The nature and experience of anxiety in bipolar disorder
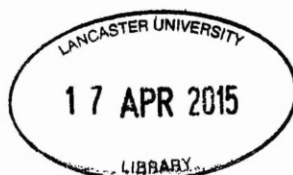

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Contents

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List of common abbreviations

AD = Anxiety disorder

Ago = Agoraphobia

BAS = Behavioural Activation System

BD = Bipolar disorder

BDI = Bipolar I disorder

BDII = Bipolar II disorder

BIS = Behavioural Inhibition System

CBT = Cognitive-Behavioural Therapy

CT = Cognitive Theory

DA = Dysfunctional attitude

DAS = Dysfunctional Attitudes Scale

ESM = Experience Sampling Method

GAD = Generalised anxiety disorder

HPS = Hypomanic personality scale

ICM = Integrative Cognitive Model

NA = Negative affect

OCD = Obsessive compulsive disorder

PA = Positive affect

PARADES = Psychoeducation Anxiety Relapse Advanced Directives Evaluation and Suicidality

PD = Panic disorder

PD_Ago = Panic disorder with agoraphobia

PTSD = Post-traumatic stress disorder

SoP = Social phobia

Sp = specific phobia

UD = Unipolar depression

Abstract

Anxiety experiences (defined either categorically as a disorder or on continua as symptoms) have been found to be highly prevalent in bipolar disorder (BD) and have been consistently associated with poorer outcomes. Current research in this area has primarily focused on prevalence rates of anxiety disorders and their association to retrospective outcomes. There is a lack of research regarding the psychological processes which may underlie the relationship between anxiety and bipolar mood experiences and current psychological models of BD have generally omitted anxiety in their explanations of mood swings. A qualitative meta-synthesis and semi-structured interviews were employed in this thesis to explore the lived experience of anxiety in BD. A longitudinal analysis of data from a large scale RCT was also conducted to assess a range of categorical and continuous measures of anxiety as predictors of outcome in BD. Finally, experience sampling methodology assessed momentary interactions between anxiety and affect in daily life for individuals with BD and non-clinical controls. Anxiety was found to be intrinsically linked to bipolar mood experiences across methodologies. Subjectively, anxiety was perceived as a trigger to both depressed and manic experiences. Anxiety about relapse due to extreme negative appraisals of mood swings was reported and impacted on several important life domains including quality of life, sleep, relationships and employment. Anxiety was consistently associated with increased depression and reduced functioning across all studies. Anxiety and mania were found to have both positive and negative associations across studies. The continuous measurement of anxiety, rather than categorical, was the most reliable predictor of outcome longitudinally when carefully controlling for a range of extraneous variables. The results provide support for anxiety as an intrinsic experience in BD and encourage the consideration of integrated psychological models and treatment approaches which include anxiety as a core feature of BD.

Declaration

This thesis is the work of the author and is substantially different from any work that has been submitted in any form for any degree at this or any other institution. Parts of this thesis have been completed in collaboration with other researchers. Data from Study 2 (Chapter 6) were collected as part of the Psychoeducation Anxiety Relapse Advanced Directives Evaluation and Suicidality (PARADES) research program. Data from Study 3 (Chapter 7) were collected in collaboration with two other doctoral students working within the Division of Health Research, Lancaster University. The exact nature of the contribution from the author has been described in full in the relevant chapters. The meta-synthesis presented in this thesis (Chapter 4) has previously been submitted to Clinical Psychology Review (November 2012), and was sent out for peer review, although was not accepted for publication at that time. Results reported in Study 3 have also been presented at relevant conferences: Division of Clinical Psychology annual conference, Manchester, December 2010 (symposium presentation); Experience Sampling Methodology in Health and Mental Health, Manchester, January 2011 (poster presentation); British Association for Behavioural and Cognitive Psychotherapies conference, London, July 2013 (symposium presentation).

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About the author

Kay Gant graduated from Lancaster University with a 1st Class BSc Honours degree in

Psychology in 2004. After spending some time working in voluntary and NHS mental health

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between November 2009 and April 2014. During this time, the author was also working full-

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evaluating a time-limited psychological intervention for anxiety in BD. The author has been

studying for the Doctorate in Clinical Psychology at the University of Manchester since

October 2013.

Chapter 1: Introduction

1.1 Overview

This thesis takes a mixed methods approach to exploring the experience and interaction of anxiety and mood experiences in bipolar disorder (BD). This chapter first provides a summary of the diagnosis and epidemiology of BD, to highlight the importance of increasing our understanding of BD and progressing research and treatment in this area. The issue of comorbidity is then considered, with particular emphasis on anxiety. Current research reports high rates of other psychiatric disorders in BD, in particular anxiety disorders (ADs) (Krishnan, 2005). Retrospective and longitudinal research has consistently found anxiety to be associated with a more severe illness course (see McIntyre, Soczynska, Bottas, Bordbar, Konarski & Kennedy, 2006, for a review). The conceptualisation of anxiety as a comorbidity in the current literature suggests that anxiety and BD are separate, but co-occurring, experiences. However, this thesis considers the possibility that anxiety may actually be an inherent part of BD, which may also explain the high rates of ADs observed in BD and the associations that anxiety has with poorer clinical outcomes. This chapter provides a narrative review of the current literature and attempts to summarise what is currently known about the prevalence and impact of anxiety in BD. As the current literature has often taken a categorical diagnostic approach to the experience of anxiety, this review also describes anxiety in this way where necessary. However, other research which has explored anxiety experiences as symptoms on a continuum is also reviewed and alternative conceptualisations of anxiety in BD are offered and evaluated in light of the current evidence. Finally, this chapter highlights potential areas for further investigation to determine the aims and direction of this thesis.

1.2 Bipolar Disorder

1.2.1 Diagnosis and symptomology

BD, previously known as 'manic depression', was first described by Kraepelin (1921) and is a mood disorder characterised by periods of extreme lows (depression) and extreme highs (hypomania / mania) in mood. According to the American Psychiatric Association's Diagnostic and Statistical Manual 5th edition (APA, 2013), to be characterised as a mood episode symptoms of depression must last for at least two weeks and interfere significantly with a person's normal functioning (see Table 1.1). Episodes of elevated mood are defined as either mania or hypomania. Manic episodes typically last at least seven days and are marked by significant impairment in functioning, with or without psychosis. Hypomanic episodes also indicate abnormally elevated mood which is out of character for an individual, but last a minimum of four days and do not interfere significantly with a person's usual functioning. Mixed states occur when symptoms of depression and mania are present simultaneously and result in significant impairment in functioning. Individuals who experience episodes of mania with or without depression are classified as having bipolar I disorder (BDI). Individuals who experience hypomanic episodes with depressed episodes are diagnosed as having bipolar II disorder (BDII). Although individuals who experience mania do not have to experience depression to meet criteria for BDI, the majority of people will experience a lifetime depressed episode (Morgan, Mitchell & Jablensky, 2005). Two additional bipolar subtypes are also defined in the DSM-5. Cyclothymic disorder is included and denotes the experience of numerous sub-threshold episodes of depression and hypomania within a two year period, with recovery from symptoms lasting a maximum of two months and where there is no evidence of a major depressed or manic episode within this time frame. BD not otherwise specified (BD-NOS) is included in DSM-5 and refers to individuals who experience variations of depressed and manic symptoms but who do not fulfil the full diagnostic criteria for any other bipolar subtype. For example, those who experience depression with sub-threshold

Table 1.1 *Symptoms of depression, mania and hypomania as defined in the DSM-5*

Depression: Five or more symptoms present in the same two week period and representing a change in usual functioning. At least one symptom is 1. or 2.	Mania: A distinct period of seven days or more of abnormally elevated or irritable mood, with three or more additional symptoms present in the same time period. Symptoms *do* cause clinically significant impairment.	Hypomania: A distinct period of four days or more of abnormally elevated or irritable mood, with three or more additional symptoms present in the same time period. Symptoms *do not* cause clinically significant impairment.
1. Depressed mood	1. Markedly elevated / irritable mood	1. Markedly elevated / irritable mood
2. Markedly diminished interest / pleasure	2. Mood change lasts at least seven days	2. Mood change lasts at least seven days
3. Unintentional weight loss or gain	3. Increased self-esteem / grandiosity	3. Increased self-esteem / grandiosity
4. Insomnia / hypersomnia	4. Decreased need for sleep	4. Decreased need for sleep
5. Psychomotor agitation / retardation	5. More talkative / pressure of speech	5. More talkative / pressure of speech
6. Significant fatigue / loss of energy	6. Flight of ideas / racing thoughts	6. Flight of ideas / racing thoughts
7. Worthlessness / excessive guilt	7. Distractible	7. Distractible
8. Reduced concentration / indecisiveness	8. Increased goal directed activity / psychomotor agitation	8. Increased goal directed activity / psychomotor agitation
9. Recurrent thoughts of death, suicide plan or attempt	9. Excessive pleasurable risk-taking activities	9. Excessive pleasurable risk-taking activities
10. Clinically significant distress / impairment	10. Clinically significant impairment	10. Clinically significant impairment
Additional criteria:	**Additional criteria:**	**Additional criteria:**
• Not better explained by a bereavement which occurred < 2 months ago • Not the result of substance use • Not better explained by a general medical condition	• Not the result of substance use • Not better explained by a general medical condition	• Not the result of substance use • Not better explained by a general medical condition

manic symptoms which cause severe impairment, violating the criteria for hypomania (BDII) but not lasting for a long enough time to meet criteria for mania (BDI). Because of this complex range of presentations within BD and similar complexity observed in other mood disorder populations, a spectrum of mood disorders has been proposed ranging from unipolar depression (UD) at one extreme to pure mania at the other (Angst et al., 2010). This spectrum includes the core and most severe symptoms of a disorder, but also 'softer' expressions of mood disorders, where people may experience more subtle but related symptoms (Fagiolini, Frank, Rucci, Cassano, Turkin & Kupfer, 2007). However, this approach still conceptualises mood experiences into categories, which has limitations. These are outlined in Section 1.2.2.

1.2.2 Limitations to diagnostic approaches in BD

There is a continuing debate regarding the usefulness of diagnostic approaches to mental health. Diagnoses can be helpful when they accurately describe an individual's experiences, predict outcomes and guide effective treatment. However, reports have consistently shown low inter-rater reliability for almost all diagnostic categories within publications such as the DSM. DSM-5 has been no exception, showing Kappa scores of 0.56 for BDI and 0.40 for BDII in adult samples (Freedman et al., 2013). Inter-rater reliability for diagnoses reported in research is much higher (Skre, Onstad, Torgersen & Kringlen, 1991; Williams, Gibbon, First & Spitzer, 1992), where ongoing training and supervision are provided to researchers. Absence of adequate training and supervision may account for low reliability of diagnosis in clinical practice, although it is likely that many other factors may also be taken into account when assessing diagnosis in this context, which may reduce reliability but potentially increase validity (Aboraya, Rankin, France, El-Missiry & John, 2006). Diagnoses are essentially lists of behavioural, mental, physiological and emotional experiences which define specific disorders, but provide no indication of the factors linked to causality and do not consider

individual differences in experiences and outcomes (Division of Clinical Psychology (DCP), 2010). For a diagnosis to be valid, it should tell us reliably about symptoms a person will experience and treatments that will help. However, individuals have been found to vary widely in their response to current pharmacological and psychological treatments (see Scott, & Gutierrez, 2004, for a review), suggesting that diagnosis alone may fail to capture individual differences which mediate or moderate treatment effects (DCP, 2010). Many individuals with a diagnosis of BD receive multiple diagnoses prior to this (see Perugi & Toni, 2012, for a review), suggesting that experiences and problems are not static and may require varying levels of support and treatment throughout the lifetime. More recently, institutions including the National Institute for Mental Health (NIMH) have criticised the diagnostic approach for being too subjective and open to cultural bias (NIMH, 2013). In particular, diagnostic categories have been criticised for their arbitrary classification of symptom clusters to denote specific disorders, creating artificial boundaries between pathological and 'normal' experiences (NIMH, 2013) and significant overlap of symptoms across disorders (Cheniaux et al., 2008; Post, 2010). Mood changes are one such example, with all individuals experiencing mood fluctuations across the life span, but not everyone experiencing problems as a result. An alternative approach to mood disorders suggests that experiences should be considered on a continuum, from usual, everyday mood swings at one end to extreme fluctuations in mood at the other. It has been suggested that emphasis is placed on where these experiences cause problems and impairments for individuals to guide research and treatment, rather than broad divisions between normal and disordered experiences (DCP, 2010). Despite limitations associated with diagnostic approaches, the majority of research in BD to date assumes that diagnosis is relevant and this has provided a degree of consistency which has enabled the progression of current understanding with regards to mood instability. In addition, to some extent diagnoses have provided a useful way of marking severity for those experiencing the most extreme mood states and have directed the

organisation of services to support people with those experiences. It is also important to note that some people do find diagnosis useful, as this may help to normalise and make sense of experiences to some extent (Proudfoot, Parker, Benoit, Manicavasagar, Smith & Gayed, 2009). Although a departure from the diagnostic approach is now called for, future directions for BD treatment and research are in their infancy. The NIMH has recently launched the Research Domain Criteria (RDoC) project, which aims to develop a new classification system based on the integration of genetic, imaging, physiological and cognitive data to identify clusters within these collated results to inform research and treatment. However, this is likely to take many years to develop. As such, this thesis is guided by the current literature and adopts a diagnostic approach where necessary, whilst being mindful of the limitations this brings.

1.2.3 Prevalence and onset of BD

Epidemiological studies of community participants report prevalence rates of approximately 1% for BDI when using DSM criteria (Cavanagh, 2004; National Institute for Health and Care Excellence (NICE), 2006; Schaffer, Cairney, Cheung, Veldhuizen & Levitt, 2006), although rates reported have ranged from 0.3 to 2.5% depending on the geographical location of the sample and the diagnostic assessment tool used (NICE, 2006). Likewise, prevalence rates for BDII have been reported as ranging between 0.2 to 2.0% (NICE, 2006). However, there is evidence to suggest that many more people may meet criteria for a bipolar spectrum disorder which is clinically significant. Faravelli, Rosi, Scarpato, Lampronti, Amedei & Rana (2006) found that, of a large sample of respondents who were interviewed using standardised assessments, 4.66% scored positive for hypomanic symptoms that were clinically significant, without meeting full criteria for BDI or II. Studies including the full range of bipolar spectrum diagnoses described in Section 1.2.1 have found prevalence rates as high as 10.9% (Angst, Gamma, Benazzi, Ajdacic, Eich & Rössler, 2003; Baldessarini, Perry & Pike,

2008; Kessler, Chiu, Demler & Walters, 2005). In general, the prevalence research is limited by the lack of consensus regarding diagnostic criteria of bipolar spectrum disorders (Hadjipavlou & Yatham, 2008) and provides further support for the consideration of mood experiences on a continuum. In summary, BDs and related mood experiences affect millions of people worldwide. Peak onset of BD occurs during adolescence and early adulthood between the ages of 15 and early twenties (Merikangas et al. 2007; Weissman et al., 1996), although very early onset occurring below the age of 13 years has also been reported (Perlis et al., 2004).

1.2.4 Factors associated with BD

A review of the epidemiological research shows that BD is equally likely to occur for both males and females (Merikangas & Pato, 2009), although illness course may differ, with females more likely to experience depression and males more prone to mania (Christensen et al., 2003; Duax, Youngstrom, Calabrese & Findling, 2007). Evidence regarding education and income as a factor associated with BD is mixed. Whilst earlier research suggested increased rates of BDs in high income populations, more recent surveys have found that those with low income and less education have increased prevalence rates (Hirschfeld et al., 2003; Merikangas & Pato, 2009). A recent publication reporting data for the first 172,751 participants in the UK Biobank study, a database of health-related data for adults recruited from the general population in the UK, found that those meeting criteria for manic symptoms had significantly higher levels of deprivation (Smith et al., 2013). Overall, individuals with BD tend to be well educated, with up to 90% completing education to secondary level (Kupfer, Frank, Grochocinski, Cluss, Houck & Stapf, 2002; Morgan et al., 2005) and significantly more achieving degree level qualifications compared to those without mood disorder diagnoses (Smith et al., 2013). However, rates of unemployment for individuals with BD are high, with two thirds out of work (Morgan et al., 2005), and between

40% and 61% claiming benefits (Kupfer et al., 2002; Morgan et al., 2005). Even for those in employment, three quarters of people affected by BD have reported having to take time off work for health reasons (Morgan et al., 2005). Relationship status has been found to be associated with BD diagnosis, with those who are separated, divorced or widowed more likely to meet criteria than those who are married or never married (Grant et al., 2005; Merikangas et al., 2007). Studies reporting differences between ethnic groups have been mixed. There is some evidence that diagnosis is equal across ethnic populations (Minsky, Vega, Miskimen, Gara & Escobar, 2003), although other research has found rates of BD to be higher in non-white individuals, in particular Asian and black populations (Sherazi, McKeon, McDonough, Daly & Kennedy, 2006; Smith et al., 2013). Discrepancies may occur due to African Americans being under-diagnosed with BD but over-diagnosed with schizophrenia in clinical practice (Kilbourne et al., 2004), despite similar presentations across groups (Perron, Fries, Kilbourne, Vaughn & Bauer, 2010). The extent to which socio-demographic factors are a cause or consequence of mood dysregulation is unclear and requires further research.

