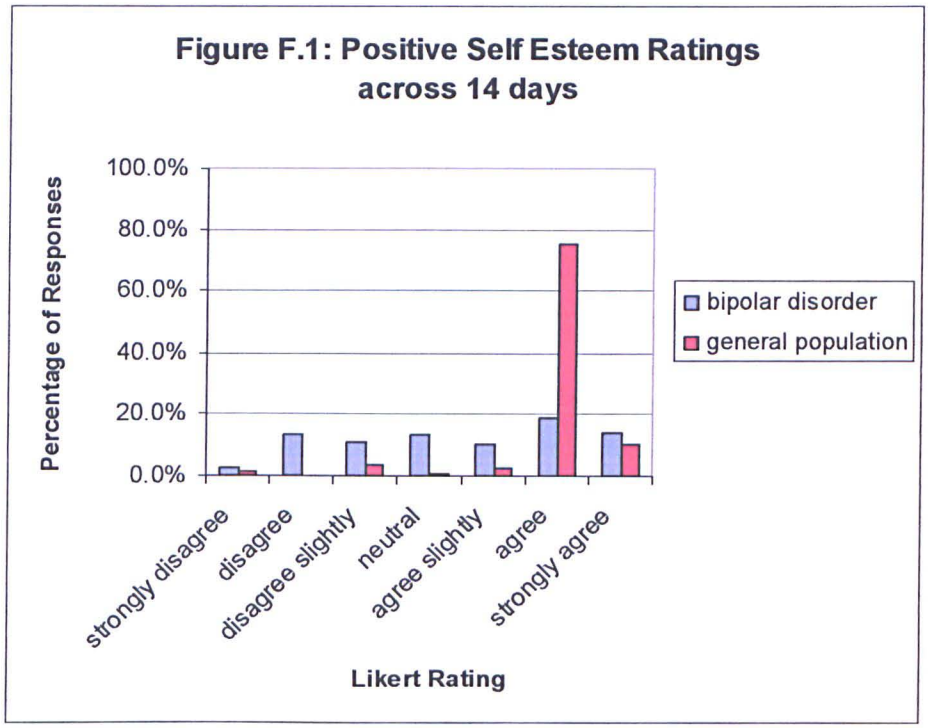
Rosenberg Self Esteem Questionnaire

This is a short questionnaire to measure thoughts about yourself.

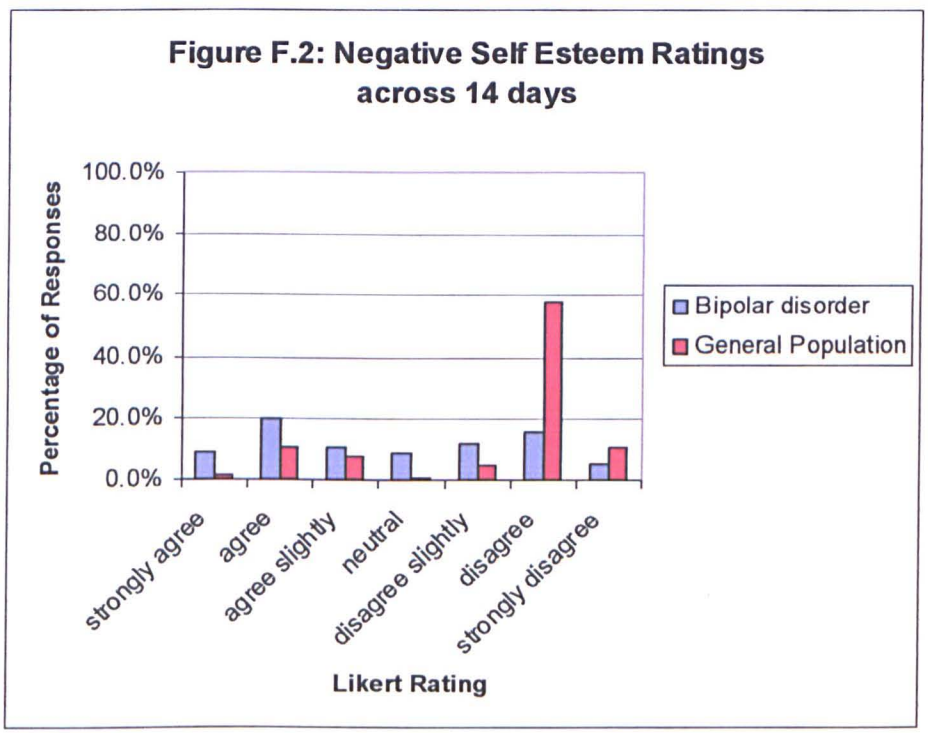
Please indicate whether you strongly agree, disagree, or strongly disagree with each statement **at the present moment,** by placing a cross (X) in the appropriate box.

Statement	**strongly agree**	**agree**	**agree slightly**	**neutral**	**disagree slightly**	**disagree**	**strongly disagree**
1. On the whole I am satisfied with myself. +							
2. At times I think I am no good at all.							
3. I feel I have a number of good qualities. +							
4. I am able to do things as well as most people. +							
5. I feel I do not have much to be proud of.							
6. I certainly feel useless at times.							

Statement	strongly agree	agree	agree slightly	neutral	disagree slightly	disagree	strongly disagree
7. I feel I am a person of worth, at least equal to others. +							
8. I wish I could have more respect for myself.							
9. All in all, I am inclined to feel I am a failure.							
10. I take a positive attitude towards myself. +							



(16.3% of ratings were missing for bipolar disorder and 0% missing for general population groups)



(10.6% of ratings were missing for bipolar disorder and 5.9% missing for general population groups)

Appendix G. Positive And Negative Affect Schedule

The Positive And Negative Affect Schedule (PANAS) was developed by Watson et al (1988). The PANAS comprises a ten item positive affect scale and a ten item negative affect scale. The + symbol denotes positive affect items. Two additional items were included in the PANAS list to measure current mood state relevant to bipolar disorder: 'elated' and 'depressed.' Items were rated on a five point Likert scale (1=very slightly or not at all, 5=extremely).

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way today by placing a cross (X) in the appropriate column. Use the following scale to record your answers.

Word	very slightly or not at all	a little	moderately	quite a bit	extremely
1. interested +					
2. distressed					
3. excited +					
4. upset					
5. strong +					
6. guilty					
7. scared					
8. hostile					
9. enthusiastic +					
10. proud +					
11. elated					
12. irritable					
13. alert +					
14. ashamed					
15. inspired +					
16. nervous					

Word	very slightly or not at all	a little	moderately	quite a bit	extremely
17. determined +					
18. attentive +					
19. jittery					
20. active +					
21. afraid					
22. depressed					

Appendix H. Publications

H.1 A systematic review of manic and depressive prodromes article

A systematic literature review of manic and depressive prodromes was conducted in December 2000. An article was drafted for publication with Dr Jonathan Cavanagh and Professor Jan Scott. The article was accepted by the Journal of Affective Disorders in July 2002 and was published in 2003.

H.2 Variability in bipolar disorders poster

A poster reporting differences in variability between bipolar disorder and general population participants was presented at the West of Scotland Research and Development conference, held in October 2004.

ELSEVIER

Journal of Affective Disorders 74 (2003) 209–217

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Review

A systematic review of manic and depressive prodromes

Alison Jackson[a], Jonathan Cavanagh[a], Jan Scott[b,*]

[a]*Department of Psychological Medicine, University of Glasgow, Gartnavel Royal Hospital, Glasgow, UK*
[b]*Division of Psychological Medicine, Institute of Psychiatry, P.O. Box 96, De Crespigny Park, Denmark Hill, London SE5 8AF, UK*

Received 8 April 2002; received in revised form 5 July 2002; accepted 19 July 2002

Abstract

Background: This paper explores whether individuals with a mood disorder can identify the nature and duration of depressive and manic prodromes. *Methods:* Seventy-three publications of prodromal symptoms in bipolar and unipolar disorders were identified by computer searches of seven databases (including MEDLINE and PSYCLIT) supplemented by hand searches of journals. Seventeen studies (total sample = 1191 subjects) met criteria for inclusion in a systematic review. *Results:* At least 80% of individuals with a mood disorder can identify one or more prodromal symptoms. There are limited data about unipolar disorders. In bipolar disorders, early symptoms of mania are identified more frequently than early symptoms of depression. The most robust early symptom of mania is sleep disturbance (median prevalence 77%). Early symptoms of depression are inconsistent. The mean length of manic prodromes (> 20 days) was consistently reported to be longer than depressive prodromes (< 19 days). However, depressive prodromes showed greater inter-individual variation (ranging from 2 to 365 days) in duration than manic prodromes (1–120 days). *Limitations:* Few prospective studies of bipolar, and particularly unipolar disorders have been reported. *Conclusions:* Early symptoms of relapse in affective disorders can be identified. Explanations of the apparent differences in the recognition and length of prodromes between mania and bipolar depression are explored. Further research on duration, sequence of symptom appearance and characteristics of prodromes is warranted to clarify the clinical usefulness of early symptom monitoring.
© 2003 Elsevier Science B.V. All rights reserved.

Keywords: Bipolar disorder; Depressive disorders; Manic depression; Prodromal symptoms

1. Introduction

Prodromes are described as cognitive, affective, and behavioural early symptoms of a disorder that appear before an episode of depression or mania (Altman et al., 1992; Keitner et al., 1996). Fava and Kellner's (1991) review stated that the duration of a prodrome is defined as the interval from the time that the first symptom is recognised to the time when the symptoms of an episode reach maximum severity. Detection of early symptoms could facilitate early intervention to prevent or reduce the impact of relapse on the individual (Joyce, 1985; Molnar et al.,

*Corresponding author.
E-mail address: j.scott@iop.kcl.ac.uk (J. Scott).

0165-0327/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0165-0327(02)00266-5

1988; Smith and Tarrier, 1992; Perry et al., 1995; Basco and Rush, 1996; Lam et al., 1999).