1.2.5 Course, burden and clinical outcome in BD

In general, individuals with BD will experience significantly more episodes of depression than (hypo)mania (de Carvalho et al., 2012). Although BDI is often thought of as the most severe, research has found that individuals with BDI and BDII may have relatively comparable mood instability, with both groups spending significantly more days depressed than (hypo)manic (Evans et al., 2005; Judd et al., 2003; Kagan, 2010) and an equivalent number of days well for both (Otto et al., 2006). Of participants meeting criteria for BD in an Australian census study, 69.9% had a recurrent episodic illness, 25% reported a chronic course with no clear periods of euthymia and 84.8% of people had used services in the past year (Morgan et al., 2005). Service use results in a high economic cost to society. A recent review of the literature converted results from international cost of illness studies of BD to average costs in US

dollars and found an estimated spend of $8,000 to $14,000 per person diagnosed with BD per year for all healthcare needs, and $2500 to $5000 per person per year for BD treatment specifically (Kleine-Budde, Touil, Moock, Bramesfeld, Kawohl & Rössler, 2013). Figures specifically for English patients indicate slightly lower costs in terms of health care (McCrone, Dhanasiri, Patel, Knapp & Lawton-Smith, 2008), which is likely due to differences in healthcare systems, but still indicates very high societal costs of BD in the UK. Use of medication, psychiatrist services and inpatient hospital admissions were the main expense in both studies. High levels of unemployment, as discussed in Section 1.2.4, add to the economic cost of BD, together with high rates of absenteeism for those who are in employment (McCrone et al., 2008; Pini et al., 2006) which are related to both physical and mental health. Overall, BD is associated with reduced global functioning (de Carvalho et al., 2012) and has previously been found to be the ninth leading cause of healthy life years lost due to disability and premature mortality in individuals aged 15 to 44 (World Health Organisation (WHO), 2001). BD is associated with poorer physical health, in particular increased cardio-vascular disorders, endocrine disorders and obesity, which are higher than for other clinical populations such as individuals with schizophrenia (de Carvalho et al., 2012; Johannessen, Strudsholm, Foldager & Munk-Jørgensen, 2006; Kemp et al., 2014; Kilbourne et al., 2004). As such, mortality rates are higher for individuals with BD compared to the general population (Crump, Sundquist, Winkleby & Sundquist, 2013). These are increased further by the finding that individuals with BD are 20 to 30 times more likely to attempt suicide than the general population (Nery-Fernandes et al., 2012; Pompili et al., 2013) and being single or male has been associated with an even greater increased risk of suicidality in BD (Nery-Fernandes et al., 2012). In summary, BD is a recurrent disorder and is associated with problems in important life domains for many people. This highlights the need for further research to better understand and help people with bipolar mood swings.

1.2.6 Treatment of BD

The most recent NICE guidelines advise pharmacotherapy as first line treatment for BD, in particular SSRI's for bipolar depression and the use of antipsychotics and mood stabilisers for the treatment of bipolar mania (NICE, 2006). Based on a review of epidemiological studies with BDI populations, approximately 50% of people were receiving current mental health treatment (Merikangas & Pato, 2009). The majority of people with BD who access services are prescribed psychotropic medications (Hirschfeld et al., 2003; Morgan et al., 2005), with most prescribed a combination of mood stabilisers, antipsychotics, antidepressants and anticonvulsants (Hirschfeld et al., 2003). A meta-analysis of the treatment literature suggested that there may be modest benefits of medications, with lithium having the strongest evidence, with relapse rates of 40% over a maximum of 24 months compared to 61% relapse rates for those allocated to placebo (Geddes, Burgess, Hawton, Jamison & Goodwin, 2004). However, there was only a significant effect on prevention of manic, but not depressive, relapse in this meta-analysis. In addition, prospective studies have often failed to find medication effective at managing BD symptoms long term (Licht, Nielsen, Gram, Vestergaard & Bendz, 2010; Reinares et al., 2013) and the evidence for the use of anti-psychotics and anti-convulsants is less robust still (Geddes & Miklowitz, 2013). Medications are often associated with severe side effects, making them intolerable for some (Leclerc, Mansur & Brietzke, 2013; Licht et al., 2010). Overall, randomised controlled trials (RCTs) of drug treatments for BD are limited by small sample sizes (n = < 50) and high attrition rates, with 70% of studies failing to perform power calculations to obtain the relevant sample size and only 66% of studies found to use structured measures to confirm diagnosis (Spanemberg et al., 2012). A review of pharmacological RCT's for BD treatment published since 2000 found that quality of reporting was poor overall, with only 42% reporting randomisation procedures adequately (Strech, Soltmann, Weikert, Bauer, & Pfennig, 2011). This is important as at least half of controlled trials are sponsored by pharmaceutical companies

and so the need to control for bias is high (Spanemberg et al., 2012). Due to the limitations of pharmacological research and associated treatments there has been increasing evaluation of psychological interventions for the treatment of BD. At present, NICE guidelines recommend psychological therapy in addition to medication following recovery from acute bipolar mood episodes, and for the treatment of moderate to severe depressive symptoms where SSRI's are proven to be ineffective (NICE, 2006). Research shows that adjunctive psychological interventions for individuals, groups and families are effective in improving long term outcomes in BD (Geddes & Miklowitz, 2013; Isasi, Echeburúa, Limiñana, & González-Pinto, 2010; Lam & Wong, 2005; Parikh et al., 2012; Romm, Avery, & Roy-Byrne, 2006). The evidence for specific psychological treatments for BD is discussed at length in the next chapter (Chapter 2). However, in general further research is needed to fully understand the mechanisms by which psychological treatments impact on variables such as sleep, activity and mood fluctuations in order to improve clinical and functional outcomes. A potential limitation of all current treatments for BD is their tendency to focus on experiences of depression and mania only. Given the high rates of other clinically relevant experiences often associated with BD such as anxiety (Merikangas et al., 2007), these may also need to be considered to develop more effective interventions and research.

1.2.7 Comorbidity in BD

Clinical comorbidity can be defined as two or more disorders co-occurring simultaneously but independently, and therefore comorbid disorders may or may not influence the outcome, treatment or illness course of another (McElroy et al., 2001). The National Comorbidity Survey Replication study (NCS-R ; Merikangas et al., 2007) reported rates of other psychiatric disorders for 9282 individuals with bipolar spectrum conditions and found that 92.3% of individuals met criteria for at least one other disorder, with 70.1% of participants meeting criteria for three or more psychiatric disorders. Disorders included

anxiety disorders (ADs) (74.9%), impulse control disorders (62.8%) and substance and alcohol use disorders (42.3%). These results have been replicated in other epidemiological studies and meta-analyses of psychiatric disorders in BDI and II populations (Di Florio, Craddock, & van den Bree, 2013; Sherazi et al., 2006), with high rates of personality disorders also being reported (Benazzi, 2006; George, Miklowitz, Richards, Simoneau, & Taylor, 2003; Turley, Bates, Edwards, & Jackson, 1992). Overall, all psychiatric disorders in BD are associated with a more severe illness course (Coryell, Solomon, Fiedorowicz, Endicott, Schettler & Judd, 2009; Loftus & Jaeger, 2006; Mandelli et al., 2012; Mazza et al., 2009) and these associations have been found to be robust after controlling for sociodemographic characteristics (Grant et al., 2005) and baseline mood symptoms (Mandelli et al., 2012). The experience of anxiety in relation to BD in particular has received attention, not only because of the high prevalence rates observed, but also because of the elevated rates of ADs compared to other clinical and non-clinical samples (Dilsaver, Benazzi, Akiskal, & Akiskal, 2008; Mueser et al., 2004). Anxiety in BD has been consistently linked to poorer clinical outcomes and a more severe illness course in BD (for a review see McIntyre et al., 2006). Current research has taken a primarily diagnostic categorical approach to explore the relationship between anxiety and mood in BD, which has led to the conceptualisation of these experiences as distinct, 'comorbid' phenomena. However, this may be inherently flawed, as symptoms across psychiatric disorders often overlap, in particular mood disorders such as BD and ADs, resulting in multiple comorbid diagnoses for one individual which may be better defined as a general underlying dysregulation of emotion. The current literature relating to the experience of anxiety in BD is reviewed next, and potential alternative conceptualisations of the association between anxiety and BD are discussed.

1.3 The experience of anxiety in BD

1.3.1 Symptoms and diagnosis of ADs

Anxiety can be defined as a "psychological, physiological and behavioural response induced by a threat to well-being or survival, either actual or potential" (Steimer, 2002). Anxiety is also a "future-oriented mood state associated with preparation for possible, upcoming negative events" (Barlow, Raffa, & Cohen, 2002). Although unpleasant, anxiety is for most people an adaptive, functional and short-term emotional response which activates an individual to cope with adverse or unexpected situations. ADs occur when anxiety becomes persistent, excessive, irrational and interferes with everyday life and functioning (Barlow et al., 2002). The DSM 4th edition (DSM-IV; APA, 2000), which much of the literature exploring anxiety in BD is based on, outlines 12 AD categories, each defined by unique diagnostic features. The most prevalent and well-researched AD categories in BD include panic disorder (PD), panic disorder with agoraphobia (PD_Ago), agoraphobia (Ago), social phobia (SoP), specific phobia (SP), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and generalised anxiety disorder (GAD) (see Table 1.2). Other ADs are not well-documented in the BD literature and so are not discussed here. DSM-5 has added a novel anxiety category to the section on BD, an 'anxious distress specifier'. However, this maintains anxiety as a separate experience and defines "patients with anxiety symptoms that are not part of bipolar diagnostic criteria" (DSM-5, APA, 2013). As with diagnostic approaches to BD, research focusing only on ADs is problematic. Firstly, all of the issues outlined in Section 1.2.2 in relation to the reliability and validity of diagnostic labels is as true for anxiety as for BD (Freedman et al., 2013). Secondly, a study by Contreras, Hare, Pacheco, Escamilla & Raventos (2010) found that a quarter of participants with BDI did not meet full diagnostic criteria for ADs but did have high trait anxiety scores and current anxiety symptoms equal to or above individuals who did meet diagnostic criteria for an AD. Another study found similar

results, with prevalence of panic symptoms being four times greater than panic disorder in

BD, but with panic symptoms still found to have a significant effect on treatment and

outcome. Therefore, focusing exclusively on diagnostic criteria may neglect potentially

important and clinically relevant anxiety symptoms. As such, this review takes an inclusive

approach and considers research of anxiety in BD which uses either a diagnostic framework,

or a symptom based approach.

Table 1.2 *DSM-IV criteria for main ADs in BD research*

AD	Key feature (DSM-IV)	Duration of symptoms
Panic Disorder (PD)	Recurrent and unexpected panic attacks; worry or concern about future attacks; behaviour change	$\geq$ One month
Panic Disorder with Agoraphobia (PD_Ago)	Symptoms of PD; avoidance and fear of situations where panic attacks may occur	$\geq$ One month
Agoraphobia (Ago)	Marked fear and avoidance of situations in which escape might be difficult or embarrassing	$\geq$ One month
Social Phobia (SoP)	Avoidance and fear of social situations due to concern regarding possible embarrassment or humiliation	$\geq$ One month
Specific Phobia (SP)	Marked fear and avoidance of specific situations or objects	$\geq$ One month
Obsessive Compulsive Disorder (OCD)	Obsessions: recurrent intrusive thoughts, images or impulses; Compulsions: recurrent repetitive behaviour or mental acts with the aim of reducing distress or neutralising obsessions	$\geq$ One month
Post-Traumatic Stress Disorder (PTSD)	Persistent re-experience, distress and avoidance of stimuli associated with a past event which involved actual or threatened death or serious injury	> One month
Generalised AD (GAD)	Chronic excessive, uncontrollable worry across a number of domains	More days than not for $\geq$ 6 months

1.3.2 Prevalence of ADs in BD

ADs are one of the most prevalent disorders reported in the general population and a recent

meta-regression adjusting for methodological differences between studies estimated current

global prevalence rates for ADs in the general population to be 7.3% (Alloy et al., 2012).

Prevalence rates of ADs in BDI and II populations exceed this, with prevalence rates up to

52.8% for current ADs (Henry, Van den Bulke, Bellivier, Etain, Rouillon, & Leboyer, 2003;

McElroy et al., 2001; Otto et al., 2006) and up to 92.9% for lifetime AD prevalence in large

community-based surveys (Kessler, 1999; Merikangas et al., 2007; Sala, Goldstein, Morcillo,

Liu, Castellanos & Blanco, 2012), although these findings are not universal (Sorvaniemi &

Hintikka, 2005). Bipolar spectrum disorders including cyclothymia have also been found to be

significantly associated with both full syndrome and sub-threshold ADs (Lewinsohn,

Shankman, Gau, & Klein, 2004; Tomba, Rafanelli, Grandi, Guidi, & Fava, 2012). Similarly,

individuals with primary ADs have been found to be at risk of manic or hypomanic episodes,

with up to 58.8% of individuals found to meet clinical threshold criteria for lifetime BD (Masi

et al., 2007; Perugi & Akiskal, 2002; Sugaya et al., 2013; van den Berg, Penninx, Zitman, &

Nolen, 2010) or cyclothymic disorder (Del Carlo, Benvenuti, Toni, Dell'Osso, & Perugi, 2013).

Individuals with PD_Ago were also found to have significantly higher prevalence rates for

hypomania (75%) compared to healthy controls, of whom only 9% met threshold criteria for

hypomanic symptoms (Del Carlo et al., 2013). A synthesis of the bipolar literature found that

ADs were the most prevalent psychiatric disorders in BD across studies, with an average of

71% of participants meeting criteria for any lifetime AD (Krishnan et al. 2005). This was in

comparison to significantly lower mean prevalence rates for other axis I disorders across

studies, such as substance use disorder (56%), alcohol abuse disorders (49%) and personality

disorders (36%). Average prevalence rates for specific ADs were also calculated and

reported as 47% for SoP, 39% for PTSD, 11% for PD (with or without Ago) and 10% for OCD

(Krishnan et al., 2005). Geographical location appears to have little effect, with high AD

prevalence rates in BD reported in Africa, China, India, Canada, USA and Europe (Altindag, Yanik &Nebioglu, 2006; Altshuler et al., 2010; Hawke, Velyvis, & Parikh, 2013; Das, 2013; Chang et al., 2012; Zutshi, Reddy, Thennarasu & Chandrashekhar, 2006).

High anxiety rates have been found to persist across the life span for individuals with BD. Studies with individuals with BD aged between 7 and 24 years of age have found lifetime ADs to range from 22.8% to 77.4% (Axelson et al., 2006; Biederman, Mick, Faraone, Spencer, Wilens, & Wozniak, 2000; Dickstein et al., 2005; Joshi et al., 2010; Kozloff et al., 2010; Masi et al., 2007; Ratheesh et al., 2011; Sala et al., 2012; Sala et al., 2010; Steinbuchel, Wilens, Adamson, & Sgambati, 2009). Prevalence rates for ADs in older adult populations have been lower but still significant. A large sample (n = 16,330) of older adults aged 60 years or more with a diagnosis of BD found that 9.7% met criteria for a current AD, in particular PTSD (5.4%). This was higher than the number of people meeting criteria for dementia (4.5%) and slightly higher than those reporting substance use disorders (8.9%) (Sajatovic, Blow, & Ignacio, 2006). Persistent anxiety in older adult samples with a diagnosis of BD has been replicated elsewhere (Goldstein, Herrmann, & Shulman, 2006; Sajatovic & Kales, 2006).

Despite overall agreement within the current literature that prevalence of ADs in BD is high, there is a wide variation in the prevalence rates reported. Once again, this questions the reliability of the categorical diagnostic assessment of ADs. However, the majority of studies report high anxiety prevalence rates independent of the diagnostic measure used (Otto, Perlman, Wernicke, Reese, Bauer & Pollack, 2004) and comparably high rates of ADs have been replicated across a number of clinical samples including inpatient (Das, 2013), outpatient (Otto et al. 2006) and community samples (Sala et al., 2012), and for individuals with BD assessed both during acute mood episodes (Frank et al., 2002; Gaudiano & Miller, 2005) and during periods of euthymia (Albert, Rosso, Maina, & Bogetto, 2008; Zutshi et al., 2006). Taking limitations of diagnostic research into account, at worst this does highlight the common occurrence of high levels of anxiety both in and out of mood episodes for

individuals with BD, and indicates this is an important experience which warrants further attention.

1.3.3 Anxiety in BDI and II

The evidence regarding whether anxiety is more prevalent in BDI or II samples is ambiguous. It has generally been accepted that ADs are more closely linked to BDII, with higher prevalence rates for ADs in comparison to BDI samples (Angst et al., 2005; Judd et al., 2003; Mula et al., 2008; Rihmer, Szádóczky, Füredi, Kiss, & Papp, 2001; Sala et al., 2010). However, several studies have found no difference (Albert et al., 2008; Dell'Osso, Buoli, Bortolussi, Camuri, Vecchi & Altamura et al., 2011; Ibiloglu & Caykoylu, 2011; Krishnan, 2005; Mantere et al., 2006; McElroy et al., 2001). This may be due to the use of variable diagnostic and sub-threshold criteria to define BDII which may artificially elevate rates of ADs in BDII populations. Alternatively, relatively limited sample sizes in some of the studies finding no significant differences are noted and may also account for the variance in findings.

1.3.4 The association between anxiety and mania in BD

It has been noted that anxiety symptoms and disorders occur to a greater extent within BD compared to other mood disorder populations (for a review see Provencher, Guimond & Hawke, 2012). Research exploring the association between anxiety and mania may be useful to understand this observation, although findings in this area are mixed. Despite high prevalence rates for anxiety in BD, there is evidence that mania may be a protective factor, with individuals who met criteria for unipolar mania found to be significantly less likely to meet criteria for ADs than those who had also experienced depressed episodes in a retrospective study of 298 individuals with BD (Andrade-Nascimento, Miranda-Scippa, Nery-Fernandes, Kapczinski, & Quarantini, 2011). This may suggest that anxiety is an inherent part of bipolar depression, which is important as individuals with BD spend a significant amount

of time in depressed episodes (Kupka et al., 2007). Research exploring temporal associations between anxiety and mania has found that several ADs are no longer evident during manic episodes for some people. Based on retrospective reports from 63 individuals with BDI and II disorder it was found that during manic episodes, criteria was no longer met for SoP for 94.7% of individuals, PD criteria was no longer met for 42.9% of the sample and OCD was no longer evident for 47.8% of participants (Perugi, Akiskal, Toni, Simonini & Germignani, 2001). Conversely, PD was found to onset in mania for 28.6% of people in the same study. The authors suggest that these results may be explained using a continuum approach, where SoP and OCD are extremes on a continuum of constraint vs. hypomanic disinhibition, explaining why PD and OCD were still prevalent during mania for some, whilst SoP was no longer evident for others. However this requires replication. Anxiety symptom scores have been found to correlate positively and equally with both depression and mania cross-sectionally elsewhere (Swann, Moeller, Steinberg, Schneider, Barratt & Dougherty, 2007) although depression and mania were not correlated. Simon et al. (2005) suggest that elevated anxiety in BD may be due to some individuals having increased anxiety sensitivity (AS). This is defined as the "excessive fear of anxiety-related sensations based on the belief that these sensations are harmful" (Simon et al., 2005). AS scores did not differ cross-sectionally between 92 euthymic individuals with UD and 110 participants with BD in this study, but being in a current manic or hypomanic episode did predict elevated scores for AS. The authors suggest that the experience of manic episodes may be a possible mediator to the development of anxiety in BD, with hypomania activating increased AS. However, it may be argued that AS is essentailly a core defining feature of anxiety in general, with fear of anxiety symptoms a main criteria of anxiety and ADs, and so it is unclear if measuring AS adds anything additional to measuring anxiety symptoms directly. Finally, a study which followed 413 youths with bipolar spectrum disorders over a five year period found that risk of developing an AD was significantly associated with increased time spent with manic or

hypomanic symptoms (Sala et al., 2012). However, the majority of current research is cross-sectional and more longitudinal data is required to fully understand the temporal and clinical relationships between anxiety and mania.

1.3.5 Factors associated with the experience of anxiety in BD

Research comparing individuals with BD with and without ADs has generally found no difference in terms of sociodemographic variables including ethnicity, marital status, age and education (Azorin et al., 2009; Goodwin & Hoven, 2002; Quarantini et al., 2010). However, although women are equally as likely as men to be diagnosed with BD (Fletcher, Parker, & Manicavasagar, 2013), there is evidence that females with BD are significantly more at risk of ADs and anxiety symptoms than their male counterparts, both cross-sectionally and over time (Altshuler et al., 2010; Goodwin & Hoven, 2002; Levander et al., 2007; Sala et al., 2012).

1.4 Clinical impact of anxiety in BD

Despite an increase in BD research since 1990, only 3% of the literature to date has addressed anxiety in BD, and only 35% of those articles have explored anxiety as the main research question, with the majority reporting on anxiety as a secondary outcome (Provencher et al., 2012). Although prevalence data is useful in highlighting the potential importance of ADs in BD, this is primarily descriptive and does not imply any particular mechanisms which may underlie this relationship (Rutter, 1994). Instead, research exploring the clinical impact of anxiety in BD is important to identify processes by which anxiety may effect mood instability and outcome.

1.4.1 Cross-sectional associations between current and lifetime ADs and outcome in BD

A large number of cross-sectional studies have found anxiety to be significantly associated with a more severe illness course retrospectively. Large community surveys including the National Epidemiological Survey on Alcohol and Related Conditions 2001-2002 (NESARC)

(e.g. Goldstein & Levitt, 2008) and the National Comorbidity Survey (NCS) (Goodwin, Hamilton, Milne, & Pine, 2002) have found that individuals with BD and ADs have worse outcomes compared to individuals with ADs or BD alone. In particular, anxiety in BD is associated with an increased number of past depressed and manic episodes (Azorin et al., 2009; Goes et al., 2012; Goldstein & Levitt, 2008; Quarantini et al., 2010), increased symptoms of depression and mania (Assion et al., 2009; Azorin et al., 2009), more severe anxiety symptoms compared to those with BD or ADs alone (Gaudiano & Miller, 2005; Goodwin & Hoven, 2002), less time well (Azorin et al., 2009; Zutshi et al., 2006), increased likelihood of rapid cycling (Kauer-Sant'Anna et al., 2007; MacKinnon, Zandi, Gershon, Nurnberger, & DePaulo, 2003; Quarantini et al., 2010), earlier age of onset of BD (Carter, Mundo, Parikh, & Kennedy, 2003; Goes et al., 2012; Henry et al., 2003; Pini et al., 2006), more likely to be prescribed a greater number of psychiatric medications (Azorin et al., 2009) but with reduced response to pharmacological treatments (Henry et al., 2003; Zutshi et al., 2006), increased use of BD-related services and more hospitalizations for BD episodes (Goldstein & Levitt, 2008; Prince et al., 2008), greater physical and social functional impairment (Assion et al., 2009; Goldstein & Levitt, 2008; Goodwin & Hoven, 2002), reduced quality of life(Albert et al., 2008; Assion et al., 2009; Kauer-Sant'Anna et al., 2007), increased likelihood and severity of psychosis (Azorin et al., 2009; Kauer-Sant'Anna et al., 2007; Zutshi et al., 2006), increased suicidality (Azorin et al., 2009; Goes et al., 2012; Perroud et al., 2007; Tsai et al., 2012) and increased likelihood of meeting criteria for other psychiatric disorders (Goodwin & Hoven, 2002; Kauer-Sant'Anna et al., 2007). ADs have been found to have a similar negative impact on outcome for children and adolescents with a diagnosis of BD (Sala et al., 2010) and for individuals with primary ADs with BD compared to individuals with ADs alone or those with anxiety and UD (Fracalanza, McCabe, Taylor & Anthony, 2011; Goldstein & Levitt, 2007; Masi et al., 2007). The association between anxiety and poorer outcomes in BD has been found to be sustained after controlling for age, gender, other psychiatric

disorders, bipolar sub-type, type of last affective episode and severity of mood symptoms (Albert et al., 2008; Frank et al., 2002; Gao et al., 2010; Goodwin & Hoven, 2002; Kauer-Sant'Anna et al., 2007). However, there is some contrasting evidence which has found no difference in clinical outcomes for individuals with BD with and without ADs (Fagiolini, Kupfer, Masalehdan, Scott, Houck, & Frank, 2005; Levander et al., 2007).

Specific ADs have also been found to be individually associated with poorer outcomes when controlling for the presence of other ADs. However, this is inconclusive as independent negative effects have been found for most ADs including PD (Otto et al., 2006; Pini et al., 2003), PTSD (Dilsaver, Benazzi, Akiskal & Akiskal, 2007; Kolodziej, Griffin, Najavits, Otto, Greenfield & Weiss, 2005), SoP (Otto et al., 2006; Perroud et al., 2007), GAD (Gao et al., 2010) and OCD (Magalhaes, Kapczinski, & Kapczinski, 2010) and there is evidence that individual effects disappear after adjusting for illness severity and sociodemographic characteristics (Simon et al., 2007). As such, it seems it is the global, rather than the specific, experience of anxiety that may be important.

1.4.2 Cross-sectional research exploring the association of anxiety symptoms and outcome in BD

The experience of panic attacks in BD has been associated with increased likelihood of meeting criteria for other ADs, specifically Ago, Sp and GAD, and with increased levels of substance use disorders (Goodwin & Hoven, 2002). In addition, lifetime history of panic attacks in BD has been linked to severity of depression historically, with panic being significantly associated with increased suicidal behaviour, greater impairment and more frequent and severe depressed episodes (Forty et al., 2009). In the same study, Forty et al. (2009) found that although anxiety was not linked to mania characteristics retrospectively, when compared to individuals with UD with history of panic attacks, the BD-panic group had worse outcomes. High levels of social anxiety symptoms have also been found to be

significantly associated with lower self-esteem and increased feelings of stigma in BD

(Aydemir & Akkaya, 2011). Other anxiety symptoms have been shown to correlate with

increased risk during bipolar depression, with worry, phobic avoidance and panic attack

frequency significantly associated with suicidal ideation and behaviour (Simon et al., 2007).

As with ADs, this suggests that it may be the overall experience of anxiety symptoms rather

than one disorder or dimension per se which is associated with poorer outcomes. Whilst

there are clear associations between concurrent anxiety and anxiety symptoms

retrospectively, it is unclear from this research alone the exact nature of the relationship

between anxiety and BD. To answer this question research assessing anxiety as a longitudinal

predictor of clinical outcomes in BD samples may be helpful.

1.4.3 Prospective impact of ADs in BD

There are only a small number of prospective studies exploring the impact of anxiety on

outcome in BD. The two largest studies to date were completed by Otto et al. (2006; n =

1000, follow-up = 12 months) and Sala et al. (2012; n = 1600; follow-up = 36 months).

Compared to individuals with no current ADs, results found that current AD at baseline

predicted increased symptoms and episodes of depression and mania, fewer days well,

reduced likelihood of recovery from depression, risk of earlier relapse, reduced quality of

life, poorer functioning, increased use of services, and increased suicidal ideation and

attempts (Otto et al., 2006; Sala et al., 2012). Gaudiano & Miller (2005) assessed the impact

of current and lifetime ADs together for 92 individuals over a 28 month follow-up period. AD

was predictive of increased bipolar symptoms, increased time to remission from acute

episodes and reduced response to pharmacotherapy and family intervention. Das et al.

(2013) also reported similar negative outcomes for individuals with current or lifetime ADs

assessed together, although the follow-up period was only 45 days. Perlis et al. (2006)

assessed the impact of current and lifetime ADs independently for 858 individuals with BD

over a mean follow-up period of 94.5 weeks. Lifetime ADs were not significantly associated

with recurrence of bipolar mood episodes. However, current ADs at inception were

associated with depressive, but not manic or hypomanic relapse. There is evidence to

suggest a dose-response relationship between number of ADs and increased poorer

outcomes in BD prospectively (Otto et al., 2006). As with the cross-sectional research

presented in Section 1.4.1, prospective associations between anxiety and outcome in BD

have been sustained after controlling for BD diagnosis, age of onset of BD, baseline mood

symptoms, other psychiatric disorders, past experience of abuse and experience of psychosis

(Gaudiano & Miller, 2005; Otto et al., 2006). Gaudiano and Miller (2005) found that severity

of depression partially mediated the association between anxiety and poorer outcomes.

Whilst longitudinal research does suggest a significant interaction between anxiety and

outcome in BD, causality between anxiety and the development and severity of BD cannot

be inferred. As such, naturalistic research is valuable, although such studies are scarce. The

Zurich study reports data from 591 participants aged 19 years at study entry and assessed as

being at risk for the development of psychiatric disorders. Over a 20-year follow-up period it

was found that those experiencing OCD and OCD symptoms (OCD-S) were significantly more

likely to meet criteria for bipolar spectrum disorders later in life, but not depressive

spectrum disorders or other ADs (Angst et al., 2005). This indicates OCD as a potential

precursor to the development and expression of BD, however this requires replication.

1.4.4. Prospective impact of anxiety symptoms in BD

Recent research suggests that anxiety symptoms may be a better longitudinal predictor of

outcome than ADs. Coryell, Fiedorowicz, Soloman, Leon, Rice & Keller (2012) assessed the

impact of eight anxiety symptom ratings on outcome for 335 individuals with a diagnosis of

BD and with an index depressed episode over an average follow-up period of 16.7 years.

Anxiety symptoms assessed were somatic anxiety, psychic anxiety, phobia, somatic pre-

occupation, depersonalisation, obsessions, compulsions, panic attacks and worry. Aggregated but not individual anxiety symptom scores were predictive of number of weeks depressed at follow-up, with the exception of OCD symptom severity. No AD other than OCD predicted outcome. Baseline depressive symptom scores were also predictive of time spent depressed, however when entered together in the same model, only anxiety symptoms retained significance. This suggested that anxiety was not purely a product of more severe depression but an independent predictor of a more severe illness course. This also indicated that global anxiety symptoms should be assessed to account for both the variety and severity of symptoms experienced. The experience of lifetime panic symptoms has also been found to be associated with increased depressed episodes and symptoms, greater suicidal ideation and greater time to recovery from an acute affective episode (Frank et al., 2002). A study reporting outcome data for 427 individuals with BD over a mean follow-up period of 17.4 years (Coryell et al., 2009) found that lifetime ADs did not predict time spent depressed prospectively after adjusting for polarity of index episode, however somatic and psychic anxiety symptoms were predictive of depressive outcomes across follow-ups. Perhaps more importantly, polarity of mood episode at baseline failed to be predictive of outcome after 10 years, whilst anxiety symptoms remained predictive throughout (Coryell et al., 2009). The sustained relationship between anxiety symptoms and depression over time suggests anxiety may be a key feature of bipolar depression. Level of anxiety symptoms has also been found to be significantly associated with hopelessness over time, which is a key risk factor for suicidality for individuals with BD (Valtonen et al., 2009). Current level of depression, current personality disorders, fewer manic symptoms and past hopelessness were also significant predictors of hopelessness longitudinally (Valtonen et al., 2009). The evidence regarding the link between manic and anxious symptoms over time is inconclusive (see also Section 1.3.4). Increased anxiety symptoms have been found to predict significantly less time spent in

manic or hypomanic episodes, suggesting a potential protective factor of anxiety against elevated mood (Coryell et al., 2009).