Recent research on psychological interventions for recurrent unipolar and bipolar disorders has utilised the identification and early management of prodromes as a core strategy (Scott, 1995, 2001; Perry et al., 1999; Lam et al., 2001; Katon et al., 2001). Likewise, user groups such as the Manic Depression Fellowship in the UK are trying to teach individuals to identify prodromes in order to employ self-management techniques.

A systematic literature search was conducted to identify what early symptoms of depression and mania have been described; to determine prodrome duration and any differences in duration between depression and mania; and to explore which early warning symptoms are most commonly identified.

2. Methods

A systematic literature review was conducted. All studies investigating early symptoms of relapse in bipolar or unipolar disorder were eligible for inclusion. Computerised databases searched were: MEDLINE (1966 to December 2000); Best Evidence (1991 to present); PsycLIT (1967 to 1990, 1991 to 1999); CINAHL (1982 to 1995, 1996 to December 2000); EMBASE (1980 to December 2000); Cochrane Database of Systematic Reviews (issue 4, 2000); PREMEDLINE (January 19, 2001).

The search used the subject headings [BIPOLAR DISORDER] or [DEPRESSIVE DISORDERS] with: [PRODROMAL] or [PRODROMES] or [PRODROME] or [EARLY WARNING SIGN] or [EARLY SIGNS] or [EARLY SYMPTOMS], and the term [MANIC DEPRESSION] linked to the subject heading [BIPOLAR DISORDER]. On-line abstracts were reviewed and reprints of potentially eligible articles were obtained. A hand search of all references of included journal articles identified further relevant articles. Researchers with an interest in prodromes were also contacted for advice and details of any other articles.

2.1. Data extraction

Two reviewers independently assessed the articles. A structured proforma recorded eligibility and relevant data such as diagnosis, early symptoms identified, and prodrome duration. Exclusion criteria were: (1) early symptoms of first onset of illness; (2) early symptoms of relapse or subsyndromal symptoms associated with sub-optimal lithium levels or discontinuation; (3) no data, preliminary data, or qualitative data; (4) residual symptoms; (5) case reports; and (6) mixed diagnostic samples, which included schizophrenia or other disorders.

Fig. 1 illustrates the article selection process for the review. Electronic searches identified 40 relevant references and a hand search identified a further 33 references. Of these, nine articles were excluded as a

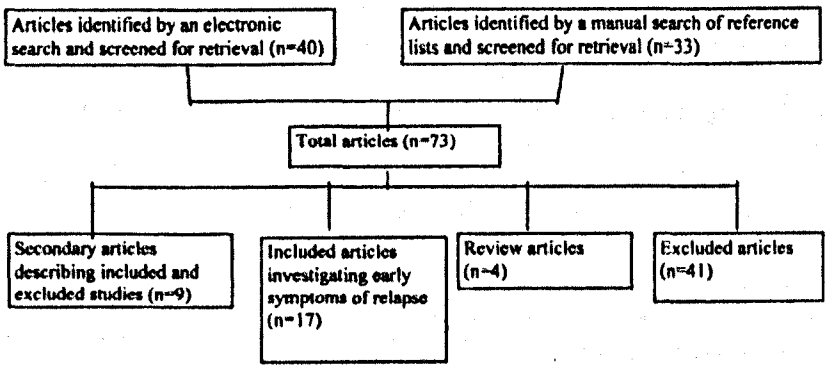


Fig. 1. Flowchart of article selection process.

secondary description of research findings (Sclare and Creed, 1987; Mander and Loudon, 1988; Miklowitz et al., 1988; Roper, 1989; Badal, 1992; Perry et al., 1995; Cates et al., 1999; Nolen, 1999; Lam et al., 2001). Another 41 articles met other exclusion criteria (Table 1). Seventeen studies, published between 1964 and 2001, met inclusion criteria.

3. Results

Demographic data for the 17 included articles is provided in Table 2. Five studies prospectively monitored early symptoms (Post et al., 1981; Altman et al., 1992; Perlis et al., 1997; Perry et al., 1999; Katon et al., 2001). Eleven studies investigated early

Table 1
Studies which met exclusion criteria

Exclusion criteria	Article
Early symptoms of first onset of illness	Hopkinson (1963)
	Hopkinson (1965)
	Winokur (1976)
	Cadoret et al. (1980)
	Murphy et al. (1989)
	Dryman and Eaton (1991)
	Ernst et al. (1992)
	Eaton et al. (1995)
	Strakowski et al. (1995)
	Eaton et al. (1997)
	Judd et al. (1997)
	Rueter et al. (1999)
	Egeland et al. (2000)
Early symptoms of relapse or subsyndromal symptoms associated with sub-optimal lithium levels or discontinuation	Mander (1990)
	Fava (1992)
	Klein et al. (1991)
	Klein et al. (1992)
	Keller et al. (1992)
No data, preliminary data, or qualitative data	Badal (1965)
	Jacobson (1965)
	Kelsey (1967)
	Loeb and Loeb (1987)
	Maj et al. (1992)
	Hagerty et al. (1997)
	Mahnert et al. (1997)
Residual symptoms	Faravelli et al. (1986)
	Fava et al. (1994, 1996, 1998)
	Paykel et al. (1995)
Case report	Stoddard et al. (1977)
	Waters (1979)
	Wehr et al. (1987)
	Wehr (1991)
	Terao (1993)
Sample included schizophrenia or other disorders	Kendler and Hays (1983)
	Fava et al. (1988)
	Subotnik and Nuechterlain (1988)
	Roper (1983)
	Birchwood et al. (1989)
	Beiser et al. (1993)
	Murphy and Moller (1996)
	Bechdolf et al. (1998)
	Novacek and Raskin (1998)

Table 2
Demographic information for studies included in systematic review

Study sample	Article	No.	Mean age	% Male
Bipolar disorders	Altman et al. (1992)	19	24	58
	Molnar et al. (1988)	20	38	45
	Smith and Tarrier (1992)	20	44	45
	Lam and Wong (1997)	40	44	42
	Joyce (1985)	50	35	44
	Perry et al. (1999)	69	45	32
	Keitner et al. (1996)	74	42	47
Mania only	Post et al. (1981)	9	37	44
	Sclare and Creed (1990)	24	41	47
	Francis and Gasparo (1994)	100	38	33
	Wong and Lam (1999)	206	44	40
Unipolar and bipolar disorders	Young and Grabler (1985)	11	median 37	36
Unipolar disorders only	Perlis et al. (1997)	14	38	29
	Fava et al. (1990)	15	45	60
	Young et al. (1991)	53	36	26
	Hays (1964)	81	48	51
	Katon et al. (2001)	386	46	26

symptoms of relapse in bipolar disorder (Joyce, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999) of which four investigated manic early symptoms only (Post et al., 1981; Sclare and Creed, 1990; Francis and Gasparo, 1994; Wong and Lam, 1999). Young and Grabler (1985) investigated early symptoms of relapse in a mixed sample of subjects with unipolar and bipolar disorders. Five studies investigated early symptoms of relapse in unipolar depression (Hays, 1964; Fava et al., 1990; Young et al., 1991; Perlis et al., 1997; Katon et al., 2001).

3.1. Early symptoms of unipolar depression

Fava et al.'s (1990) small-scale study ($n = 15$) reported 100% of individuals could identify early symptoms of unipolar relapse. Sleep disruption was frequently cited as an early symptom, but no prevalence data are reported (Young and Grabler, 1985; Fava et al., 1990; Young et al., 1991; Perlis et al., 1997). Fava et al.'s (1990) study identified that the two most common symptoms of unipolar depression retrospectively identified were generalised anxiety (87%) and irritability (60%).

The duration of the prodromal period for major depression was 7–133 days. In a mixed sample of unipolar and bipolar disorders, the median duration of a depressive prodrome was 28 days (Young and Grabler, 1985). Data from other studies is difficult to interpret as the samples were sub-divided a priori according to clinical characteristics (e.g. Hays, 1964).

3.2. Early symptoms of bipolar depression

Eight studies reported the existence of early symptoms of bipolar depressive relapse (Joyce, 1985; Young and Grabler, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999). The majority of individuals (70–100%; median 82%) can identify early symptoms of bipolar depression. Three studies reported percentages of individuals retrospectively reporting specific early symptoms (Molnar et al., 1988; Smith and Tarrier, 1992; Lam and Wong, 1997). The median prevalence of early symptoms was: mood change (48%), psy-

chomotor change (41%), increased anxiety (36%), appetite change (36%), suicidality (29%), sleep disturbance (24%), and other symptoms (22%). However, no symptom was consistently identified (Table 3).

The duration of the prodromal period for bipolar depression in heterogeneous samples showed considerable variation, ranging between 2 and 365 days (Young and Grabler, 1985; Molnar et al., 1988; Altman et al., 1992; Smith and Tarrier, 1992). In studies comprising only bipolar subjects (Table 4), the mean duration of a depressive prodrome was 11–19 days (Molnar et al., 1988; Smith and Tarrier, 1992).

3.3. Early symptoms of mania

Eleven studies reported the existence of a prodromal period for mania (Post et al., 1981; Joyce, 1985; Molnar et al., 1988; Sclare and Creed, 1990; Altman et al., 1992; Smith and Tarrier, 1992; Francis and Gasparo, 1994; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999; Wong and Lam, 1999). Seventy-five to 100% (median 93%) of

Table 3
Early symptoms identified in bipolar disorder

	Early symptoms	Range of sample size	% of individuals identifying this early symptom	Median (%)
Bipolar depression	Mood change	20–40	10–88	48
	Psychomotor symptoms	20–40	10–86	41
	Increased anxiety	20–40	18–59	36
	Appetite change	20–40	10–53	36
	Suicidal ideas/intent	20	29–64	29
	Sleep disturbance	20–40	17–57	24
	Other	20	14–29	22
Mania	Sleep disturbance	20–206	53–90	77
	Psychotic symptoms	20–206	7–80	47
	Mood change	20–206	14–100	43
	Psychomotor symptoms	20–206	10–100	34
	Other	20	20–35	30
	Appetite change	20–206	12–67	20
	Increased anxiety	20–40	11–20	16

Data from Molnar et al. (1988), Sclare and Creed (1990), Smith and Tarrier (1992), Lam and Wong (1997), Wong and Lam (1999).