1.5 Understanding the link between anxiety and poorer outcomes in BD

Although research exploring mechanisms by which anxiety may predict poorer outcomes and increased mood instability in BD is limited, there is some preliminary research which should be noted and which may provide important directions for future work.

1.5.1 Anxiety leading to interpersonal difficulties in BD

Interpersonal difficulties can be defined as a person's ability to trust others, develop secure attachments and have intimate relationships. Problems with interpersonal effectiveness have been hypothesised as a mediatory link between PTSD and worse outcomes in BD (Maguire, McCusker, Meenagh, Mulholland & Shannon, 2008). Maguire et al. (2008) found that childhood and adult trauma predicted interpersonal difficulties in BD, and that interpersonal difficulties partially mediated the relationship between trauma and depressive symptoms and reduced quality of life (Maguire et al., 2008). Interpersonal sensitivity, defined as the ability to perceive and respond appropriately in social situations, has also been found to be impaired for individuals with ADs and cyclothymia (Del Carlo et al., 2013) and it has been proposed that anxiety may lead to avoidance of situations such as social encounters and roles, leading to mood instability (Tomba et al., 2012). For example, avoidance may lead to negative life events, such as breakdown of relationships or loss of employment, which may trigger depression. Social relationships have been found to be a protective factor for relapse prevention (Johnson, Lundstrom, Aberg-Wistedt & Mathe, 2003), and as a result it has been posited that trauma and PTSD may lead to the inability to establish secure and trusting relationships, resulting in limited social networks and restricted social support, and a more severe illness course for those with BD and trauma-related ADs.

Interpersonal difficulties have also been posited as a potential barrier to establishing positive therapeutic relationships with health professionals, which may explain reduced response to treatments for those with ADs such as SoP and PTSD (Maguire et al., 2008). However, these hypotheses are currently speculative and require specific testing.

1.5.2 Anxiety, emotional processing and suicidality in BD

Emotional processing refers to the way in which an individual recognises, responds to and copes with changes in affect. Expression of emotions has been linked with adaptive coping (see Smyth & Pennebaker, 1999), whilst suppression of emotion is linked to dysfunction as it does not allow relief from psychological or physiological emotional experiences (Gross & Levenson, 1997). In psychological research this has been measured using the Emotional Approach Coping Scale (EACS; Stanton, Kirk, Cameron & Danoff-Burg, 2000), where active emotional processing and emotional expression are measured as separable forms of affect-approach coping. Emotional processing has been found to be impaired in individuals with BD compared to healthy controls (Howells, Laurie-Rauch, Ives-Deliperi, Horn & Stein, 2013; Marchand et al., 2011; McKenna & Eyler, 2012). Simon et al. (2007) suggest that anxiety may elevate suicidality in BD through increased ruminative responses and poorer coping with emotion. Anxiety, depression and suicidal ideation and behaviour were assessed in a group of 98 participants taking part in the STEP-BD program (Simon et al., 2007). Rumination, anxiety symptoms, decreased emotional processing and impaired emotional expression were all associated with increased suicidal behaviour. Depressive rumination and anxiety were positively correlated, whilst anxiety and emotional processing showed a significant negative correlation. When entered together in a statistical model and controlling for sociodemographic and illness variables, Simon et al. (2007) found that only ruminative response style and emotional processing remained significant predictors of suicidality. As a result, it was suggested that increased anxiety symptoms lead to increased rumination and

simultaneous decreased emotional processing in response to depressive symptoms, leading

to increased suicidal behaviour. This was proposed to be due to individuals with BD being

impaired in their ability to process emotions in response to stress, which is made worse by

the presence of severe anxiety symptoms. Whilst this is possible, and links to existing

theories regarding DAs and depressogenic cognitive styles in BD (e.g. Alloy et al., 1999a), it

may also be that the close association between anxiety, depression and cognitive processes

in this study meant that the individual effects of anxiety and depression were cancelled out

when entered together in the model. Further research is required to replicate and

understand this potential association.

1.6 The conceptual relationship between anxiety and BD

Attempts have been made to conceptualise the experience of anxiety in BD elsewhere

(Freeman, Freeman, & McElroy, 2002; Holmes, Geddes, Colom & Goodwin, 2008). Logically,

anxiety could be conceptualised within BD in a number of ways. The following are potential

explanations of anxiety in BD based on the literature reviewed in this chapter, although this

is by no means an exhaustive list: 1) the experience of BD leads to anxiety (BD as a

mediator); 2) the experience of anxiety leads to BD (anxiety as a mediator); 3) causal factors

trigger anxiety and BD separately, and these disorders are separate and co-occur (anxiety

and BD as true comorbidities); 4) anxiety and BD are both manifestations of an underlying

core defect of emotion regulation, with these experiences being inextricably linked. Each

potential explanation is discussed below in the context of the current evidence.

1.6.1 The experience of BD leads to anxiety

It has been suggested that anxiety may primarily be an inevitable consequence of having a

severe and enduring mental health problem, with increased anxiety marking a more severe

illness course but not having a direct impact on the experience of mood episodes per se.

Whilst this cannot be ruled out, this seems unlikely due to evidence that prevalence of ADs in BD is higher than prevalence rates reported for individuals with other mental health problems of similar severity, for instance UD (Dilsaver et al., 2007; Dilsaver et al., 2008; Kessler et al., 2003; Mueser et al., 2004; Simon et al., 2003) and schizophrenia (Mueser et al., 2004; Young, Pfaff, Lewandowski, Ravichandran, Cohen & Öngür, 2013). There is also evidence that anxiety persists at times of euthymia, therefore contraindicating that anxiety relates solely to the severity of mood symptoms (Albert et al., 2008; Simon et al., 2004). In addition, high rates of ADs have been found for individuals with childhood BD (see Section 1.3.2) and for those experiencing their first index bipolar mood episode (Conus, Cotton, Abdel-Baki, Lambert, Berk & McGorry, 2006), although this may still be severe. ADs have not been found to be associated with illness variables such as treatment with anti-psychotic medication or treatment seeking behaviour (Dickstein et al., 2005; Pashinian et al., 2006) which indicates that anxiety is unlikely to be due to illness burden alone. As described in Section 1.5.2 above, Simon et al. (2007) have found evidence that anxiety may lead to depressive symptoms and increased rumination and simultaneous decreased emotional processing, leading to increased suicidal behaviour. However, anxiety and depressive cognitive styles were highly correlated in this study and the results may be better explained by shared cognitive and emotional processes underlying these mood experiences.

1.6.2 The experience of anxiety leads to BD

There is evidence that anxiety may play a role in the development of BD. Anxiety has been found to precede the onset of BD for up to 94.7% of individuals (Issler et al., 2005; Masi, Toni, Perugi, Mucci, Millepiedi & Akiskal, 2001; McElroy et al., 2001; Pini et al., 2006; Perroud et al., 2007; Perugi et al., 2001) and is associated with earlier age of onset of BD (Fagiolini et al., 2007; Goes et al., 2012; Henry et al., 2003; Pini et al., 2006). ADs in adolescence have been found to be a unique predictor of BD in later life, whilst youth BDs

were not predictive of later anxiety (Johnson, Cohen, & Brook, 2000). The presence of ADs has also been found to predict switching to BD, but not schizophrenia, in individuals initially diagnosed with UD or psychosis (Holma, Melartin, Holma, & Isometsa, 2008; Gilman, Dupuy & Perlis, 2012; Krishnan et al., 2005), indicating that anxiety may hasten the onset of BD. Maguire et al. (2008) also found evidence that inter-personal difficulties partially mediated the association between early trauma-related ADs and later depression and reduced quality of life (see Section 1.5.1. However, due to problems with diagnostic assessments of psychiatric disorders and the over-lapping symptoms which occur between disorders such as BD and anxiety, it is unclear from this research if early ADs may have been an indicator of a general underlying instability of mood which manifested primarily as anxiety but may also have involved instability of other affective domains. Additional research which explores the experience of anxiety and mood swings prior to the onset of BD is required.

1.6.3 Anxiety and BD as truly comorbid disorders

Research which has found that anxiety occurs outside of bipolar mood episodes has been suggested as evidence that BD and anxiety are true comorbidities (e.g. Perugi et al., 2001). However, the wealth of retrospective and, more recently, longitudinal research reviewed in this chapter indicates repeated significant associations between anxiety and bipolar mood experiences and poorer outcomes in BD when controlling for other potentially important variables (see Section 1.4.3. and 1.4.4). In addition, there is research to show that there may be similar psychological processes which underlie the experience of emotions such as anxiety and bipolar mood experiences (Bird, Mansell, Dickens, & Tai, 2013). For example, cognitive and behavioural processes are implicated in the experience of depression, mania and anxiety, which have been suggested to differ qualitatively in content but ultimately are maintained, at least in part, due to general dysfunctional cognitive styles and behavioural responses (Segerstrom, Tsao, Alden, & Craske, 2000). Bird et al. (2013) found that thought

suppression, experiential avoidance and worry were equally predictive of depression and anxiety whether considered separately or as a single factor. Cognitive and behavioural processes are also a key feature of psychological models of manic experiences, which are discussed at length in Chapter 2. Whilst this does not infer causality, it does suggest that anxiety and BD are unlikely to be completely separate experiences which simply co-occur.

1.6.4 Anxiety and BD as core features of emotion dysregulation

Because of the wealth of evidence linking bipolar and anxiety, it is proposed in this thesis that bipolar mood experiences and anxiety are on a continuum of emotional experiences which clinically overlap and are not necessarily distinct. More recently it has been proposed that anxiety and BD are transdiagnostic features of the same condition, where anxiety is integral to the development and instability of mood which is characteristic of BD. This marks a return to earlier conceptualisations of 'manic depression', when anxiety was recognised as a specific symptom of BD, specifically relating to 'nervous energy' during mania and 'restless agitation' during depression (Diefendorf, 1907). There is evidence to support a transdiagnotic theory. There is a huge overlap of symptoms observed for individuals with ADs and BD. These include sleep disruption, irritability, anger and impulsivity (DSM-IV) which may indicate a shared etiology. Several of the same risk factors have been found to be associated with both anxiety and BD, including increased exposure to trauma in childhood and later life, greater neuroticism, low social support and lower economic status compared to individuals with no mental health difficulties (Lu, Mueser, Rosenberg, & Jankowski, 2008; Sugaya, Hasin, Olfson, Lin, Grant & Blanco, 2012), suggesting that BD and anxiety may be underpinned by at least some of the same psychological processes. Previously thought to be a core symptom of GAD only, research has found that levels of worry are associated with acute UD, BD and other ADs, even after controlling for the presence of GAD (Kertz, Bigda-Peyton, Rosmarin, & Bjorgvinsson, 2012). Depressogenic cognitive styles and responses such

as rumination have also been found to be a core symptom extending across multiple clinical groups, with individuals with UD, BD, GAD and OCD found to have comparable rumination scores on testing (Kim, Yu, Lee, & Kim, 2012), although rumination was higher for individuals with BD after controlling for concurrent symptoms of anxiety and depression. However, these results require replication with larger samples and controlling for sociodemographic characteristics. Emotion regulation has been found to be equally impaired across individuals with a diagnosis of BD, UD and ADs during periods of euthymia compared to healthy controls, in particular on the domains of engagement in goal directed behaviour, impulse control and having limited emotion regulation strategies (for a review see Mercer & Becerra, 2013). Like BD, many ADs have also been found to have an episodic course and presentation, including OCD and PD (Tukel et al., 2007) and shared cognitive processes in BD and anxiety have been found (Bird et al., 2013, see Section 1.6.3 above). In addition, other similar processes have also been implicated across both BD and ADs, for example high levels of intrusive mental imagery found for both clinical groups (Holmes et al., 2008). Imagery has been proposed to escalate anxiety and bipolar mood symptoms and increase misinterpretations of triggers and behavioural responses (Holmes et al., 2008). However, the specific factors which may determine if dysregulation of emotion manifests as a more typical BD presentation or a 'quieter' anxious presentation are currently unclear and imagery research in BD is limited. However, Holmes et al. (2008) suggest that progression to primarily BD or anxious presentations may be determined by strength and content of imagery processes, with these likely to differ across affective states. Further research which explores imagery processes in BD and other clinical groups is also required. In particular, it would be beneficial to explore how imagery may interact with other important psychological processes in anxiety and BD such as cognitions and behavioural responses.

1.7 The treatment of anxiety in BD

Both pharmacotherapy and psychological interventions have been found to be effective in the treatment of anxiety and BD separately, and are recommended as treatment in NICE guidelines for both disorders individually. However, comprehensive guidelines regarding the treatment of anxiety in BD are noticeably absent in both the UK and around the world. Current NICE guidance for BD (NICE, 2006) takes a categorical approach to the provision of treatment for anxiety and recommends additional, separate intervention for anxiety where individuals meet diagnostic threshold for ADs. Specifically current guidance states that "for patients with significant comorbid ADs, psychological treatment focused on anxiety or treatment with a drug such as an atypical antipsychotic should be considered" (NICE, 2006). However, due to the convergence of evidence highlighting the importance of anxiety in BD, and anxiety as a potential reason for reduced response to current treatments (Henry et al., 2003; Maguire et al., 2008), interventions which target anxiety and BD together are increasingly the focus of research and are reviewed below.

1.7.1 Pharmacological treatment of anxiety in BD

Research has highlighted relatively early on that that addressing anxiety as part of bipolar treatment may be key to treating BD successfully (Feske et al., 2000) and efforts have been made to develop and evaluate transdiagnostic interventions. In terms of pharmacological treatment, selective serotonin re-uptake inhibitors (SSRIs) are often prescribed for the treatment of both anxiety and depression. However, there is some contraindication for their use in BD due to the potential for mood instability to be increased by triggering manic episodes (El-Mallakh & Hollifield, 2008; Faedda, Baldessarini, Glovinsky, & Austin, 2004; Jana, Praharaj, & Sinha, 2012; Khazaal, 2007). These risks appear higher for those who are medicated on the same regime for long periods of time (For a review see El-Mallakh & Hollifield, 2008) and for those with ADs (Masi et al., 2001). Antipsychotic drugs have more

recently been trialled as an alternative treatment for anxiety in BD. The largest controlled trial to date was completed by Tohen et al. (2007) and found that of 833 participants with BD, those with anxiety had reduced mood and anxiety symptoms in response to treatment with olanzapine and olanazapine-fluoxetine combination therapy compared to placebo. However, overall response was still found to be reduced compared to those with no anxiety (Tohen et al., 2007). Individuals with BD and ADs also tend to be prescribed significantly more medications and report more side effects (Azorin et al., 2009), and so this, together with research highlighting the importance of psychological factors in the relapse and maintenance of mood instability (Lam & Wong, 2005), suggests that psychological interventions as alternatives or adjuncts to medication are required.