Table 4
Estimated duration of prodromes for bipolar depression and mania

	Study	No.	Duration of prodrome (days)	Mean length of prodrome (days)
Bipolar depression	Molnar et al. (1988)	20	2–31	10.96
	Smith and Tarrier (1992)	20	3–365	18.8
	Young and Grabler (1985)	11	7–133	median 28*
Mania	Francis and Gasparo (1994)	100	2–112	23
	Sclare and Creed (1990)	24	2–120	median 22
	Molnar et al. (1988)	20	1–83	20.5
	Smith and Tarrier (1992)	20	1–84	28.9

*NB Mixed sample of unipolar and bipolar depressive disorders.

individuals were able to identify one or more early symptom of mania (Molnar et al., 1988; Sclare and Creed, 1990; Smith and Tarrier, 1992; Keitner et al., 1996; Lam and Wong, 1997; Perry et al., 1999). Five studies identified the percentage of individuals retrospectively reporting each specific early symptom. As shown in Table 3, the majority identified sleep disturbance as an indicator of manic prodromes. The median prevalence of early symptoms was: sleep disturbance (77%), psychotic symptoms (47%), mood change (43%), psychomotor change (34%), other symptoms (30%), appetite change (20%), and increased anxiety (16%).

The duration of the manic prodrome ranged from 1 to 120 days (Post et al., 1981; Molnar et al., 1988; Sclare and Creed, 1990; Smith and Tarrier, 1992; Francis and Gasparo, 1994). As shown in Table 4, in studies reporting mean and median durations, manic prodromes lasted for: 21–29 days (Molnar et al., 1988; Sclare and Creed, 1990; Francis and Gasparo, 1994; Smith and Tarrier, 1992).

4. Discussion

There are three key issues that arise from this systematic review: the limitations of the current research on affective prodromes, the findings on the nature of manic and depressive prodromes, and the implications for clinical practice and future research.

4.1. Limitations of current research

Less than one in a 1000 papers on the clinical features of affective disorders addresses prodromes. Although the sample reviewed exceeded 1100 subjects, the data on prodromes in unipolar disorder is inadequate. There is marginally more data on bipolar disorders, but findings from these studies are limited by the heterogeneity of the samples and methodologies. Although many studies used recognised standardised interview schedules to collect symptom data, most retrospectively investigated early symptoms of relapse, which may involve biased or distorted recall (Fava and Kellner, 1991). Many studies had small sample sizes that also limit the generalisation of findings (median $N = 40$).

4.2. The findings

Four out of five individuals with unipolar or bipolar disorders can identify one or more early symptoms before a full relapse. In bipolar disorders, early symptoms of mania were reported by a higher percentage of individuals in comparison to early symptoms of bipolar depression (median 97% for mania vs. 82% for bipolar depression). Greater diversity has also been found to exist in the symptoms of depressive in comparison to manic prodromes (Lam and Wong, 1997; Gillin, 1998). The most robust early symptom of mania was sleep disturbance. A phenomenon also reported by Wehr et al. (1987). The most prominent early symptom of bipolar depression was mood change. However, the latter was identified by less than 50% of individuals. This review suggests that the mean duration of a manic prodrome (mean >20 days) is longer than that of bipolar depression (mean <19 days). However, comparison of the range of duration indicates greater inter-individual variation in the former (bipolar depression 2–365 days; mania 1–120 days). This raises the possibility that, unlike mania, duration of depressive prodromes is not normally distributed statistically (Francis and Gasparo, 1994).

The difference in mean duration of manic as compared to depressive prodromes may relate to different biological processes, or it may be an artefact because early symptoms of mania are readily identifiable. Scott (2001) noted that early features of mania are more distinctive as the symptoms differ qualitatively from the individuals' day-to-day experiences. Early symptoms of bipolar depression may represent a less overt quantitative shift in affect or behaviour, particularly in individuals with residual depressive symptoms (Scott et al., 2000; Fava, 1999). Such subtle changes in functioning may not be recognised as warning signals of depressive relapse until they become more severe or persistent or they are accompanied by more memorable symptoms. This would give an impression of a briefer prodrome. This notion is supported by Fava et al. (1990, 1991) who reported at least one early symptom of relapse was evident prior to the onset of depressed mood, yet mood change was the subjective experience most frequently recalled.

4.3. Implications for clinical practice and future research

Monitoring and intervening when early symptoms arise has been deemed effective in preventing or minimising the impact of relapse in affective disorders (Kupfer et al., 1989; Mander, 1990; Scott, 1995; Perry et al., 1999). The use of prompts, such as Smith and Tarrier's (1992) 40-item early symptom checklist may facilitate identification. Individuals are only likely to benefit from monitoring early symptoms if this approach is used in combination with effective coping strategies. Lam's work (Lam and Wong, 1997; Lam et al., 2001) demonstrates that effective self-management strategies for the early symptoms of mania and depression are associated with better clinical and social outcomes.

Evidence that manic prodromes are longer and easier to identify than the bipolar depressive prodromes suggests early intervention by the mental health services is more feasible for mania than for depression. Perry et al. (1999) found early symptom recognition and intervention in patients with bipolar disorders significantly reduced manic but not depressive relapses. They also noted that, once warning signals were recognised, it was easier to introduce effective pharmacological treatments for acute mania than for bipolar depression. Katon et al.'s (2001) relapse prevention program similarly reported difficulties in reducing depressive relapses (although there were other benefits). The implication of this review is that early recognition and treatment of bipolar depression is the greater challenge. This is unfortunate as evidence suggests that outcomes are also worse: clinical remission is significantly less likely to be achieved in bipolar depression than in mania (59% vs. 100%) and, even when achieved, it occurs significantly less rapidly (Hlastala et al., 1997).

Future research should involve prospective monitoring of early symptoms to provide more detailed descriptions of the duration and specific symptoms associated with prodromes of mania, bipolar depression, and unipolar depression. Investigation of prodrome duration will determine whether manic prodromes are truly longer than depressive prodromes and may determine the clinical usefulness of early symptom monitoring. Comparison of the prodromes of bipolar depression and unipolar depression may provide insights into the similarities and differences between these disorders.

Acknowledgements

Professor Scott's research on bipolar disorder is supported by a Legacy from the Searle Foundation.

References preceded with an asterisk indicate studies included in the systematic review.

References

*Altman, E.S., Rea, M.M., Mintz, J., Miklowitz, D.J., Goldstein, M.J., Hwang, S., 1992. Prodromal symptoms and signs of bipolar relapse: A report based on prospectively collected data. Psychiatry Res. 41, 1–8.

Badal, D.W., 1965. Transitional and pre-psychotic symptoms in depression. Bull. Philadelphia Psychoanal. Soc. 15, 10–25.

Badal, D.W., 1992. Change in ideational content as a prodromal symptom in affective disorders (letter). Am. J. Psychiatry 149, 427–428.

Basco, M.R., Rush, A.J., 1996. Symptom monitoring: An early warning system. In: Basco, M.R., Rush, A.J. (Eds.), Cognitive Behavioural Therapy for Bipolar Disorder. Guilford Press, Guilford, pp. 65–85.

Bechdolf, A., Halve, S., Schultze-Lutter, F., Klosterkotter, J., 1998. Self experienced vulnerability, prodromic symptoms and coping strategies before schizophrenic and affective episodes (German). Fortschr. Neurol. Psychiatr. 66, 378–386.

Beiser, M., Erickson, D., Fleming, J.A., Iacono, W.G., 1993. Establishing the onset of psychotic illness. Am. J. Psychiatry 150, 1349–1354.

Birchwood, M., Smith, J., Macmillan, F., Hogg, B., Prasad, R., Harvey, C., Bering, S., 1989. Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. Psychological Medicine 19, 649–656.

Cadoret, R.J., Widmer, R.B., Troughton, E.P., 1980. Somatic complaints, harbinger of depression in primary care. J. Affect. Disord. 2, 61–70.

Cates, C., Morriss, R., Tarrier, N., 1999. Teaching patients with bipolar disorder to identify early symptoms of relapse (multiple letters). Br. Med. J. 318, 1557–1558.

Dryman, A., Eaton, W.W., 1991. Affective symptoms associated with the onset of major depression in the community: Findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. Acta Psychiatr. Scand. 84, 1–5.