1.7.2 The psychological treatment of anxiety in BD

Psychological interventions including psychoeducation and CBT for individuals, groups and families have an evidence base in the treatment of depression, anxiety and BD individually (Barlow, Ellard, Hainsworth, Jones, & Fisher, 2005; El-Mallakh & Hollifield, 2008; Jones, Deville, Mayes, & Lobban, 2011; Parikh, LeBlanc, & Ovanessian, 2010; Sasson, Chopra, Harrari, Amitai, & Zohar, 2003). Perhaps one of the key justifications for exploring anxiety-mood associations and treatments in BD is that whilst certain risk factors for worse outcomes are static, such as previous number of episodes and age of onset, anxiety symptoms can be targeted and potentially reduced at any time. Although there are still relatively few trials which have evaluated combined interventions, preliminary results are encouraging. Mindfulness-based cognitive therapy (MBCT) has been found to be effective at preventing the increase of anxiety symptoms in a pilot study with 17 BD and 51 UD depressed participants compared to waitlist controls where anxiety increased, although treatment failed to significantly reduce anxiety symptoms for either group (Williams et al., 2008). Other psychological treatments have been found to be equally effective for

individuals with BD with and without anxiety, despite not including a specific anxiety component. One such example is the bipolar-collaborative care model (B-CCM) which consists of three treatment components: evidenced-based medication regime, the increasing of individual self-management skills enabled via group psychoeducation sessions and enhanced access to community support (Kilbourne, Biswas, Pirraglia, Sajatovic, Williford & Bauer, 2009). When compared longitudinally over a period of three years, re-analysis of data for 290 individuals taking part in an RCT comparing B-CCM and treatment as usual found that all participants in the B-CCM condition had fewer weeks manic, increased quality of life and improved social functioning, irrespective of ADs. However, anxiety was not included as an outcome measure. Similarly, a study by Hawke et al. (2013) completed a secondary analysis of data from 204 participants taking part in an RCT comparing group psychoeducation and individual CBT for BD. When anxiety was included as a covariate, individuals with ADs had similar improvements in functioning, mood and anxiety symptoms in both treatment conditions, and had significantly greater improvement on one measure of depression compared to those without ADs (Hawke et al, 2013). In contrast, Deckersbach et al. (2014) analysed data from 269 participants taking part in the STEP-BD RCT evaluating psychotherapy for bipolar depression compared to collaborative care (CC). Individuals with one lifetime AD were significantly more likely to recover from a depressed episode at 12 months after receiving psychotherapy than following a CC intervention, and psychotherapy showed a large effect size. However, individuals with no lifetime AD or multiple lifetime ADs showed no difference in response to either treatment (Deckersbach et al., 2013). As Holmes et al. (2008) observe, psychosocial treatments such as B-CCM, family therapy, IPSRT and psychoeducation may have indirect effects on anxiety due to involving the avoidance or management of stressors as part of therapy. Although these results suggest successful treatment of mood and anxiety symptoms in BD through existing psychological interventions, these studies have involved secondary analysis of data and randomisation has

not been stratified by anxiety. In addition, current research has not evaluated current psychological interventions for BD compared to combined interventions for anxiety and mood. Due to the growing evidence for transdiagnostic symptoms and psychological processes in BD and ADs, there has been a move to transdiagnostic treatment approaches (Mansell, 2008). One such example which has been evaluated for its effectiveness to treat mood and anxiety disorders is the 'Unified Protocol for Transdiagnostic Treatment of Emotional Disorders' (UP) (Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010). This is a psychosocial CBT treatment which draws on research from neuropsychology, genetics, behavioural, psychological and physiological research. UP is based on the assumption that individuals with mood and ADs are vulnerable to intense emotions which they perceive as uncontrollable and respond to these experiences with inefficient coping strategies to regulate emotions. UP aims to target and improve those emotional processes and to develop more effective strategies to deal with those experiences. This is currently delivered over 15 sessions and consists of eight modules. Initial results suggest UP is effective in treating anxiety and depressed symptoms in individuals with primary ADs (Alloy, Bender, Wagner, Abramson, & Urosevic, 2009) and preliminary case study data suggests some effectiveness for UP in treating anxiety symptoms in BD also (Ellard, Deckersbach, Sylvia, Nierenberg, & Barlow, 2012), although these results require replication in a formal trial. Existing psychological interventions have been found to lack vital input from service-users in their development and also neglect the evaluation of cost-effectiveness, accessibility and cultural issues (Jones et al., 2011). An on-going pilot study is currently in progress which assesses a service-user informed psychological intervention for anxiety in BD, taking into account economic factors and efficacy (Jones et al., 2013), although results are not yet available.

1.8 Summary

There is a limited amount of research which explores the link between anxiety and mood experiences in BD. There is undoubtedly a high prevalence of anxiety symptoms and disorders occurring in BD samples, which appear to expand across the lifespan and are irrespective of sociodemographic characteristics. Current research shows significant concurrent, retrospective and prospective associations between anxiety and poorer outcomes in BD, although there are fewer longitudinal studies assessing anxiety correlates as predictors of illness course compared to cross-sectional data. Cross-sectional research does not provide any real indication as to the underlying mechanisms and interactions which may explain the anxiety-BD link. Whilst the link between anxiety and depression in BD is relatively well-established, the link between anxiety and mania is less understood and findings thus far are mixed. In addition, both cross-sectional and longitudinal research often focuses on ADs in BD, which may underestimate the importance of anxiety symptoms and leads to conceptualisations of anxiety and BD as separate, comorbid disorders and neglects the possibility that anxiety may also be an inherent feature of emotion dysregulation in BD. Initial research has begun to explore the psychological processes which may underlie the relationship between mood and anxiety in BD, with some preliminary evidence that anxiety and BD may be underpinned by shared cognitive and behavioural processes. Treatment studies which are currently ongoing will be important in determining if combined interventions targeting both mood and anxiety symptoms produce better outcomes and prognosis for individuals with BD.

Despite the evidence for anxiety as an important clinical experience in BD, current theoretical models of BD do not include anxiety as a primary feature of mood instability. However, the development of such a model may be premature at this stage based on the limitations of the current research and the lack of understanding regarding psychological processes that may link anxiety and BD, as described in this chapter. As such, more

information is needed to understand the interaction between anxiety and BD in more detail. As a starting point for this thesis, dominant models within the bipolar literature are reviewed in Chapter 2 to evaluate the ability of these models to explain and account for the experience of anxiety in BD in light of what is currently known about those experiences.

Chapter 2: Psychological models of BD

2.1 Overview

The following chapter provides an overview of current dominant models of BD within the literature. As this is a psychological thesis, consideration is given primarily to psychological models of BD, although the role of biological and genetic factors is also outlined briefly. A review of all psychological models is beyond the scope of this thesis, and this is by no means an exhaustive review. Broadly speaking, current models of BD tend to take a cognitive or biopsychosocial approach to explaining mood instability and this section reviews the evidence for four prominent models of BD in the current literature. These models were chosen as they have the largest evidence base, although other models do exist which may be equally valid. A final summary is provided at the end of this chapter which summarises what is currently known about mood instability in BD in terms of important psychological processes and how this knowledge may be applied or adapted to account for the experience of anxiety in BD. Finally, an outline of the aims and directions of this thesis is given, drawing together information presented regarding anxiety in BD (Chapter 1) and the psychological models of BD presented in this chapter.

2.2 Biological and genetic models of BD

There is a large body of research highlighting familial links for BD, with individuals with a close relative diagnosed with BD being up to ten times more likely to receive a diagnosis of BD themselves compared to those with unaffected relatives (Mortensen, 2003). Heritability rates as high as 80% have also been reported in twin and adoption studies (McGuffin et al, 2003). This has been suggested to highlight the strength of the biological link whilst controlling for contextual and environmental factors. However, whilst genes appear to be an important risk factor for the development of BD, genetic models cannot account for the substantial individual differences in timing, duration or severity of mood episodes and

differing outcomes observed for individuals with BD, nor do they explain the protective factors which account for why the majority of people who are genetically predisposed to BD do not go on to experience extreme mood states. In addition, results regarding genetic vulnerability in BD are often inconsistent (Burmeister, McInnis, & Zöllner, 2008; Kato, 2007), limited by small sample sizes (Edvardsen et al., 2008) and lack specificity, with the same genes conferring risk for a number of mental health problems such as intellectual disabilities, autism, BD and schizophrenia (Owen, 2012). As such, it is important to also understand psychological factors which may contribute to the development of BD in order to inform relevant research and intervention.

2.3 The behavioural inhibition system (BIS) / behavioural activation system (BAS) model of BD

2.3.1 Overview of theory

The BIS/BAS model was originally proposed by Gray (1990) as a biopsychological theory of personality which hypothesised that two basic motivational systems residing in the brain underlie all human behaviour and emotion. The BIS is an aversive motivational system which is sensitive to cues associated with punishment, non-reward, novelty and failure. The BIS is proposed to inhibit behaviour which may lead to negative outcomes, resulting in avoidance and reduced goal-pursuit. Gray (1987, 1990) also hypothesised that BIS activation results in negative affect in response to relevant cues, including fear, anxiety, frustration and sadness. The BAS is an appetitive motivational system which is sensitive to reward-related stimuli, either internal, such as expectancies regarding goal attainment, or external, such as presence of a desired goal, and regulates approach and goal-seeking behaviour (Alloy et al., 2012; Gray, 1982). BAS activation is proposed to result in positive affect, including happiness, elation and hope. Individual differences in sensitivity of the BIS and BAS have been proposed to underlie mood instability in mood disorders such as BD (Depue & Iacono, 1989). Gray

(1990) suggests that mania is the result of low BIS activity and co-occurring high BAS activity. The finding that BIS and BAS items have a low correlation on self-report measures such as the BIS/BAS scale supports this argument for two separate subsystems (Carver & White, 1994). However, although there is evidence that the BAS is predictive of (hypo)mania and disinhibition in BD, BIS scores have not been found to predict current or prospective depression, inhibition or negative affect in studies with individuals with a diagnosis of BD and those assessed as high risk (Hirshfeld-Becker, Biederman, Henin, Faraone, Cayton & Rosenbaum, 2006; Meyer, Johnson, & Winters, 2001; Meyer & Hofmann, 2005). As such, researchers have focused primarily on the BAS to explain mood instability in BD, known as the BAS dysregulation or hypersensitivity theory (Alloy & Abramson, 2010; Depue & Iacono, 1989; Johnson, 2005; Urošević, Abramson, Harmon-Jones & Alloy, 2008). This is a stress-vulnerability model which proposes that those with and at risk of BD have an over-active and easily dysregulated BAS which leaves them vulnerable to extreme fluctuations in activation (mania) and deactivation (depression) in response to relevant stimuli (stress), resulting in extreme variability in affect across situations and over time (Alloy & Abramson, 2010; Alloy et al., 2012) . Reward and goal-related cues such as achievement and positive life events are thought to trigger this excessive BAS activation, resulting in manic symptoms such as goal-directed behaviour, increased energy, reduced sleep and elevated mood (Alloy & Abramson, 2010). Conversely, negative stimuli including failure, punishment and negative life events are hypothesised to lead to excessive deactivation of the BAS, resulting in disengagement from activities, lack of motivation and other symptoms of depression (Depue & Iacono, 1989; Molz, Black, Shapero, Bender, Alloy & Abramson, 2013). BAS hypersensitivity is therefore proposed to be a trait neurobiological vulnerability which interacts with life events and stressors, either positive or negative, which activate or deactivate the BAS excessively leading to the experience of depressed or manic symptoms.

2.3.2 Measuring BAS sensitivity

The BIS/BAS scale derived by Carver & White (1994) includes a BIS scale which attempts to capture sensitivity to the occurrence of negative events (Jorm, Christensen, Henderson, Jacomb, Korten & Rodgers, 1999), and three subscales of BAS activity: drive - goal pursuit; fun-seeking – the desire and willingness to approach potentially rewarding events; and reward responsiveness – positive responses to the anticipation or actual occurrence of rewards (Carver & White, 1994). The Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia, Ávila, Moltó, & Caseras, 2001) has also been used as a measure of BIS/BAS sensitivity and has two scales which measure the reactivity and responsitivity of the BIS/BAS dimensions.

2.3.3 BAS sensitivity as a specific vulnerability to BD

Increased BAS sensitivity is thought to reflect a greater likelihood to engage in goal-directed behaviour and to experience positive affect. Analogue studies using retrospective and cross-sectional designs have found BAS sensitivity to be associated with higher lifetime experience of hypomanic symptoms and more hypomanic personality characteristics (Applegate, El-Deredy, & Bentall, 2009; Fulford, Johnson, & Carver, 2008; Jones & Day, 2008; Meyer, Beevers, Johnson, & Simmons, 2007). Furthermore, prospective studies have found that BAS sensitivity is predictive of the prospective development of (hypo)manic symptoms and the onset of BD in non-clinical samples after controlling for confounding variables including baseline depressed and manic symptoms and family history of BD (Alloy et al., 2008; Alloy et al., 2012). High BAS scores have been found to predict lifetime diagnosis of BDII disorder, but not 'softer' bipolar spectrum conditions such as cyclothymia and BD-NOS (Alloy et al., 2006a). This suggests that high BAS sensitivity may be a specific trait marker of vulnerability to BD. In addition, there is evidence that BAS sensitivity is negatively associated with lifetime vulnerability to and experience of depression (Meyer et al., 2007). However, other research has failed to find a significant difference in BAS scores for those with or at risk of BD and

non-clinical controls (Hayden et al., 2008; Holzwarth & Meyer, 2006; Jones, Tai, Evershed, Knowles, & Bentall, 2006), although sample sizes in these studies were relatively small.

2.3.4 BAS sensitivity associated with symptoms of mania and depression

Cross sectional studies have found BAS sensitivity scores to be associated with current manic symptoms and positive affect for individuals with a diagnosis of BD (Van der Gucht, Morriss, Lancaster, Kinderman, & Bentall, 2009) and with hypomanic symptoms in non-clinical samples (Johnson & Carver, 2006; Meyer, Johnson, & Carver, 1999). In addition, sensitivity to reward assessed using the SPSRQ was found to be significantly higher for euthymic individuals with BDI compared to controls (Salavert et al., 2007). BAS dysregulation theory would also predict lower BAS scores correlate with symptoms of depression and there is evidence to support this in analogue samples (Applegate et al., 2009; Jones & Day, 2008). However, Johnson & Carver (2006) failed to find a significant negative association between BAS scores and depressive symptoms in a large sample of 888 students. Other research has also failed to find associations between BAS scores and depression for individuals with BD (Meyer et al., 2001; Van der Gucht et al., 2009). Longitudinal research may provide more robust information about associations between BAS scores and bipolar mood symptoms. Meyer et al. (2001) found that BAS sensitivity scores were related to the intensification of manic symptoms assessed three times over a six month period for 59 individuals with a diagnosis of BDI. BAS scores predicted shorter time to onset of (hypo)manic episodes in a student sample with bipolar spectrum diagnoses who were followed up every four months for an average of 33 months (Alloy et al., 2008) and elevated SPSRQ scores were related to hypomanic but not depressive relapse for individuals with BDI compared to a control group 18 months post-baseline (Salavert et al., 2007). BAS scores have been found to be associated with increased and more variable manic symptoms and positive affect for analogue participants in a diary study where symptoms were assessed twice daily for 17 days (Meyer

& Hoffman, 2005). However BAS scores were not found to be predictive of symptom severity or mood episode status for 151 individuals with BDI and II elsewhere (Fletcher et al., 2013), although this study involved only one follow-up assessment at six months, which may have been insufficient time to assess predictive validity of BAS scores. Overall, BAS appears to be a valid predictor of future manic and hypomanic symptoms, but less robust as a prospective indicator of depression.

2.3.5 Studies of goal attainment, attitudes towards goals and appraisals in BD

BAS-dysregulation theory proposes that individuals with BD will have increased goal-motivation and approach behaviour compared to other clinical samples and controls. Individuals with BD have been found to make elevated and sustained effort when completing reward-related tasks compared to controls, but no difference when completing tasks which are not incentivised or which are punishment-related (Harmon-Jones et al., 2008). A large body of research exploring BAS dysregulation in BD has focused on beliefs about goal attainment and approach behaviour. Increased positive goal appraisal and belief in one's ability to be successful has been significantly associated with vulnerability to hypomania in analogue samples (Meyer & Krumm-Merabet, 2005) and current hypomanic symptoms (Meyer, Beevers, & Johnson, 2004), as has approach motivation (Jones, Shams, & Liversidge, 2007; Meyer et al., 2007). Research using the Willingly Approached Set of Seriously Unrealistic Pursuits (WASSUP; Johnson & Carver, 2006) has found that those prone to hypomania and current hypomanic symptoms are related to unrealistic goal-setting, and associations remained significant when controlling for BIS/BAS sensitivity (Alloy et al., 2012; Gruber & Johnson, 2009) and current symptoms (Fulford et al., 2008). These associations may also be explained by the fact that all of these concepts likely overlap and so are likely to correlate. Ambitious goal-striving has also been found to be predictive of the onset of bipolar spectrum disorders (Alloy et al., 2012) and partially mediated the effect of high BAS scores in

this study. Positive goal appraisals, unrealistic goal setting and approach motivation have

been found to be negatively associated with depression (Johnson & Carver, 2006; Meyer et

al., 2007; Meyer & Krumm-Merabet, 2003). These results have been replicated when

comparing individuals with BD to control participants, with history of mania being related to

increased expectations of personal success, in particular in the domains of public recognition

including wealth and fame (Johnson, Eisner, & Carver, 2009). Individuals with BDI who score

highly on measures of goal-attainment have been found to identify and value characteristics

of mild hypomanic states and to be more likely to engage in behaviours which may escalate

their elevated mood from sub-threshold to a (hypo)manic episode (Lee, Lam, Mansell, &

Farmer, 2010). In addition, there is evidence to suggest that individuals with BD may respond

differently following goal achievement. Whilst most people will try to maintain and

moderate positive affect in some way, individuals with BD have been found to attempt to

increase positive affect following goal attainment through further continued goal pursuit,

and as such may be less able to self-regulate emotion and behaviour (Fulford, Johnson,

Llabre, & Carver, 2010; Meyer et al., 2004). Compared to controls, individuals with BD tend

to set goals which are difficult to attain and are less likely to respond to cues regarding goal

progress, continuing to strive even when goals have been achieved (Fulford et al., 2010;

Johnson, Fulford, & Carver, 2012). Whilst this research is promising, the majority of findings

are cross-sectional and require replication longitudinally.

2.3.6 The experience of BAS-relevant positive and negative life events in BD

BAS sensitivity is associated with mood variability (see Section 2.3.5), suggesting that BAS

over-activation results in increased reactivity to external stimuli and events. Retrospective

and prospective studies have found increased life events prior to relapse for individuals with

BD (see Alloy et al., 2009 for a review). As such, research has attempted to assess the types

of events which may trigger bipolar symptoms, and both negative and positive events have

been proposed to play a role in BAS activation and expression of bipolar episodes. Negative life events, such as loss and failure, may be BAS-activating or de-activating due to these events obstructing goal achievement, either ceasing goal-pursuit (deactivation) or prompting individuals to strive to overcome obstacles (activation). Consistent with this, there is evidence that BAS is activated in response to frustrative non-reward and anger (Carver, 2004; Harmon-Jones et al., 2002). As such, BAS dysregulation theory proposes that individuals with BD are overly sensitive to both BAS-activating cues related to potential rewards leading to (hypo)mania, and overly sensitive to cues signalling failure or loss, which lead to anger and irritable mood (hypomania) or depression (Alloy et al, 2010). Specifically, goal-attainment events have been found to predict manic but not depressed symptoms prospectively in BD, whilst general positive life events not related to goal achievement did not (Johnson et al., 2008; Johnson et al., 2001). Compared to controls assessed as being at low-risk of BD, individuals with BDII and cyclothymia have been found to experience increased BAS-activating life events, such as working on an important project at work (goal striving) and increased BAS de-activating events, such as failing to complete work targets (Urošević et al., 2010), which may increase the risk of mood episodes further. Both positive and negative events, such as loss or failure, have been found to precede (hypo)manic episodes (see Alloy et al., 2009 for a review), which is consistent with this model of reward focus and over-coming threats to reward. Negative life events have also been found to predict depressive relapse and increased time to recovery from depression in BD (for a review see Alloy, Reilly-Harrington, Fresco, Whitehouse & Zechmeister, 1999b). However, subsequent research using more sophisticated analysis such as multi-level modelling to control for repeated assessments within individuals has not found negative life events to be predictive of depression or mania for 125 participants with BDI followed-up over 27 months (Johnson et al., 2008). Discrepancies in findings may be due to many studies exploring life events having high attrition rates and failing to use a control group for comparison. Studies

have also used different methods of assessing and classifying life events, which may also account for apparent discrepancies.

2.3.7 Limitations of the BAS dysregulation theory

There is a large evidence base to support the theory of a dysregulated BAS in the vulnerability to and experience of bipolar mood episodes. This has implications for improving the focus of psychological interventions, including targeting behavioural responses to negative and positive life events to reduce relapse. It should be noted that several studies reviewed here have failed to control for current mood in their analysis and so cannot provide definitive results for the presence of trait behaviour and emotion regulation systems. In addition, much of the current research is cross-sectional and prospective studies in BD are required to explore if BAS sensitivity and relevant life events are predictive of mood symptoms over time. The current evidence base has often used self-report measures such as the BIS/BAS which have been found to have low reliability in some studies with BD participants (e.g. Meyer & Hofmann, 2005) and other clinical samples (Dissabandara, Loxton, Dias, Daglish, & Stadlin, 2012), suggesting this may not be a valid measure of what is essentially a neurobiological construct. The BAS dysregulation model is not a specific model of BD and has been found to be a risk factor for other mental health problems, such as oppositional defiant disorder (ODD) and conduct disorders (Hirshfeld-Becker et al., 2007). As such, BAS sensitivity may not be a unique vulnerability factor for BD, and the same risk factor may result in many different outcomes, likely developing through many different pathways, with BAS dysregulation being one of many risk factors to the development of BD. The fact that reduced BAS activation has not been found to be reliably predictive of depression means this model may only be able to account for elevated moods experienced in BD (Johnson, Turner, & Iwata, 2003; Meyer et al., 2001). In addition to extreme mood episodes, BD is also characterised by other aspects such as psychosis, mixed affective states and, most

relevant to this thesis, anxiety. As a two dimensional approach to BD, the BAS dysregulation model may not account for the full spectrum of experiences observed. The neglect of the potential role of the BIS in more recent accounts of this theory has also limited the ability of this model to account for anxious experiences in BD.

2.4 Depressogenic schemas and maladaptive cognitive styles in BD

2.4.1 Overview of theory

Beck (1967) originally developed the cognitive vulnerability model as a theory of unipolar depression but this was later adapted and applied to other emotional disorders including BD. Cognitive theory states that mood instability arises due to an individual's faulty appraisal of situations, sensations or mental events, with behavioural responses as a consequence of those interpretations also maintaining dysregulated emotion (Beck 1967, Wells, 1997). Specifically this model proposes that distortions in thinking accompany emotions such as depression and mania, which operate at surface level as automatic thoughts but which reflect underlying fixed beliefs and assumptions about oneself, the world and others, known as 'schemas' (Beck, 1967). Beck (1967) proposes that negative schemas develop during childhood as a result of negative life events and adversity. In depression, these schemas are generally thought to be related to the need to be loved, self-worth, loss and failure (Alloy, Abramson, Walshaw, Keyser & Gerstein (2006b). As such, those who are vulnerable to depression are thought to have stable, underlying negative schemas which can be activated when life events occur which have significant personal meaning and in some way resemble previous negative schema-forming experiences. Research exploring cognitive vulnerability in depression has identified the importance of negative appraisal styles, dysfunctional attitudes (DAs) and beliefs, negative automatic thoughts, and maladaptive coping strategies such as rumination or avoidance as risk factors (See Alloy et al., 1999a, for a review). More recently, similar cognitive vulnerability-stress models have also been proposed to conceptualise the

vulnerability to the development of BD (Hammen, Ellicott, & Gitlin, 1992) which describe the same vulnerability processes for depression (Lam, Jones, Hayward, & Bright, 1999; Newman, Leahy, Beck, Reilly-Harrington, & Gyulai, 2002). In addition, it has been proposed that these schemas may shift in polarity depending on mood state and the type of activating stressor present. This suggests that at one time overly positive appraisals may be elicited, leading to symptoms and behaviours characteristic of mania, and at other times extreme negative appraisals and beliefs may be activated, leading to depression. As such, research has attempted to assess if individuals with BD have a unique cognitive profile which differentiates them from individuals with UD, and to explore if this is a vulnerability factor to BD.

2.4.2 Cognitive appraisals of positive and negative life events in BD

The cognitive-vulnerability model proposes that individuals with underlying depressogenic styles and schemas are at risk of experiencing mood episodes when encountering life stressors and events, due to the way in which those events are appraised. Negative life events have been found to precede depression, whilst both positive and negative life events have been found to precede (hypo)manic episodes (see Section 2.3.6). As such, the cognitive model of BD interprets these findings as a function of cognitive appraisals of life events and suggests that it is the appraisal of negative events in particular that is important in determining vulnerability to mania (Alloy et al., 2006a). The Attributional Style Questionnaire (ASQ; Peterson et al., 1982) measures causal attributions for positive and negative life events, in particular it assesses whether causes are attributed as being internal or external, global or specific, and stable or unstable. Attributional style has been found to be state-dependent, with depression being negatively associated with the attribution of positive events to self, and positively associated with attributing negative events to self and positive events to others in a longitudinal study with 253 individuals with BD (Pavlickova et al., 2013).

Mixed episodes have also been associated with negative attributional style, with increased negative ASQ scores found during mixed episodes compared to pure manic or depressed episodes for 395 individuals with BD (Reilly-Harrington et al., 2010). Mania was also weakly, but significantly correlated with attributing negative events to others and inversely correlated with attributing negative events to self in the same study. Reilly-Harrington et al. (1999) found that cognitive appraisal style was linked to outcome, with ASQ scores interacting with life events to predict both depressed and manic episodes at four week follow-up. A study exploring symptoms over a period of four months found that characteristics such as being more self-critical and having higher self-standards interacted with negative life events to predict depressive symptoms and positive life events to predict hypomanic symptoms (Francis-Raniere, Alloy, & Abramson, 2006). Alloy et al. (1999b) also explored the interaction between cognitive style and life events for individuals meeting criteria for sub-threshold BD and those with no lifetime diagnosis. Bipolar mood symptoms, cognitive style and life events were assessed at three time points determined by naturally occurring changes in mood state. Healthy controls were also assessed at time points matched to follow-up in the clinical sample. DAs and negative attributions remained stable across all groups at follow-up and individuals with cyclothymia had comparable negative cognitive styles to those with dysthymia. Baseline attributional styles assessed in euthymic mood state at time one were found to interact with life events to significantly predict depressive symptoms at all subsequent time points, and to predict manic symptoms at time two but not at time three (Alloy et al., 1999b).

2.4.3 DAs and negative information processing styles as a cognitive vulnerability to BD

The dysfunctional attitudes scale (DAS) (Weissman & Beck, 1978) has been commonly used to assess negative cognitive styles in depression and BD, and is a self-report inventory of beliefs based on Beck's (1967) theory. The DAS has three sub-scales related to achievement,

dependency and goal attainment, allowing the exploration of general and specific types of

DAs which may be linked to mood instability in BD. Results regarding DAs in BD are mixed.

Although some studies have found that individuals with BD have increased DAs and biases to

negative information processing during periods of euthymia compared to controls (Alloy et

al., 1999a; Bian, Yang, & Li, 2007; Fuhr, Hautzinger, & Meyer, 2013; Scott, Stanton, Garland,

& Ferrier, 2000), other research has failed to replicate these results (Jones, Mansell, &

Waller, 2006; Reilly-Harrington et al., 1999). Increased DAs have been found for individuals

with BD compared to controls during times of depressed and (hypo)manic episodes

(Goldberg, Gerstein, Wenze, Welker, & Beck, 2008; Lex, Hautzinger, & Meyer, 2011; Tzemou

& Birchwood, 2007), suggesting DAs may be state dependent rather than a trait

characteristic of BD.

   Cognitive vulnerabilities which may differentiate between UD and BD have also been

explored. Lam et al. (2004) found that 143 euthymic BD participants and 109 UD participants

had no significant differences on the DAS when the full sample was compared. After

excluding those who were potentially in a current mood episode, a sub-sample of 25 UD and

49 BD participants were found to be significantly different on one DAS subscale only, with BD

participants having higher scores for negative goal attainment attitudes (Lam et al., 2004).

Scott & Pope (2003) found no significant differences in DAs when comparing individuals with

UD (n = 16) and BD (n = 77) in a clinical study after accounting for symptoms of depression.

Within-group comparisons found that depressed individuals with BD had higher levels of DAs

compared to their euthymic counter-parts (Scott & Pope, 2003). Jones et al. (2005) assessed

DAs and self-esteem in a large sample of BD (n = 118), UD (n = 265) and healthy controls (n =

268) and found no difference between individuals with BD and UD when controlling for

current depression, but that both clinical samples had higher scores for DAs than controls.

Finally, a study with student participants found that those meeting criteria for dysthymia and

cyclothymia scored higher on the DAS and measures of negative attributional style than

individuals meeting criteria for hypomania or controls with no diagnosis (Alloy et al., 1999b).

Taken together, these results suggest that individuals with BD and UD have similar levels of

DAs, but higher levels than healthy controls, suggesting negative DAs may confer risk to

depression but not mania.

2.4.4 DAs and attributional style as a state marker of BD

Individuals with BD have been found to score significantly higher on the DAS during episodes

of depression and mania compared to those in remission (Scott & Pope, 2003), suggesting

that DAs may be exacerbated by mood state. Again this is a finding mirrored with individuals

with UD (Ingram, Miranda, & Segal, 1998) and studies comparing these two clinical groups

have found similar levels of negative automatic thoughts, DAs and negative attributional

styles during depressed episodes (Fuhr et al., 2013; Hollon, Kendall, & Lumry, 1986; Reilly-

Harrington et al., 1999). Depressed and manic mood states have been found to be

significantly but differentially associated with cognitive factors for individuals with BD.

Depression has been shown to be significantly associated with DAs and negative self-

appraisals cross-sectionally, whilst mania was only weakly associated with increased

likelihood to make internal attributions about positive events and elevated scores on the

DAS achievement scale (Pavlickova et al., 2013). DAs and negative attributional styles were

assessed for 395 participants taking part in the STEP-BD program and found that individuals

in mixed episodes had significantly more DAs and negative attributions compared to those

who were euthymic, manic or hypomanic (Reilly-Harrington et al., 2010). Sub-syndromal

depressive symptoms have also been found to be related to increased DAs, lower self-

esteem and perfectionism for individuals with remitted BD and UD (Fuhr et al., 2013).

Individuals in a current episode of BD depression were found to explicitly attribute negative

events internally more often than positive events in comparison to those in manic episodes

or who were euthymic (Lyon, Startup, & Bentall, 1999). However, implicit tests of

attributional style found that both manic and depressed participants attributed more

negative than positive events internally compared to controls, suggesting continued low self-

esteem and self-criticism even during periods of mania.

2.4.5 Mood induction studies to observe DAs and appraisal style in BD

As Beck's theory states, schemas are proposed to be underlying and activated in the

presence of a relevant internal or external cue. As such, studies finding no difference

between healthy controls and euthymic individuals with BD may be the result of schemas

not being activated during periods of mood stability (Persons & Miranda, 1992). Mood

induction procedures have been used to assess beliefs and attitudes in the presence of a

mood change and have used TV clips, films, music and autobiographical recall of life events

to elicit changes in mood (Babakhani & Startup, 2012; Wright, Lam & Newsom-Davis, 2005).

Using happy and sad mood induction conditions, Babakhani & Startup (2012) controlled for

baseline mood symptoms and found that achievement and goal attainment DAs were

significantly more elevated following the sad mood induction than the happy condition for

individuals with BD. In contrast, DAS subscale scores were not significantly different

following either mood induction after controlling for baseline mood. Compared to controls,

individuals with BD had significantly higher achievement DAs following both mood

inductions, although there was no baseline assessment of DAs for comparison. Compared to

euthymic individuals with UD and healthy controls, individuals with BDI who were also

euthymic were found to have significantly higher scores on the DAS overall following a

positive mood induction task. This suggests that BD participants had reduced dysfunctional

thinking to a lesser extent than other participants and that there may be a failure to

deactivate unhelpful thinking styles and assumptions in BD, even in response to increases in

positive mood (Wright et al, 2005). Wright et al. (2005) suggest that it may be these static

DAs which interact with initial elevated mood to perpetuate mood increase and lead to

symptoms of mania and hypomania. However, the mechanism by which this happens was not defined. A later study also found manic symptoms correlated significantly with DAS scores (Goldberg et al., 2008), suggesting that negative attitudes persist during mania and should potentially be targeted as a focus for treatment irrespective of presenting mood state. Gruber, Hay & Gross (2013) compared euthymic individuals with BDI and healthy controls on a cognitive appraisal task. Participants were exposed to three film clips designed to elicit positive, negative or neutral emotional responses, and asked to watch the film carefully (uninstructed control). Participants in the cognitive reappraisal condition were then show three further neutral, happy and sad film clips, but asked to watch these in an objective, detached and unemotional way (cognitive re-appraisal). It was found that for individuals with BD and healthy controls, cognitive re-appraisal was effective for reducing positive and negative affect. Whilst it is arguable that cognitive reappraisal in this study may actually be better described as cognitive distancing, it does suggest that changing the way in which information is processed leads to changes in affect, and therefore cognitive dysfunction may be important in the maintenance and treatment of emotion dysregulation in BD.