Eaton, W.W., Badawi, M., Melton, B., 1995. Prodromes and

precursors: Epidemiologic data for primary prevention of disorders with slow onset. Am. J. Psychiatry 152, 967–972.
Eaton, W.W., Anthony, J.C., Gallo, J., Cai, G., Tien, A., Romanoski, A., Lyketsos, C., Chen, L., 1997. Natural history of Diagnostic Interview Schedule/DSM-IV Major Depression: The Baltimore Epidemiologic Catchment Area Follow-up. Arch. Gen. Psychiatry 54, 993–999.
Egeland, J.A., Hostetter, A.M., Pauls, D.L., Sussex, J.N., 2000. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. J. Am. Acad. Child Adolesc. Psychiatry 39, 1245–1252.
Ernst, C., Schmid, G., Angst, J., 1992. The Zurich Study. XVI. Early antecedents of depression. A longitudinal prospective study on incidence in young adults. Eur. Arch. Psychiatry Clin. Neurosci. 242, 142–151.
Faravelli, C., Ambonetti, A., Pallanti, S., Pazzagli, A., 1986. Depressive relapses and incomplete recovery from index episode. Am. J. Psychiatry 143, 888–891.
Fava, G.A., Grandi, S., Canestrari, R., 1988. Prodromal symptoms in panic disorder with agoraphobia. Am. J. Psychiatry 145, 1564–1567.
*Fava, G.A., Grandi, S., Canestrari, R., Molnar, G., 1990. Prodromal symptoms in primary major depressive disorder. J. Affect. Disord. 19, 149–152.
Fava, G.A., Kellner, R., 1991. Prodromal symptoms in affective disorders. Am. J. Psychiatry 148, 823–830.
Fava, G.A., Molnar, G., Grandi, S., Sonino, N., 1991. Prodromal symptoms and intermittent drug medication in mood disorders. Pharmacopsychiatry 24, 28–30.
Fava, G.A., 1992. Measurement of prodromal and subclinical symptoms in mood and anxiety disorders. In: Fava, M., Rosenbaum, J.F. (Eds.), Research Designs and Methods in Psychiatry. Elsevier, Amsterdam, pp. 223–230.
Fava, G.A., Grandi, S., Zielezny, M., Canestrari, R., Morphy, M.A., 1994. Cognitive behavioural treatment of residual symptoms in primary major depressive disorder. Am. J. Psychiatry 151, 1295–1299.
Fava, G.A., Grandi, S., Zielezny, M., Rafanelli, C., Canestrari, R., 1996. Four year outcome for cognitive behavioural treatment of residual symptoms in major depression. Am. J. Psychiatry 153, 945–947.
Fava, G.A., Rafanelli, C., Grandi, S., Canestrari, R., Morphy, M.A., 1998. Six year outcome for cognitive behavioural treatment of residual symptoms in major depression. Am. J. Psychiatry 155, 1443–1445.
Fava, G.A., 1999. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. Psychol. Med. 29, 47–61.
*Francis, A., Gasparo, P., 1994. Interval between symptom onset and hospitalisation in mania. J. Affect. Disord. 31, 179–185.
Gillin, J.C., 1998. Are sleep disturbances risk factors for anxiety, depressive and addictive disorders? Acta Psychiatr. Scand. Suppl. 393, 39–43.
Hagerty, B.M., Williams, R.A., Liken, M., 1997. Prodromal symptoms of recurrent major depressive episodes: A qualitative analysis. Am. J. Orthopsychiatr. 67, 308–314.
*Hays, P., 1964. Modes of onset of psychotic depression. Br. Med. J. 2, 779–784.
Hlastala, S.A., Frank, E., Mallinger, A.G., Thase, M.E., Ritenour, A.M., Kupfer, D.J., 1997. Bipolar depression: an underestimated treatment challenge. Depression Anxiety 5, 73–83.
Hopkinson, G., 1963. The onset of affective illness. Psychiatr. Neurol. 146, 133–140.
Hopkinson, G., 1965. The prodromal phase of the depressive psychosis. Psychiatr. Neurol. 149, 1–6.
Jacobson, J.E., 1965. The hypomanic alert: A program designed for greater therapeutic control. Am. J. Psychiatry 122, 295–299.
*Joyce, P.R., 1985. Illness behaviour and rehospitalisation in bipolar affective disorder. Psychol. Med. 15, 521–525.
Judd, L.L., Akiskal, H.S., Paulus, M.P., 1997. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J. Affect. Disord. 45, 5–18.
*Katon, W., Rutter, C., Ludman, E.J., Von Korff, M., Lin, E., Simon, G., Bush, T., Walker, E., Unutzer, J., 2001. A randomised trial of relapse prevention of depression in primary care. Arch. Gen. Psychiatry 58, 241–247.
*Keitner, G.I., Solomon, D.A., Ryan, C.E., Miller, I.W., Mallinger, A., Kupfer, D.J., Frank, E., 1996. Prodromal and residual symptoms in bipolar I disorder. Comp. Psychiatry 37, 362–367.
Keller, M.B., Lavori, P.W., Kane, J.M., Gelenberg, A.J., Rosenbaum, J.F., Walzer, E.A., Baker, L.A., 1992. Subsyndromal symptoms in bipolar disorder: A comparison of standard and low serum levels of lithium. Arch. Gen. Psychiatry 49, 371–376.
Kelsey, F.D., 1967. Early signs of mental illness. I. Nursing Times 63, 413–414.
Kendler, K.S., Hays, P., 1983. Schizophrenia subdivided by the family history of affective disorder: A comparison of symptomatology and course of illness. Arch. Gen. Psychiatry 40, 951–955.
Klein, E., Mairaz, R., Pascal, M., Hefez, A., Lavie, P., 1991. Discontinuation of lithium treatment in remitted bipolar patients: Relationship between clinical outcome and changes in sleep wake cycles. J. Nerv. Ment. Dis. 179, 499–501.
Klein, E., Lavie, P., Meiraz, R., Sadeh, A., Lenox, R.H., 1992. Increased motor activity and recurrent manic episodes: Predictors of rapid relapse in remitted bipolar disorder patients after lithium discontinuation. Biol. Psychiatry 31, 279–284.
Kupfer, D.J., Frank, E., Perel, J.M., 1989. The advantage of early treatment intervention in recurrent depression. Arch. Gen. Psychiatry 46, 771–775.
*Lam, D., Wong, G., 1997. Prodromes, coping strategies, insight and social functioning in bipolar affective disorders. Psychol. Med. 27, 1091–1100.
Lam, D.H., Jones, S.H., Hayward, P., Bright, J.A., 1999. Cognitive Therapy for Bipolar Disorder. A Therapist's Guide to Concepts, Methods and Practice. Wiley, New York.
Lam, D., Wong, G., Sham, P., 2001. Prodromes, coping strategies and course of illness in bipolar affective disorder – a naturalistic study. Psychol. Med. 31, 1397–1402.
Loeb, F.F., Loeb, L.R., 1987. Psychoanalytic observations on the effect of lithium on manic attacks. J. Am. Psychoanal. Assoc. 35, 877–902.

Mahnert, F.A., Reicher, H., Zalauder, K., Zapotoczky, H.G., 1997. Prodromal and residual symptoms in recurrent depression: Preliminary data of a long term study under prophylactic treatment conditions. Eur. Neuropsychopharmacol. 7, 159–160.

Maj, M., Veltro, F., Pirozzi, R., Lobrace, S., Magliano, L., 1992. Pattern of recurrence of illness after recovery from an episode of major depression: A prospective study. Am. J. Psychiatry 149, 795–800.

Mander, A.J., Loudon, J.B., 1988. Rapid recurrence of mania following abrupt discontinuation of lithium. Lancet 2, 15–17.

Mander, A.J., 1990. The early signs of manic relapse after lithium discontinuation and their clinical implications. Ir. J. Psychol. Med. 7, 42–44.

Miklowitz, D.J., Goldstein, M.J., Nuechterlein, K.H., Snyder, K.S., Mintz, J., 1988. Family factors and the course of bipolar affective disorder. Arch. Gen. Psychiatry 45, 225–231.

*Molnar, G., Feeney, M.G., Fava, G.A., 1988. Duration and symptoms of bipolar prodromes. Am. J. Psychiatry 145, 1576–1578.

Murphy, J.M., Sobol, A.M., Olivier, D.C., Monson, R.R., Leighton, A.H., Pratt, L.A., 1989. Prodromes of depression and anxiety: The Stirling county study. Br. J. Psychiatry 155, 490–495.

Murphy, M.F., Moller, M.D., 1996. The three R's program: A wellness approach to the rehabilitation of neurobiological disorders. Int. J. Psychiatr. Nurs. Res. 3, 308–317.

Nolen, W.A., 1999. Teaching patients to recognise early symptoms of relapse reduced manic relapses in bipolar disorder. Evidence Based Med. 4, 106.

Novacek, J., Raskin, R., 1998. Recognition of warning signs: A consideration for cost effective treatment of severe mental illness. Psychiatr. Serv. 49, 376–378.

Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., Barocka, A., 1995. Residual symptoms after partial remission: An important outcome in depression. Psychol. Med. 25, 1171–1180.

*Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X., Kupfer, D.J., 1997. Self reported sleep disturbance as a prodromal symptom in recurrent depression. J. Affect. Disord. 42, 209–212.

Perry, A., Tarrier, N., Morriss, R., 1995. Identification of prodromal signs and symptoms and early intervention in manic depressive psychosis: A case example. Behav. Cognit. Psychother. 23, 399–409.

*Perry, A., Tarrier, N., Morriss, R., McCarthy, E., Limb, K., 1999. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. Br. Med. J. 318, 149–153.

*Post, R.M., Ballenger, J.C., Rey, A.C., Bunney, W.E., 1981. Slow and rapid onset of manic episodes: Implications for underlying biology. Psychiatry Res. 4, 229–237.

Roper, P.D., 1983. Harbingers of relapse in psychiatric illness. Ann. R. Coll. Physicians Surg. Can. 16, 44–49.

Roper, P.D., 1989. Prodromal symptoms (letter). Am. J. Psychiatry 146, 941–942.

Rueter, M.A., Scaramella, L., Wallace, L.E., Conger, R.D., 1999. First onset of depressive or anxiety disorders predicted by the longitudinal course of internalising symptoms and parent–adolescent disagreements. Arch. Gen. Psychiatry 56, 726–732.

*Sclare, P., Creed, F., 1987. Life events and mania (letter to the editor). Br. J. Psychiatry 150, 875.

Sclare, P., Creed, F., 1990. Life events and the onset of mania. Br. J. Psychiatry 156, 508–514.

Scott, J., 2001. Overcoming Mood Swings: A Self-Help Guide Using Cognitive and Behavioural Techniques. Constable Robinson and NY Press, London and New York.

Scott, J., Stanton, B., Garland, A., Ferrier, I., 2000. Cognitive vulnerability in patients with bipolar disorder. Psychol. Med. 30, 467–472.

Scott, J., 1995. Review: Psychotherapy for bipolar disorder—An unmet need? Br. J. Psychiatry 167, 581–588.

*Smith, J.A., Tarrier, N., 1992. Prodromal symptoms in manic depressive psychosis. Soc. Psychiatry Psychiatr. Epidemiol. 27, 245–248.

Stoddard, F.J., Post, R.M., Bunney, W.E., 1977. Slow and rapid psychobiological alterations in a manic depressive patient: clinical phenomenology. Br. J. Psychiatry 130, 72–78.

Strakowski, S.M., Keck, P.E., McElroy, S.L., Lonczak, H.S., West, S.A., 1995. Chronolgy of comorbid and principal syndromes in first-episode psychosis. Comp. Psychiatry 36, 106–112.

Subotnik, K.L., Nuechterlam, K.H., 1988. Prodromal signs and symptoms of schizophrenic relapse. J. Abnorm. Psychol. 97, 405–412.

Terao, T., 1993. Prodromal symptoms of depression and self administration of lithium. Biol. Psychiatry 34, 198–199.

Waters, B.G., 1979. Early symptoms of bipolar affective psychosis: research and clinical implications. Can. J. Psychiatry 24, 55–60.

Wehr, T.A., Sack, D.A., Rosenthal, N.E., 1987. Sleep reduction as a final common pathway in the genesis of mania. Am. J. Psychiatry 144, 201–204.

Wehr, T.A., 1991. Sleep loss as a possible mediator of diverse causes of mania. Br. J. Psychiatry 159, 576–578.

Winokur, G., 1976. Duration of illness prior to hospitalisation (onset) in the affective disorders. Neuropsychobiology 2, 87–93.

*Wong, G., Lam, D., 1999. The development and validation of the coping inventory for prodromes of mania. J. Affect. Disord. 53, 57–65.

*Young, M.A., Grubler, P., 1985. Rapidity of symptom onset in depression. Psychiatry Res. 16, 309–315.

*Young, M.A., Watel, L.G., Lahmeyer, H.W., Eastman, C.I., 1991. The temporal onset of individual symptoms in winter depression: Differentiating underlying mechanisms. J. Affect. Disord. 22, 191–197.

Variability in bipolar disorders

Jackson, A.[1] McCabe, E.[2] Espie, C.[1] & Scott, J.[3]

1 Section of Psychological Medicine, University of Glasgow, 2 Forth Valley Primary Care NHS Trust,
3 Division of Psychological Medicine, Institute of Psychiatry, London

RESEARCH QUESTION

Do individuals with bipolar disorder display greater day-to-day variability in biological, behaviour, self esteem and affect measures during inter-episode periods, in comparison to individuals from the general population?

INTRODUCTION

Bipolar Disorder is characterised by acute episodes of mania and depression. Symptoms include changes in mood, cognition and behaviour. The primary treatment of bipolar disorder is pharmacotherapy, although even with prophylactic treatment, risk of relapse remains high. About 65% of individuals with bipolar disorder have been observed to relapse over the course of 2 years (Silverstone et al, 1998).

Inter-episode symptoms are common in bipolar disorder and can increase risk of relapse. A recent review identified sleep disturbance as a robust early symptom of mania, although no consistent early symptom of bipolar depression was evident (Jackson et al, 2003). Inter-episode symptoms as well as biological, psychological and social factors may influence the long term course of bipolar disorder. Limited research to date has been conducted on day-to-day psychobiosocial functioning in bipolar disorders.

METHOD

Participants with bipolar I or II disorders were recruited from a Lithium Clinic and individuals from the general population were recruited through opportunity sampling. Participants completed prospective self report questionnaires to measure social rhythms, behavioural activation/inhibition, self esteem and affect. Self report measures included: Social Rhythm Metric, Behavioural Inhibition System/Behavioural Activation System Subscales, Rosenberg Self Esteem Questionnaire, Positive and Negative Affect Schedule and elation and depression ratings. Continuous actigraph monitoring over 14 days provided an objective estimation of the sleep-wake cycle.

RESULTS

Twenty participants with bipolar disorder (mean age 43, sd 11) and ten participants from the general population (mean age 41, sd 14) completed prospective monitoring for a minimum 14 days.

Further demographic characteristics for bipolar disorder participants are displayed in Table 1.

Table 1:
Demographic characteristics of participants with bipolar disorder

Variable	Bipolar disorder participants (N=20)
Bipolar I Disorder	8 (40%)
Bipolar II Disorder	4 (20%)
Rapid Cycling	8 (40%)
Prescribed lithium	15 (75%)
Prescribed mood stabilising drugs	12 (60%)
Median duration of illness (in years)	10 (6-15)
Median number of bipolar episodes	7 (4-10)

Mean and variability scores were calculated for each variable across a 14 day period for each participant to produce group scores. Variables were grouped into biological/behavioural and self esteem/affective measures since correlations between variables were hypothesised to be higher within each grouping. Multivariate analyses of variance (MANOVA) were conducted to investigate group differences in average level and variability of measures. However, assumptions of homogeneity of variances and normal distributions were not met for most measures, suggesting tentative interpretation of the MANOVA analyses. Accordingly, non-parametric Mann-Whitney U analyses were conducted to investigate between group differences, using Holm's correction for multiple comparisons.

Non-parametric analyses indicated seven of the dependent variables differed significantly between the bipolar disorder and general population groups. Results for these variables are displayed in Table 2. Lower self esteem, lower positive affect, higher negative affect, higher depressed ratings, and greater variability in night waking time, sleep efficiency and self esteem were evident in bipolar disorder participants compared to general population participants across a 14 day period.

Table 2:
Between group differences observed in sleep, self esteem and affect

Variable	Bipolar mean (SD)	Control mean (SD)	Effect size	U	p
Night waking time variability (in minutes)	33 (21)	14 (8)	1.0	15	0.001
Sleep efficiency variability (%)	9 (5)	4 (2)	1.0	20	0.003
Positive affect level	21 (7)	29 (5)	-1.0	27.5	0.001
Negative affect level	17 (8)	13 (4)	0.6	45.5	0.016
Depression level	2.1 (1.2)	1.2 (0.3)	0.9	35.5	0.004
Self esteem level	41 (16)	56 (8)	-1.0	39	0.014
Self esteem variability	4.5 (2.6)	1.8 (0.8)	1.1	24	0.002

LIMITATIONS

Power analysis suggested a larger sample size (N=50) would be necessary to detect moderate effect size between group differences.

CONCLUSIONS

Greater variability in sleep efficiency, night waking time and self esteem were observed in individuals with bipolar disorder during inter-episode periods compared to individuals from the general population. Findings are consistent with other reports of a disturbed sleep-wake cycle in euthymic bipolar disorder compared to the general population (Millar et al, 2004) and self esteem variation across mood states in bipolar disorder (Scott & Pope, 2003).

REFERENCES

Jackson, A. Cavanagh, J. & Scott, J. (2003) A systematic review of manic & depressive prodromes. Journal of Affective Disorders 74 209-217.

Millar, A. Espie, C. & Scott, J. (2004) The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. Journal of Affective Disorders 80 145-153.

Scott, J. & Pope, M. (2003) Cognitive styles in individuals with bipolar disorders. Psychological Medicine 33 1081-1088.

Silverstone, T. McPherson, H. Hunt, N. & Romans, S. (1998) How effective is lithium in the prevention of relapse in bipolar disorder? A prospective follow up study. Australian & New Zealand Journal of Psychiatry 32 61-66.

Acknowledgements

Professor Scott's research on bipolar disorder is supported by a Legacy from the Searle Foundation.

Appendix I. Skewness and kurtosis of sample data

The distribution of mean and variability participant scores was examined by calculating z scores for skewness and kurtosis for each of the dependent variables. The skewness z score was computed by dividing the skewness value by the standard error for skewness. The kurtosis z score was computed by dividing the kurtosis value by the standard error for kurtosis. Twelve of the averaged measures and 17 of the variability measures did not display a normal distribution of scores. Over 60% of the variables had significant skewness and /or kurtosis z scores outwith ±1.96 which indicates with 95% confidence that the distributions of these variables were not normal (Kerr et al, 2002). Tables I.2 and I.2 provide skewness and kurtosis z scores for the mean and variability participant scores.

Table I.1: Skewness and kurtosis of participant mean and variability scores

Variable	Mean scores		Variability scores	
	Skewness z score	Kurtosis z score	Skewness z score	Kurtosis z score
Time in bed	0.73	-0.07	5.54*	11.22*
Sleep duration	-1.05	2.39*	4.16*	5.38*
Night waking time	3.37*	4.60*	4.50*	6.03*
Sleep efficiency	-3.66*	4.86*	4.11*	4.35*
Sleep latency	2.13*	0.18	3.17*	2.55*
Fragmentation index	3.99*	6.40*	3.49*	2.98*
Interdaily stability	0.10	-1.13	4.57*	7.81*
Intradaily variability	-0.52	-0.73	5.43*	8.72*
Night time activity level	5.04*	7.71*	4.66*	5.32*
Night time activity onset time	8.12*	18.23*	-	-
Day time activity level	5.39*	9.72*	3.49*	2.66*
Day time activity onset time	.57	-0.67	-	-

Variable	Mean scores		Variability scores	
	Skewness z score	Kurtosis z score	Skewness z score	Kurtosis z score
Relative amplitude	-2.10*	-0.20	3.03*	1.61
SRM regularity	-1.07	-0.81	0.72	0.60
DALI	0.38	2.47*	0.47	-0.33
Positive SE	-1.39	-1.12	2.57*	1.23
Negative SE	-0.70	-1.35	1.25	0.32
SE total	-1.09	-1.26	3.20*	2.29*
PA	0.02	-0.75	0.34	-1.12
NA	5.79*	10.16*	2.15*	0.48
Elated	1.05	-0.81	0.79	0.10
Depressed	3.84*	2.92*	1.57	-0.28
BIS	-0.23	-1.32	0.86	-0.65
BAS Reward responsiveness	0.01	-0.27	5.03*	8.39*
BAS Drive	1.45	0.54	3.08*	2.53*
BAS Fun seeking	3.11*	3.87*	2.02*	0.74

* Values outwith ±1.96 indicate the distribution is not normal (Kerr et al, 2002)

Appendix J. MANOVA results not meeting parametric assumptions

Although parametric analyses may be considered relatively robust to violation of parametric assumptions, consideration of the small sample size suggested caution in the interpretation of findings. Three parametric assumptions were investigated: Box's M homogeneity of variance statistic; Levene's homogeneity of variance; and the normal distribution of data. If two of these assumptions were not met, the multivariate analysis of variance was discarded in favour of non-parametric Mann-Whitney tests. Nine groups of variables were investigated with MANOVAs (see Section 4.3 for more information). Following investigation of homogeneity of variance and the normality of data, non-parametric analyses were considered more appropriate for seven of these nine groups of variables. The MANOVA results discarded are provided in the following tables.