Implicit tests have also been employed to access the content of dysfunctional schemas and beliefs in BD. Using a sentence completion task, Lomax & Lam (2011) compared remitted individuals with BDI and healthy controls before and after a positive mood induction condition. Prior to mood induction, individuals with BD were found to use more dysfunctional constructs to complete sentences than controls, whilst after mood induction use of dysfunctional constructs decreased in both groups. This indicates that DAs may reduce in periods of elevated mood, however are still at a higher level than those observed for controls irrespective of mood state. In particular, beliefs related to autonomy and goals were resistant to change, indicating that these may be highly accessible for individuals with BD independent of current mood (Lomax & Lam, 2011).

2.4.6 DAs linked to outcome in BD

DAs linked to reward have been found to be correlated with number of previous hospitalisations for manic episodes and number of BD episodes overall (Lam et al, 2004). DAs and negative cognitive styles have also been assessed longitudinally. A large study of 253 participants with BD followed up for 18 months found that only low self-esteem was found to predict depression prospectively but not DAs or other measures of negative attributions and appraisal style (Pavlickova et al., 2013). Negative cognitive styles including concerns about performance, beliefs about autonomy linked to goal achievement and failure, and self-criticism have been found to be elevated in BD compared to controls (Alloy et al, 2009). After controlling for baseline mood and number of previous episodes, higher autonomy and self-criticism predicted manic episodes prospectively, whilst higher autonomy predicted reduced depressive relapse over a mean follow-up period of three years for individuals with BD (Alloy et al., 2009). Similarly, DAs, self-criticism and neediness were significantly associated with prospective increases in depressive symptoms for 161 adolescents at risk of BD (Stange et al., 2013). Brooding and emotional self-clarity were found to interact with cognitive style to mediate outcome, with brooding increasing and clarity decreasing depression (Stange et al, 2013).

2.4.7 Treatment of BD with cognitive therapy

Cognitive-Behavioural Therapy (CBT) is the primary psychological treatment offered to individuals with BD and is based on the principles of Beck's cognitive theory that changing the way in which individuals think and act in response to internal and external triggers, such as life events or changes in mood, will reduce relapse and increase the ability to regulate emotions. CBT packages for BD typically include psychoeducation, cognitive reattribution and behavioural experiments to challenge and change underlying DAs, and support to develop skills to monitor and cope with early warning signs and the longer term effects of BD

(Lam et al., 2000). A pilot longitudinal study of CBT for BD found that CBT reduced symptoms of depression and increased functioning compared to a waitlist control group, and reduced relapse and hospital admission compared to pre-treatment data (Scott, Garland, & Moorhead, 2001). A prospective RCT evaluating CBT in comparison to TAU in a sample of 103 BD participants found reduced hospital admissions for bipolar mood episodes, reduced relapse and fewer days unwell over a 12 month period for the CBT group (Lam et al., 2003). The CBT group also showed reduced fluctuation in manic symptoms and showed increased coping with manic prodromes. However, improvements in ratings of depression, activation and hopelessness observed at early follow-ups were not sustained at 12 months in the same study. The same sample were followed up for a further 18 months and the CBT group were found to have fewer bipolar episodes and fewer days unwell overall (Lam, Hayward, Watkins, Wright, & Sham, 2005). In particular, DAs related to goal attainment were significantly lower for the CBT group across all follow-ups. Results reported controlled for medication use and number of previous episodes. Scott et al. (2006) report results from a multi-centre RCT for 253 individuals with BD randomised to either CBT or TAU and followed up every eight weeks for 18 months. Results found no difference between groups on outcomes of relapse, bipolar mood symptoms or medication adherence, and suggested that CBT was less effective for those who had experienced more than 12 bipolar episodes previously. However, this trial has been criticised due to a third of participants being in acute episodes at inception and 40% of participants did not receive all modules of the intervention, both of which are likely to have negatively affected outcome (Lam, 2006). In addition, Lam (2006) highlights that Scott et al. (2006) base their 12 episode threshold for response to treatment on a median split of number of past episodes, which may not be an accurate method for continuous data. An RCT involving 52 participants with BD randomised to either CBT, which incorporated emotive techniques such as imagery, or TAU found reduced depressive symptoms and DAs for the CBT group immediately post-treatment (Ball, Mitchell,

Corry, Skillecorn, Smith, & Malhi, 2006). However these differences were not maintained at 12 months, and although there was a trend for the CBT group to have greater time to depressed relapse after controlling for baseline depression and reduced symptoms of mania at 12 months, these findings were not significant. Relapse rates and number of days unwell did not differ between the two groups in the same study. The Systematic Treatment Enhancement Program (STEP-BD) assessed outcomes for participants with bipolar depression receiving 30 sessions of CBT, family-focused therapy (FFT), or interpersonal social rhythm therapy (IPRST)(n = 163) compared to those receiving three collaborative care sessions (n = 130). Throughout a nine month treatment period and three months post-treatment, psychotherapy was found to predict increased recovery from depression in the full sample, and increased functioning for a sub-sample of participants (for a review of the STEP-BD outcomes see Bowden et al., 2012). There were no differences between psychotherapy treatments in the STEP-BD trial. Finally, an RCT with a small sample of individuals with BD assessed as being treatment resistant (n = 40) found that a combined intervention of CBT plus pharmacotherapy was superior at reducing hospital admission and symptoms of depression, anxiety and mania post-treatment compared to pharmacological treatment alone (Isasi et al., 2010). There are few trials exploring the effectiveness of group CBT. Those that exist have found improvements in psychosocial functioning but not symptoms post-treatment (Palmer, Williams, & Adams, 1995; Patelis-Siotis et al., 2001), although results require replication over extended follow-up periods and with larger samples.

2.4.8 Summary and limitations

Research into cognitive styles and attitudes in BD has provided mixed findings to date. Alterations in cognitive processes appear to be related to depressed symptoms but have not been found to be robustly related to vulnerability to mania in BD. There is evidence to

suggest that DAs are important in the experience and maintenance of depression and elevated DAs have been found in BD when controlling for current mood and other illness variables. However, these results are not universal and other studies have failed to find evidence that DAs can discriminate between individuals with BD and those with UD or healthy controls. In addition, the majority of the available literature exploring DAs as predictors of mood symptoms supports this as a primary predictor of depression but a weaker predictor of mania. Finally, it is unclear in this model how or why the same stressor may activate depressed and manic schemas at different times. Whilst this model is attractive as it provides key areas for intervention, the focus of this model on a single level of information processing (the perception of stressors) and one mechanism by which emotion is generated (DAs), is too simplistic. In addition, it suggests that affective states will be either all negative (depression) or all positive (mania). This does not fit with frequently reported clinical observations of complex presentations in BD, such as mixed episodes and anxiety, and therefore does not tell us anything about the interaction of emotions in BD. As a starting point, the research highlights the importance of considering cognitive factors in BD, but also the need to identify cognitive styles which may be unique to BD and which can account more accurately for the generation of emotion in manic and mixed affective states. In addition, given research which highlights shared cognitive processes between anxiety and depression in BD (Bird et al., 2013; Raghunathan & Pham, 1999), this model could feasibly be adapted to include anxiety. However, further research is required to understand if there are also shared cognitive processes which link experiences of mania and anxiety.

2.5 Disruption of circadian rhythms and extreme positive internal attributions in BD

2.5.1 Overview of theory

Circadian rhythms refer to an individual's natural daily pattern of behavioural and physiological processes over a 24-hour period and include sleep, appetite, alertness, body

temperature and hormones. Disturbance of sleep patterns is a core symptom of BD for both

depression and mania (DSM-IV) and other observed clinical features such as seasonal

patterns of relapse and daily mood fluctuations in BD indicate that circadian rhythms may be

involved in mood instability (Jones, 2001; Levenson & Frank, 2011; Mansour et al., 2005). It

has also been proposed that links between interpersonal factors, environmental factors,

medication and manic episodes may be mediated by the impact that these factors have on

sleep patterns, which disrupts circadian rhythms. Reduced sleep has been linked to the onset

of mania, whilst persistent reduced need for sleep is thought to exacerbate and maintain

manic symptoms. Events which occur to disrupt these patterns or rhythms have been

proposed as triggers to relapse in BD. Jones (2001) expanded this theory in BD by integrating

disruption of circadian rhythms with the Schematic Propositional Analogical Associative

Representational Systems (SPAARS) multi-level model of emotion (Power & Dalgeish,

1999).The SPAARS model suggests that emotions are integrated across multiple processes,

involving cognition, physiology and behaviour, and proposes four stages at which processing

occurs. The first level is the initial perception of stimuli, which occurs in the analogical level

and involves sight, sound, taste, touch and smell. Following perception, the three remaining

levels of processing are thought to occur in parallel. The associationist and propositional

systems process specific explicit and implicit information, whilst the schematic unit draws

from all systems to create meaning. The propositional unit refers to information that can be

explained through normal language, whilst the associationist unit has no such limits, for

example images and smells. Although initially the propositional system is key in establishing

these language-emotion links, eventually repeated experience and response to stimuli

become internalised and can generate emotion directly via the associative or schematic

routes. The SPAARS model suggests that there are five basic human emotions: sadness,

disgust, happiness, anger and fear. These core emotions are thought to form the basis of all

other affective experiences, with mood disorders proposed to be complex combinations of

basic emotions, for example sadness and disgust in depression, or happiness and anger in

mania. By combining the literature on circadian rhythms with the multi-level model of

emotion, Jones (2001) proposes that mood fluctuations occur in BD due to the disruption of

circadian rhythms *and* the way in which these disruptions or changes are appraised.

Specifically, that events occur which trigger changes in circadian rhythms, for example

changes in sleep patterns due to jet lag or over-working . This results in internal changes

such as increased energy or fatigue, which are then appraised as having extreme personal

meaning. Based on previous literature showing elevated dysfunctional attitudes and internal

attributions in BD, It is suggested that self-concepts in BD are modularised compared to

controls, displaying more extreme all-negative or all-positive self-appraisals. As such, these

changes are appraised and attributed internally, and are integrated into either a positive

schema (e.g. "I am invincible") or a negative schema (e.g. "I feel tired and dull due to my own

faults"). This in turn leads to either increased energy and activity associated with mania, or

reduced motivation associated with depression, depending on the appraisal made. Extreme

positive appraisals of internal states are therefore thought to lead to an individual engaging

in activities, cognitive processing and behaviour which serves to enhance these feelings and

experiences, leading to mania. As a consequence, this leads to further disturbances to

circadian rhythms and perpetuates mood symptoms. As pairings between disruptions and

responses are repeated, person-environment feedback loops become established and there

may be a lower threshold for triggering mood symptoms as these experiences increase.

Jones (2001) suggests that the severity of circadian disruption may determine if positive or

negative appraisals are made, with some preliminary evidence that mania is associated with

more severe disruptions (for a review see Healy & Williams, 1989), although this requires

replication.

2.5.2 The disruption of circadian rhythms in BD

2.5.2.1 Assessment of social rhythms to measure circadian instability in BD

Social rhythms refer to daily patterns of social and lifestyle activities. The timing of activities such as sleeping and waking, eating meals, starting physical activity and so on is thought to be in part driven by the body's internal clock, the circadian system, but also influenced by external factors such as environment and social norms and behaviours (Bullock, Judd, & Murray, 2011). Irregular social rhythms are thought to be generated due to dysregulation of the circadian system, and likewise disruptions to daily routines may also lead to changes in the circadian system. As such, social rhythms have been assessed as a way of exploring circadian disruption and mood instability in BD. Social rhythms have been assessed via the Social Rhythm Metric (SRM; Monk et al., 1990), a self-report questionnaire which measures and quantifies the regularity of daily routines including wake time, leaving and returning home, meal times, physical activity, social contact and sleep patterns. Other validated self-report measures have also been used to assess circadian rhythms in BD, including the Composite Scale of Morningness (CSM, Smith, Reilly & Midkiff, 1989) and the Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976) which measure the timing of activities and when an individual is at their most active and alert. In addition, circadian rhythms in BD have been measured objectively with the use of actigraphs; microprocessors worn on the wrist to measure motility levels and changes, including sleep and activity (Salvatore et al, 2008). Evidence from each of these measures is presented next.

2.5.2.2 Circadian instability as a vulnerability to BD

Individuals with BD have been found to have significantly less regular daily routines and lower levels of activity overall compared to healthy controls (Ashman et al, 1999). These differences have been shown to remain both within and between affective episodes. For

example, studies using actigraphy have found that individuals with BD had decreased daytime activity and increased day time sleeping during inter- and intra-episode periods compared to controls (Jones et al., 2005; Salvatore et al., 2008), although actigraphy data was recorded for only a relatively short period of time (7 and 72 hours respectively), limiting generalisability. Sub-syndromal mood symptoms and medication were not found to be associated with actigraphy data during euthymia in either study. Twin studies exploring circadian rhythms in pairs of twins where only one had BD have suggested an increased sensitivity to environmental changes in BD. One study found that circadian rhythms had a seasonal pattern for affected twins, with sleep and mood dependent on time of year and sunny days being associated with increased well-being scores for twins with compared to those without BD (Hakkarainen et al, 2003).

There is also evidence of a phase delay in terms of timing of diurnal activities in BD compared to controls, with individuals with BD completing daily activities later based on scores on the CSM (Wood et al., 2009). More variable and later daily activity patterns have also been observed compared to controls with no mood disorder using actigraphy (Jones et al., 2005).Whilst circadian instability is a core symptom of several affective disorders, circadian rhythms have been found to differ for individuals with BD compared to other clinical groups. Based on the CSM, more pronounced 'eveningness' effects and late diurnal activity patterns have been observed for individuals with a history of depressed episodes only compared to those with BD (Chung et al., 2012). In contrast, a study by Mantour et al. (2005) found that individuals with BD had bimodal distributions on the CSM, scoring significantly higher or significantly lower than individuals with schizophrenia, schizoaffective disorder and healthy controls. Being younger and meeting criteria for rapid cycling was linked to scoring for eveningness in BD, whilst age of onset and duration of most severe depressed episode was correlated with morningness, suggesting potentially earlier circadian phases as length and severity of illness increase (Mantour et al., 2005). CSM scores have

been found to be stable over time for BD populations (Wood et al., 2009). In addition, CSM scores for eveningness have been found to be elevated in individuals with BD who use alcohol regularly, suggesting that alcohol further impacts on circadian patterns (Hatonen, Forsblom, Kieseppa, Lonnqvist & Partonen, 2008). Reduced quality and regularity of sleep is also indicated in BD, with increased time to fall asleep and greater variability in sleep pattern between days for individuals with remitted BD compared to controls (Millar, Espie & Scott, 2004). Circadian instability may also be a vulnerability factor for the development of BD. Disruption of daily activity patterns have been reported for samples assessed as being at high-risk for BD, including those with close relatives with a diagnosis of BD (Jones et al, 2006) and those identified as at risk based on psychometric assessments (Ankers & Jones, 2009, Wold, 1990). Individuals with high hypomanic personality traits have also been found to have less regular daily activity patterns than those at risk of depression and healthy controls (Meyer & Maier, 2006).

2.5.2.3 Circadian instability as a state marker of BD

Self-reports of early warning signs of mood episodes in BD show sleep disturbance to be the most commonly reported indicator of a manic episode, and the sixth most common prodrome of depression (Jackson et al., 2003). Sleep disturbance is also associated with reduced quality of life for individuals with BD (Giglio et al., 2009; Michalak, Yatham, Maxwell, Hale & Lam, 2007). In comparison to their own diurnal patterns when in episode, individuals with remitted BD have significantly more night time sleep, significantly less day time sleeping and more total sleep during euthymic periods (Salvatore et al, 2008), suggesting mood does impact on circadian rhythms. However, even during periods of euthymia, individuals with BD have also been found to have dysregulated sleep patterns more comparable to an insomnia control group than healthy controls (Harvey et al, 2005). Phase delays of activity have been found to increase during periods of depression compared to timings of activities during

hypomanic and manic episodes for individuals with rapid cycling (Ashman et al., 1999). A study comparing individuals with BD depression, mania, cycling episode and UD found that significantly more manic patients experienced social rhythm disruption events and more severe life events prior to onset of their manic episode than those with unipolar or cycling episodes (Malkoff-Schwartz et al., 2000). Although increased social rhythm regularity has been shown to be associated with reduced diurnal variation in mood symptoms, this was not consistently associated with symptoms of mania or depression in one study (Meyer & Maier, 2006).