Table J.1: Averaged sleep measures comparison between groups

Sleep variable	df	F	Significance
Time in bed (min.)	23	3.816	0.064
Sleep duration (min.)	23	0.001	0.977
Night waking time (min.)	23	4.976	0.036*
Sleep efficiency (%)	23	4.434	0.047*
Sleep latency (min.)	23	2.804	0.108
Fragmentation index	23	5.082	0.034*

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table J.2: Sleep variability comparison between groups

Sleep variable	df	F	Significance
Time in bed variability (min.)	23	2.183	0.154
Sleep duration variability (min.)	23	4.189	0.053
Night waking variability (min.)	23	8.085	0.009*
Sleep efficiency variability (%)	23	7.052	0.014*
Sleep latency variability (min.)	23	4.395	0.048*
Fragmentation index variability	23	6.608	0.017*

[1] Based on participant mean scores over 14 days for N=14 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table J.3: Social and circadian rhythm variability comparison between groups

Social/circadian rhythm variable	df	F	Significance
Regularity score variability	21	0.082	0.778
DALI variability	21	0.441	0.514
L5 variability	21	3.422	0.079
M10 variability	21	3.192	0.089
RA variability	21	4.517	0.046*
IS variability	21	0.234	0.634
IV variability	21	3.680	0.069

[1] Based on participant mean scores over 14 days for N=12 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Variables: DALI, Daily activity level index; L5, Night time activity level; M10, Day time activity level; RA, Relative amplitude; IS, Interdaily stability; IV, Intradaily variability

Table J.4: Averaged behavioural activation/inhibition measures comparison between groups

BIS/BAS	df	F	Significance
BIS	25	3.262	0.083
BAS reward responsiveness	25	0.088	0.770
BAS drive	25	0.048	0.829
BAS fun seeking	25	1.621	0.215

[1] Based on participant mean scores over 14 days for N=16 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table J.5: Averaged self esteem and affect measures comparison between groups

Self esteem and affect	df	F	Significance
SE	27	7.156	0.013*
PA	27	9.959	0.004*
NA	27	2.812	0.106
Elated	27	4.167	0.051
Depressed	27	6.355	0.018*

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table J.6: Self esteem and affect variability comparison between groups

Self esteem and affect	df	F	Significance
SE variability	27	10.088	0.004*
PA variability	27	0.962	0.336
NA variability	27	3.514	0.072
Elated variability	27	4.520	0.043*
Depressed variability	27	2.984	0.096

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Table J.7: Average level and variability of positive and negative self esteem comparison between groups

Self esteem	df	F	Significance
Positive SE level	27	6.768	0.015*
Negative SE level	27	6.858	0.015*
Positive SE variability	27	11.434	0.002*
Negative SE variability	27	4.465	0.044*

[1] Based on participant mean scores over 14 days for N=18 bipolar disorder participants

[2] Based on participant mean scores over 14 days for N=10 general population participants

* Indicates large effect size and/or statistically significant finding, $p<0.05$

Appendix K. Parametric analyses over longer monitoring period for bipolar disorder

Participants with bipolar disorder prospectively completed questionnaires for two to 24 weeks (median 8 weeks). The analyses in sections 4.4 to 4.6 were based on participants mean and variability scores over a 14 day period. However, preliminary evidence has suggested longer monitoring periods may be necessary for bipolar disorder to provide a trait level for a measure (e.g. Monk et al, 1991; Ashman et al, 1999). The present study hypothesised greater variability would be observed during inter-episode periods in bipolar disorder since inter-episode symptoms are commonly experienced. Thus, whilst a 14 day period may be an accurate reflection of how individuals from the general population fluctuate over time, a longer period may be necessary to capture the extent of fluctuations in bipolar disorder. Consequently group comparisons were repeated using the level and variability of measures for participants with bipolar disorder over their full monitoring period and the two week period for general population participants.

Eight multivariate analyses were produced along with two tests for homogeneity, Box's M statistic and Levene's homogeneity test. The eight following tables provide the mean level and variability of measures across the full monitoring period for participants with bipolar disorder and across a 14 day period for general population participants along with the univariate analyses for each measure. In brief, comparing the mean level and variability of measures across a longer monitoring period for bipolar disorder participants provided similar results to the comparison of a 14 day monitoring period. The bipolar disorder group was observed to have lower levels of self esteem and positive affect and a higher level of depressed ratings. Greater variability in bipolar disorder was observed for sleep efficiency, fragmentation index, relative amplitude, self esteem, negative affect and depressed ratings. All remaining measures were not observed to differ between general population and bipolar disorder groups.

Table K.1: Averaged sleep measures comparison between bipolar disorder and general population groups

Sleep variable	Bipolar Disorder (N=15)		General Population (N=10)		Effect	df	F	p
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*			
Time in bed (min.)	640 (351)	445-834	499 (45)	467-530	0.5	24	1.573	0.222
Sleep duration (min.)	416 (88)	367-464	427 (33)	403-451	-0.2	24	0.149	0.703
Night waking time (min.)	98 (66)	61-134	47 (24)	30-64	0.9*	24	5.281	0.031
Sleep efficiency (%)	73 (15)	65-81	86 (6)	82-90	-1.0	24	7.335	0.013
Sleep latency (min.)	55 (59)	23-88	21 (17)	9-32	0.7	24	3.224	0.086
Fragmentation index	46 (22)	33-58	25 (11)	17-33	1.0*	24	7.173	0.013

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis for six averaged sleep measures (Pillai's trace) F=3.090, df 6, 18, p=0.029

Box's M=107.970, F=3.547, df 21, 1362.499, p=0.000

Levene's test was significant for sleep duration (F=4.888, df 1, 23, p=0.037), sleep efficiency (F=7.482, df 1, 23, p=0.012) sleep latency (F=4.478, df1, 23, p=0.045) and fragmentation index (F=5.179, df 1, 23, p=0.033)

Table K.2: Sleep variability comparison between bipolar disorder and general population groups

Sleep variable	Bipolar Disorder (N=15)		General Population (N=10)		Effect	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*			
Time in bed variability (min.)	99 (64)	64-134	59 (22)	43-75	0.7	24	3.584	0.071
Sleep duration variability (min.)	87 (34)	68-106	53 (21)	38-68	1.0*	24	7.692	0.011
Night waking variability (min.)	55 (57)	24-87	14 (8)	9-19	0.9*	24	5.154	0.033
Sleep efficiency variability (%)	11 (6)	8-15	4 (2)	3-6	1.2*	24	11.797	0.002*
Sleep latency variability (min.)	54 (65)	18-90	18 (10)	10-25	0.7	24	3.082	0.092
Fragmentation index variability	17 (8)	12-21	8 (2)	6-9	1.1*	24	10.677	0.003*

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis for six sleep variability measures (Pillai's trace) F=2.399, df 6, 18, p=0.070

Box's M=73.419, F=2.412, df 21, 1362.499, p=0.000

Levene's test was significant for variability in night waking (F=4.637, df 1, 23 p=0.042), sleep efficiency (F=11.543, df 1, 23 p=0.002), sleep latency (F=4.350, df 1, 23, p=0.048) and fragmentation index (F=14.771, df 1, 23 p=0.001)

Table K.3: Average social and circadian rhythm measures comparison between bipolar disorder and general population groups

Social/circadian rhythm variables	Bipolar Disorder (N=14)		General Population (N=10)		Effect Size*	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI				
Regularity score	3.84 (0.49)	3.56-4.12	3.88 (0.84)	3.28-4.47	-0.1	23	0.019	0.893
DALI	12 (2)	10-13	13 (1)	12-14	-0.5	23	3.632	0.070
L5	1825 (1458)	983-2667	754 (715)	243-1266	0.8*	23	4.564	0.044
M10	20724 (9300)	15354-26093	17853 (7580)	12431-23275	0.3	23	0.644	0.431
RA	0.84 (0.10)	0.78-0.90	0.91 (0.06)	0.87-0.96	-0.8*	23	3.998	0.058
IS	0.52 (0.11)	0.45-0.58	0.52 (0.14)	0.42-0.62	0	23	0.009	0.924
IV	0.80 (0.17)	0.70-0.90	0.88 (0.15)	0.78-0.99	-0.5	23	1.569	0.224

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis of mean and variability for four social rhythm measures (Pillai's trace) F=1.132, df 7, 16, p=0.391

Box's M=73.427, F=1.647, df 28, 1309.218, p=0.018

Levene's test was significant for regularity score (F=8.940, df 1, 22, p=0.007) and L5 (F=5.759, df 1, 22, p=0.025)

Table K.4: Social and circadian rhythm variability comparison between bipolar disorder and general population groups

Social/circadian rhythm variables	Bipolar Disorder (N=14)		General Population (N=10)		Effect Size*	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI				
Regularity score variability	0.87 (0.33)	0.68-1.06	0.59 (0.33)	0.35-0.82	0.8*	23	4.241	0.051
DALI variability	1.55 (0.49)	1.26-1.83	1.15 (0.27)	0.96-1.35	0.9*	23	5.142	0.034
L5 variability	853 (1028)	259-1446	102 (90)	38-167	0.9*	23	5.235	0.032
M10 variability	6273 (5770)	2941-9604	1752 (1632)	585-2920	0.9*	23	5.742	0.026
RA variability	0.05 (0.04)	0.03-0.08	0.01 (0.02)	-0.001-0.02	1.0*	23	9.176	0.006*
IS variability	0.09 (0.06)	0.05-0.12	0.05 (0.04)	0.02-0.08	0.8*	23	2.938	0.101
IV variability	0.20 (0.22)	0.07-0.33	0.19 (0.17)	0.06-0.31	0.1	23	0.023	0.880

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis of mean and variability for four social rhythm measures (Pillai's trace) F=2.762, df 7, 16, p=0.044

Box's M=99.236, F=2.226, df 28, 1309.218, p=0.000

Levene's test was significant for variability in L5 (F=8.557, df 1, 22, p=0.008), M10 (F=8.478, df 1, 22, p=0.008) and RA (F=5.152, df 1, 22, p=0.033)

Table K.5: Averaged behavioural activation/inhibition measures comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder (N=16) M (SD)[1]	95% CI	General Population (N=10) M (SD)[2]	95% CI	Effect Size*	df	F	Significance
BIS	23 (4)	20-24	20 (5)	16-23	0.8*	25	3.067	0.093
BAS reward	15 (3)	14-17	15 (2)	14-16	0	25	0.071	0.792
BAS drive	10 (3)	8-11	10 (2)	8-11	0	25	0.010	0.920
BAS fun	10 (2)	9-11	9 (1)	9-10	0.5	25	1.327	0.261

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis for five averaged self esteem and affect measures (Pillai's trace) F=1.850, df 4, 21, p=0.157)

Box's M=25.935, F=2.072, df 10, 1689.922, p=0.024

Levene's test was significant for BAS reward (F=8.058, df 1, 24, p=0.009)

Table K.6: Behavioural activation/inhibition variability comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder (N=13)		General Population (N=8)		Effect	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*			
BIS variability	1.4 (0.6)	1.1-1.8	1.2 (1.0)	0.3-2.0	0.3	20	0.692	0.416
BAS reward variability	1.5 (1.0)	0.9-2.1	1.1 (0.9)	0.3-1.8	0.4	20	1.105	0.306
BAS drive variability	1.1 (0.9)	0.6-1.7	0.8 (0.8)	0.1-1.5	0.4	20	0.828	0.374
BAS fun variability	0.9 (0.5)	0.6-1.1	1.0 (1.1)	0.1-1.9	-0.1	20	0.113	0.740

Multivariate analysis for five averaged self esteem and affect measures (Pillai's trace) F=0.344, df 4, 16, p=0.844

Box's M=19.552, F=1.449, df 10, 1011.619, p=0.153

Levene's test was significant for variability in BAS fun (F=8.417, df 1, 19, p=0.009)

Table K.7: Averaged self esteem and affect measures comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder (N=19) M (SD)[1]	95% CI	General Population (N=10) M (SD)[2]	95% CI	Effect Size*	df	F	Significance
SE	42 (14)	35-48	56 (8)	50-62	-1.0*	28	8.770	0.006*
PA	21 (6)	18-25	29 (5)	25-33	-1.1*	28	10.178	0.004*
NA	19 (9)	15-23	13 (4)	10-16	0.8*	28	4.122	0.052
Elated	1.8 (0.7)	1.4-2.1	2.3 (0.7)	1.8-2.8	-0.7	28	2.973	0.096
Depressed	2.3 (1.1)	1.7-2.8	1.2 (0.3)	0.9-1.4	1.0*	28	9.249	0.005*

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis for five averaged self esteem and affect measures (Pillai's trace) F=2.638, df 5, 23, p=0.050

Box's M=53.027, F=2.681, df 15, 1359.286, p=0.000

Levene's test was significant for SE (F=6.255, df 1, 27, p=0.019) and depressed (F=12.031, df 1, 27, p=0.002)

Table K.8: Self esteem and affect variability comparison between bipolar disorder and general population groups

Self esteem and affect	Bipolar Disorder (N=18)		General Population (N=10)		Effect	df	F	Significance
	M (SD)[1]	95% CI	M (SD)[2]	95% CI	Size*			
SE variability	6.3 (3.7)	4.5-8.2	1.8 (0.8)	1.2-2.4	1.2*	27	14.036	0.001*
PA variability	5.4 (3.4)	3.8-7.1	5.1 (2.2)	3.5-6.6	0.1	27	0.101	0.753
NA variability	5.1 (3.2)	3.5-6.7	2.1 (2.3)	0.5-3.7	0.9*	27	6.877	0.014*
Elated variability	0.6 (0.5)	0.4-0.9	0.8 (0.4)	0.5-1.1	-0.4	27	6.869	0.360
Depressed variability	0.8 (0.4)	0.5-1.0	0.3 (0.3)	0.1-0.5	1.0*	27	9.561	0.005*

* Indicates large effect size and/or statistically significant finding, $p<0.05$ Holm correction for multiple comparisons

Multivariate analysis for five self esteem and affect variability measures (Pillai's trace) F=3.403, df 5, 22, p=0.020

Box's M=26.998, F=1.360, df 15, 1390.279, p=0.159

Levene's test was significant for variability in SE (F=9.231, df 1, 26, p=0.005

Appendix L. Admissions in high and low variability subgroups of bipolar disorder participants

		Median	Interquartile range	Admission		Total	Fisher's exact test
				No	Yes		
Self esteem	**Low SE variability**	4.0	1.7	6 (60%)	4 (40%)	10	
	High SE variability	8.3	5.6	6 (67%)	3 (33%)	9	
	Total	4.9	4.4	12	7	19	p=0.570
Night waking	**Low night waking variability**	24.4	6.8	5 (62%)	3 (38%)	8	
	High night waking variability	74.0	30.0	3 (43%)	4 (57%)	7	
	Total	31.5	50.0	8	7	15	p=0.405
Sleep efficiency	**Low sleep efficiency variability**	6.4	1.5	5 (71%)	2 (29%)	7	
	High sleep efficiency variability	15.0	8.0	3 (60%)	5 (63%)	8	
	Total	9.8	8.8	8	7	15	p=0.214

Appendix M. Exploratory Kaplan-Meier survival analyses

Table M.1: Kaplan-Meier life table analysis of admissions in bipolar disorder

Time (days)	Status	Number at risk	Cumulative admissions	Cumulative survival rate	Standard error
40	admission	20	1	0.9500	0.0487
137	admission	19	2	0.9000	0.0671
247	admission	18	3	0.8500	0.0798
252	admission	17	4	0.8000	0.0894
315	admission	16	5	0.7500	0.0968
627	admission	15	6	0.7000	0.1025
1126	admission	14	7	0.6500	0.1067
1139	censored	13	7		
1157	censored	12	7		
1163	censored	11	7		
1174	censored	10	7		
1240	admission	9	8	0.5778	0.1167
1258	censored	8	8		
1261	censored	7	8		
1270	censored	6	8		
1286	censored	5	8		
1304	censored	4	8		
1307	censored	3	8		
1314	censored	2	8		
1319	censored	1	8		

Table M.2: Log-rank statistics for continuous variability in self esteem, night waking and sleep efficiency and admission in bipolar disorder

Continuous variable	Median	Interquartile range	Total N	Admission	No admission	Statistic	df	p
Self esteem variability	4.9	4.4	19	7	12	43.98	18	0.0006
Bipolar I Disorder	4.2	3.2	8	5	3	14.07	7	0.0500
Bipolar II Disorder	8.9	12.3	4	1	3	3.00	3	0.3916
Rapid Cycling Disorder	5.9	4.2	7	1	6	6.00	6	0.4232
Night waking variability	31.5	50.0	15	7	8	33.62	14	0.0023
Bipolar I Disorder	26.3	135.2	5	4	1	6.91	4	0.1409
Bipolar II Disorder	31.5	66.8	3	1	2	2.00	2	0.3679
Rapid Cycling Disorder	32.5	41.7	7	2	5	8.69	6	0.1916
Sleep efficiency variability	9.8	8.8	15	7	8	33.62	14	0.0023
Bipolar I Disorder	11.6	11.2	5	4	1	6.91	4	0.1409
Bipolar II Disorder	6.8	13.6	3	1	2	2.00	2	0.3679
Rapid Cycling Disorder	9.8	8.8	7	2	5	8.69	6	0.1916

* Indicates statistically significant finding, $p<0.05$

Exploratory Kaplan-Meier survival analysis of continuous measures of variability in self esteem, night waking and sleep efficiency

The significance of self esteem, night waking and sleep efficiency variability and subsequent admission to hospital were investigated with log-rank tests. The results are displayed in Table M.2. The Mantel-Cox log-rank tests suggested variability in self esteem, night waking and sleep efficiency predicted admission. When diagnostic strata were considered, high self esteem variability predicted admission specifically in bipolar I disorder. Findings are tentative due to the small sample, particularly when analysed by diagnostic strata.

Exploratory Kaplan-Meier survival analysis of categorical measures of variability in self esteem, night waking and sleep efficiency

Participants were categorised into low and high variability subgroups for self esteem, night waking and sleep efficiency. Log-rank tests were repeated with these categorical groups. The results are displayed in Table M.3. Results suggested no significant association between variability and subsequent admission. When diagnostic strata were considered, no significant associations between diagnosis and categorical variability groups emerged for prediction of admission.

Table M.3: Log-rank statistics for categorical variability in self esteem, night waking and sleep efficiency and admission in bipolar disorder

Categorical variable	N	Statistic	df	p
Self esteem variability	19	0.16	1	0.6903
Night waking variability	15	0.88	1	0.3471
Sleep efficiency variability	15	2.80	1	0.0944

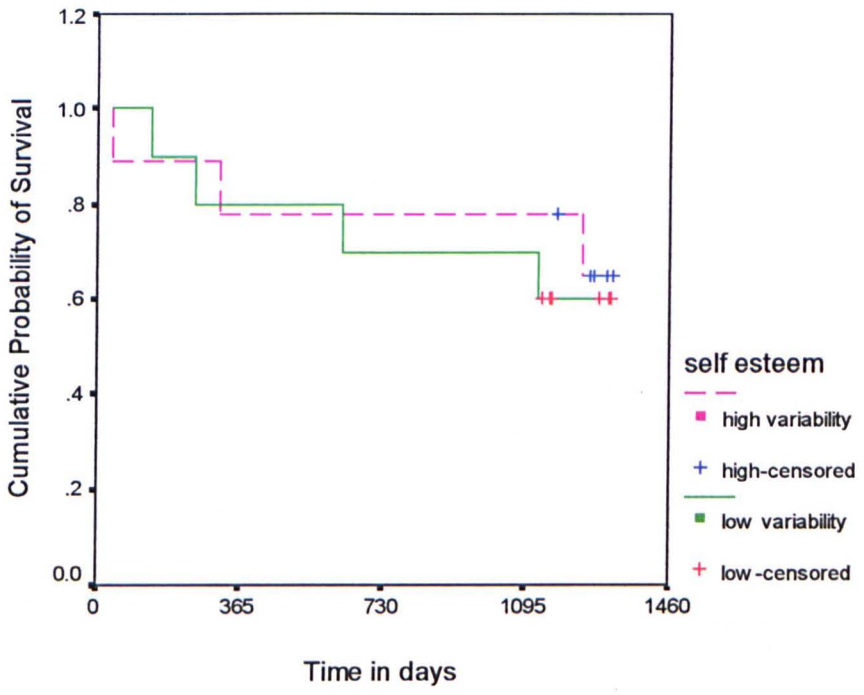
The cumulative probabilities of survival for self esteem, night waking and sleep efficiency variability subgroups were calculated and plotted. The survival rates for subgroups are available in Tables, M.4, M.5 and M.6; the plots are displayed in Figures M.1, M.2 and M.3. The survival rates for each of the variability subgroups will be briefly outlined in turn.

The final cumulative survival rates for low and high self esteem variability subgroups were 0.60 at 1314 days and 0.65 at 1319 days. There were four admissions (40% of N=10) across 137 to 1126 days in the low self esteem variability subgroup. The remaining six low self esteem variability participants were censored across 1139 to 1314 days with no admission. There were three admissions (33% of N=9) across 40 to 1240 days in the high self esteem variability subgroup. There was a censored case at 1174 days between the second and third admission; the remaining cases were censored across 1258 to 1319 days with no admission. No significant differences in time to admission between low and high self esteem variability participants were observed. The cumulative survival rates for self esteem variability subgroups provided in Table M.4 are plotted in Figure M.1.

Table M.4: Kaplan-Meier life table analysis of low and high self esteem variability subgroups

Subgroup	Time (days)	Status	Number at risk	Cumulative admissions	Cumulative survival rate	Standard error
Low SE variability (N=10)	137	admission	10	1	0.9000	0.949
	252	admission	9	2	0.8000	0.1265
	627	admission	8	3	0.7000	0.1449
	1126	admission	7	4	0.6000	0.1549
High SE variability (N=9)	40	admission	9	1	0.8889	0.1048
	315	admission	8	2	0.7778	0.1386
	1240	admission	6	3	0.6481	0.1653

Figure M.1: Kaplan-Meier survival curve for self esteem variability and admission

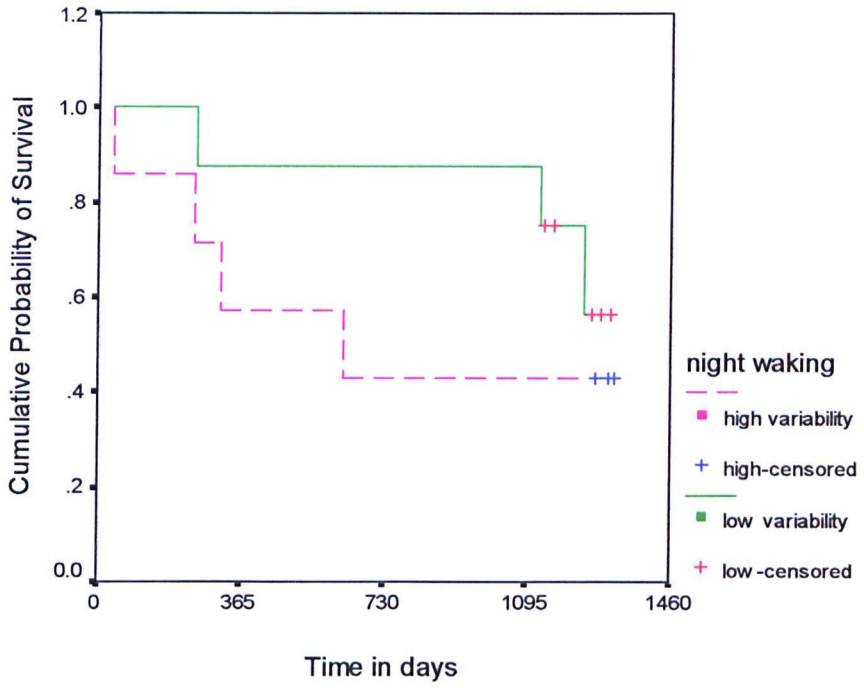


There were three admissions (38% of N=8) across 252 to 1240 days in the low night waking variability subgroup. The remaining five low night waking variability participants were censored, with no admission, across 1139 to 1307 days. There were four admissions (57% of N=7) across 40 to 627 days in the high night waking variability subgroup; three participants were censored across 1270 to 1319 days. Although no significant difference in time to admission between low and high night waking variability participants was observed, the cumulative probabilities of survival for night waking display trends towards high variability being associated with earlier time to admission. The cumulative survival rates for night waking variability subgroups are provided in Table M.5 and plotted in Figure M.2.

Table M.5: Kaplan-Meier life table analysis of low and high night waking variability subgroups

Subgroup	Time (days)	Status	Number at risk	Cumulative admissions	Cumulative survival rate	Standard error
Low NWT variability (N=8)	252	admission	8	1	0.8750	0.1169
	1126	admission	7	2	0.7500	0.1531
	1240	admission	5	3	0.5625	0.1989
High NWT variability (N=7)	40	admission	7	1	0.8571	0.1323
	247	admission	6	2	0.7143	0.1707
	315	admission	5	3	0.5714	0.1870
	627	admission	4	4	0.4286	0.1870

Figure M.2: Kaplan-Meier survival curve for night waking variability and admission

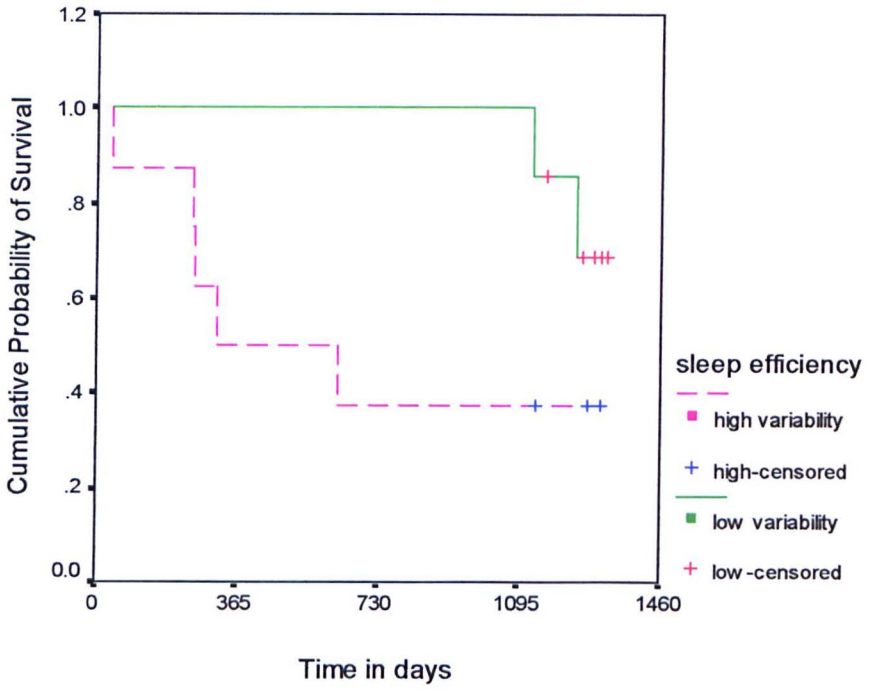


There were two admissions (29% of N=7) at 1126 and 1240 days in the low sleep efficiency variability subgroup, leaving five participants censored across 1163 to 1319 days. In the high sleep efficiency variability subgroup, there were five admissions (63% of N=8) across 40 to 627 days. The remaining three participants were censored across 1139 to 1304 days. No significant differences in time to admission were observed between subgroups. Similarly, to night waking variability, the cumulative probabilities of survival for sleep efficiency variability display trends towards high variability being associated with earlier time to admission. The cumulative survival rates for sleep efficiency variability subgroups are provided in Table M.6 and are plotted in Figure M.3.

Table M.6: Kaplan-Meier life table analysis of admission in low and high sleep efficiency variability subgroups

Subgroup	Time (days)	Status	Number at risk	Cumulative admissions	Cumulative survival rate	Standard error
Low sleep efficiency variability (N=7)	1126	admission	7	1	0.8571	0.1323
	1240	admission	5	2	0.6857	0.1863
High sleep efficiency variability (N=8)	40	admission	8	1	0.8750	0.1169
	247	admission	7	2	0.7500	0.1531
	252	admission	6	3	0.6250	0.1712
	315	admission	5	4	0.5000	0.1768
	627	admission	4	5	0.3750	0.1712

Figure M.3: Kaplan-Meier survival curve for sleep efficiency variability and admission



GLASGOW UNIVERSITY LIBRARY