2.5.2.4 Circadian instability as a predictor of mood symptoms and relapse

Within the general population sleep disruption is associated with increased negative mood and irritability and decreased positive mood, whilst high levels of emotion can also disrupt sleep patterns, indicating a bi-directional relationship between sleep and mood stability (for a review see Murray & Harvey, 2010). Mood symptoms and episodes have been found to lead to interpersonal problems and disruptions in normal daily activities and sleep, and likewise disruptions to social rhythms, sleep deprivation and relationship problems have been found to be predictors of relapse in BD (see Frank et al., 2009 for a review). Social rhythm disruptions are significantly more frequent in the period prior to onset of manic episodes compared to control time periods for individuals with BD (Malkoff-Schwartz et al, 1998; 2000) and disruptions to social rhythms have been found to be a stronger predictor of manic episodes than stressful life events in the same study (Malkoff-Schwartz et al, 1998). Boland, Bender, Alloy, Conner, Labelle & Abramson (2012) found that, compared to a control population, individuals with BD had more frequent life events, were more sensitive to those events and experienced significantly more disruption to sleep and social rhythms following both positive and negative events independent of event severity. The effect of life events on sleep disturbance was sustained after controlling for baseline SRM-trait scores, days spent in

episode and total number of life events. Boland et al. (2012) did not find evidence for social rhythms moderating sleep loss, however decreased social rhythmicity has been found to significantly predict time to onset of next mood episode elsewhere (Shen, Alloy, Abramson, & Sylvia, 2008). Life events that disrupt social rhythms have also been found to predict both depressed and manic episodes, although the predictive strength with regards to mania has been modest (Sylvia, Verdon, Alloy, Gauger, Hafner & Abramson, 2009). Naturalistic studies have observed circadian rhythm disruption in BD following changes in eating patterns. A study which monitored 20 individuals with BD fasting during Ramadan found that relapse rates were high, with 45% of participants experiencing a relapse, 71.4% of which were manic episodes (Kadri, Mouchtaq, Hakkou, Moussaoui, 2000). Even for those who did not relapse, rates of anxiety and insomnia were elevated compared to baseline. Lithium blood levels were monitored and remained stable throughout, indicating this wasn't an effect of medication-blood levels. However, a subsequent study found no effects of fasting on mood in a larger sample (Farooq et al., 2010).

2.5.2.5 Psychological treatments for BD targeting routine and social rhythms

Because the circadian system is adaptive and open to external cues, it is a potential target for intervention in BD. Interpersonal and social rhythm therapy (IPSRT; Frank et al., 2002) was developed with the aim of stabilising daily routines and sleep/wake patterns to reduce relapse, however results so far are mixed. The largest trial to date evaluated IPRST in comparison to an intensive clinical management (ICM) control group (Frank et al., 2005). In total, 175 participants in an acute BD mood episode were randomised to either treatment, and received either the same treatment or switched to the other condition following stabilisation of mood. Results found that although IPSRT successfully stabilised social rhythms and improved occupational functioning post-treatment, time to remission did not differ between the two groups at two year follow-up. However, those who received IPRST

had longer time to relapse following stabilisation and reduced likelihood of recurrence. An internet based application which helped individuals to track their daily activities and routines was found to increase the stability of social rhythms over time and to have a modest but significant effect on symptom reduction after 90 days in a pilot study with 64 participants with BD (Lieberman, Swayze, & Goodwin, 2011). However, there was no control group for comparison. Overall, evidence for IPRST is mixed and has a less robust evidence base than other psychological treatments such as CBT and psychoeducation.

2.5.3 Positive internal attributions of circadian disruptions and relevant experiences in BD

2.5.3.1 The measurement of specific, mood-relevant appraisals in BD

Jones (2001) suggests that individuals with BD make extreme, self-relevant appraisals of internal states, potentially triggered by changes in circadian rhythms, which lead to the increase and maintenance of manic symptoms. Criticism of previous cognitive models of BD suggest that these are limited by the tendency to focus only on negative appraisals and attributions, and may explain the limited effects of CBT in BD to date if the specific beliefs and assumptions which underlie manic experiences are not addressed (Scott et al., 2006). In addition, DAs have not consistently been found to differentiate between healthy controls and individuals with BD during periods of euthymia (Lex et al., 2011) or between individuals with BD and UD (e.g. Jones et al., 2005, Lex et al., 2008). This has led to the development of psychometric scales to assess thinking styles which may be unique to BD. One such measure is the Hypomanic Interpretations Questionnaire (HIQ; Jones, Mansell & Waller, 2006), a measure of positive self-dispositional appraisals and the actual occurrence of hypomania-relevant experiences (e.g. "If I thought my thoughts were going too fast I would probably think it was because I was intelligent and full of good ideas"). The Interpretations of Depression Questionnaire (IDQ; Jones & Day, 2008) was also developed to assess the appraisal of depression-relevant experiences in a comparable way. Another measure which

assesses extreme positive and negative self-relevant appraisals of internal states is the

Hypomanic Appraisals and Positive Predictions Inventory (HAPPI; Mansell & Jones, 2006).

The HIQ and the HAPPI have been found to be correlated (Mansell & Jones, 2006) and both

measures significantly distinguish clinical from non-clinical control groups when controlling

for current mood (Mansell & Jones, 2006). The following section focuses primarily on

research using the HIQ, with evidence from the HAPPI reviewed in Section 2.6.

2.5.3.2 Extreme positive appraisals of internal states as a risk factor to BD

The appraisal and occurrence of hypomanic experiences assessed using the HIQ have been

found to uniquely predict HPS scores in analogue samples (Jones, Mansell & Waller, 2006;

Jones & Day, 2008). IDQ scores have also been found to be modestly but significantly

correlated with HPS scores (Jones & Day, 2008). Johnson & Jones (2009) assessed

dysfunctional cognitive appraisals associated with hypomanic experiences in a large

analogue sample of 658 participants. It was found that four cognitive factors correlated with

HPS scores; acting before thinking, overly positive appraisals of hypomania-relevant

experiences, overly confident responses to successes, and tendencies to dampen positive

affect. These findings remained consistent after controlling for gender, nationality and

current mood. Jones & Day (2008) found that negative appraisals measured with the IDQ

correlated significantly with sub-syndromal mood symptoms in an analogue sample of 231

participants. IDQ scores and reward also independently predicted depressed symptoms after

adjusting for current mood, hypomanic personality and recent experience of hypomanic or

depression-relevant events in the same study. Whilst these results suggest that extreme,

self-dispositional appraisals of hypomania and depression-relevant experiences may be

associated with risk of mood instability, a study using the HIQ and HPS with children with

parents with (n = 23) and without diagnoses of BD (n = 24) found conflicting results. Whilst

more children of affected parents received bipolar spectrum diagnoses, there was no

difference between groups on the HIQ or HPS, suggesting that familial risk for BD is not

associated with a cognitive vulnerability of appraisal style (Espie, Jones, Vance & Tai , 2012).

With regards to extreme appraisals in clinical samples, HIQ scores have been found to be

elevated in individuals with BD compared to controls (Mansell & Jones, 2006; Jones, Mansell

& Waller, 2006), even when controlling for current mood symptoms. Additional research

pertaining to extreme appraisals as assessed using the HAPPI is discussed later.

2.5.4 Summary and limitations

The convergence of literature on circadian disruptions and extreme appraisals of relevant

internal states and events suggests that these are key features in the development and

maintenance of mood instability in BD. The amount and timing of sleep appears important

and dysregulated in BD, whilst activity appears to be more variable and reduced. Although

there is too little evidence to conclude if circadian disruption is a state or trait characteristic

of BD, studies of euthymic participants do suggest that instability of circadian rhythms exists

outside of mood episodes, but worsens prior to and during episodes of mania and

depression. While it seems sleep disruption and circadian dysregulation are key elements of

BD, the mechanisms which underlie the association between the two are still relatively

unclear. In addition, the majority of research into sleep and circadian rhythm disturbance is

based on sleep deprivation, however bipolar depression is often characterised by periods of

hypersomnia, which has received less attention. The finding that extreme appraisals

regarding positive and negative internal states are correlated with bipolar mood symptoms

and vulnerability to BD highlights potential areas for intervention. The experience of

problematic mood swings across a number of psychological disorders such as BD, UD and

anxiety suggests that similar underlying cognitive and behavioural processes may exist across

populations. The SPAARS model of emotion provides an explanation of more complex

emotional experiences as opposed to depression and mania alone, which may better

account for anxiety as a core feature of bipolar mood symptoms and instability. However,

research which assesses how anxiety may relate to apparent extreme negative and positive

appraisals of internal states in BD would be beneficial. Based on these findings, a

transdiagnostic, integrative cognitive model of mood instability has been formulated

(Mansell, Morrison, Reid, Lowens & Tai, 2007), which is reviewed below.

2.6 An integrative cognitive model of mood swings and BD

2.6.1 Overview of theory

Based on evidence for existing psychological models in BD described in previous sections of

this chapter, the integrative cognitive model (ICM) attempts to explain the development and

maintenance of mood swings in BD and other disorders of emotion (Mansell et al., 2007).

The ICM aims to improve on limitations of other models, including the over-emphasis on

behavioural aspects in the BAS model of BD, the lack of explanation for why depression or

mania may be triggered at a specific time in other cognitive theories, and the inability to

account for mixed states across all models. As with the disruption of circadian rhythms and

positive attributions model, the ICM proposes that bipolar mood swings are preceded by

changes in internal state (physiological, cognitive or emotional) which are appraised by an

individual as having extreme personal meaning. In contrast to other models, the ICM

suggests that individuals will have multiple and conflicting extreme dysfunctional appraisals,

with only one appraisal being held in awareness at a time, but with an individual constantly

switching between interpretations. The appraisals elicited include themes of impending

catastrophe, imminent personal success or perceived personal weakness, and are

hypothesised to relate to previous experiences of mood swings. For example, the

catastrophic consequences of becoming manic, a personal success of overcoming early

warning signs of depression, or thoughts that one is weak for getting over-excited. These

extreme appraisals trigger behavioural responses to either avoid catastrophe (descent

behaviours), or to achieve success (ascent behaviours). Ascent behaviours attempt to control and enhance internal states, for example staying awake through the night or taking part in more activities, leading to hypomanic or manic symptoms. Decent behaviours, such as withdrawal and avoidance, aim to avoid perceived impending catastrophes, but unintentionally lead to depression. These behavioural responses escalate and maintain mood instability as they prevent the reappraisal of internal states in a less extreme way and do not allow for the resolution of conflicting appraisals. Appraisals and behavioural responses are thought to depend on individual beliefs about the self and others, procedural beliefs regarding information processing strategies, and metacognitive beliefs about mood swings, all of which develop through early and ongoing life experiences. Ascent and descent behaviours may trigger relevant life experiences, such as changes in the environment or reactions from others, leading to changes in internal state. Appraisals and attempts to modify internal states will trigger further alterations in internal states which confirm extreme and dysfunctional beliefs and maintain the cycle of distorted appraisal and behaviours, escalating mood and arousal and leading to bipolar mood episodes. Although described sequentially here, the model is dynamic and proposes that the cycle can be 'entered' at any point. Integrating evidence from other existing models such as the BAS, Mansell et al. (2007) suggest that neuropsychological factors at times of extreme arousal may prevent individuals from breaking the cycle of escalating mood. In addition, genetic factors are proposed to potentially predispose individuals to have more extreme reactivity and changes in internal states. As evidence regarding aspects of this model, such as life events as triggers to changes in internal states and bipolar mood episodes has been reviewed elsewhere, the following sections review evidence for the novel aspects of this model only.

2.6.2. Extreme, conflicting appraisals of changes in internal state as a cognitive vulnerability to BD

The ICM proposes that a change in internal state may trigger multiple extreme and conflicting appraisals for individuals with BD. For example, a reduction in energy may be interpreted catastrophically as "I am a failure", but may also be appraised in a self-activating way as "if I don't keep on the go all the time I will have a complete breakdown". The HAPPI (Mansell & Jones, 2006) was developed to assess multiple, conflicting appraisals of internal states and measures self-critical and catastrophic beliefs about changes in internal states in addition to positive, self-dispositional appraisals. As these appraisals are thought to confer cognitive vulnerability to BD and to trigger behavioural responses which exacerbate mood symptoms, research has assessed extreme appraisals as an indicator of BD. A study comparing 24 students scoring high on the Hypomanic Personality Scale (HPS, Eckblad & Chapman, 1986) and 24 students who were low HPS-scorers found those in the high HPS group rated themselves significantly higher than they rated people close to them on all adjectives of positive, negative and neutral valence, and those related to high and low activation (Pyle & Mansell, 2010). Compared to low-HPS scorers, the high HPS group also made significantly higher ratings of neutral and positive high-activation words. These results were interpreted as suggesting a self-referent bias for those at risk of BD, and therefore linked to the tendency for individuals with BD to make extreme self-appraisals of changes in internal states. HAPPI scores have been found to be elevated in individuals with BD compared to controls (Mansell & Jones, 2006; Mansell, 2006). Mansell et al. (2011) compared HAPPI scores across individuals with remitted BD, remitted UD, healthy controls and non-clinical controls with a history of hypomanic experiences. HAPPI scores were significantly higher for individuals with BD compared to all control groups after adjusting for education, age and bipolar mood symptoms on the Internal State Scale (ISS), a self-report instrumented validated for discriminating mood states in BD (Bauer, Crits-Christoph, Ball, &

Dewees, 1991). The HAPPI also distinguished UD participants from non-clinical controls, providing support that cognitive style confers an underlying vulnerability for mood swings which lie on a continuum. Whilst no significant differences were found between individuals with remitted BD, UD and healthy controls on the DAS, a separate study also found individuals with BD to have significantly higher scores on the HAPPI than individuals with UD and healthy controls (Alatiq, Crane, Williams & Goodwin, 2010). Specifically, BD participants scored higher on the HAPPI subscales of response style, the need to respond to symptoms of elevated mood, and beliefs about negative responses from others.

2.6.3 Extreme conflicting appraisals related to mood state

Based on the ICM, extreme appraisals should be associated with bipolar mood symptoms. HAPPI scores have been found to be positively correlated with current activation, well-being and conflict, and negatively associated with current depression in both clinical and analogue samples compared to healthy controls (Dodd, Mansell, Morrison & Tai, 2011b; Mansell & Jones, 2006; Mansell, Rigby, Tai, & Lowe 2008). The HAPPI has also been found to correlate with both past and current mood symptoms independently from the BIS/BAS scales, the HPS, and when controlling for age and gender (Mansell et al., 2008). There is evidence to support individuals at risk of BD having concurrent positive and negative self-appraisals. Following a positive mood induction, 30 students with high scores on the HPS described their own performance on a goal-directed task using more extreme positive and negative adjectives than 30 low HPS scorers (Taylor & Mansell, 2008).

2.6.4 Beliefs about mood swings in BD

There is currently relatively little research exploring specific dysfunctional beliefs about affect regulation. Individuals with BD who rate themselves highly on a measure of positive self-dispositional traits and individuals with BD and current depressed symptoms have been

found to report a preference for mania as an ideal mood state (Lee et al., 2010). A qualitative

study with 12 individuals with experiences of hypomania but not depression found that

individuals made either external, situational attributions to hypomanic experiences, or

reported having not given much thought to those experiences, suggesting that external, non-

extreme appraisals may be a protective factor to problematic mood experiences (Seal,

Mansell & Mannion, 2008). However, additional research in this area is required.

2.6.5 Evidence for ascent and descent coping behaviours in BD

Qualitative research has linked the tendency to dampen positive affect to concerns about

progression into manic episodes (Mansell, Powell, Pedley, Thomas, & Jones, 2010). This was

reported as being both helpful and unhelpful, preventing relapse in some instances, but also

resulting in over-control of behaviour, reducing positive experiences, for example by limiting

social contact or pleasurable activities to avoid mania. This in turn was proposed to

potentially disrupt routines and lead to mood episodes unintentionally. A study exploring

usual responses to hypothetical, goal-orientated situations associated with mild hypomania

for 54 Individuals with BDI found that DAs related to goal attainment predicted increased

activity as a coping response to situations such as multiple challenges at work (Lee et al.,

2010). A study exploring coping in response to feelings of low mood in 112 non-clinical

participants found that those scoring in the upper quartile of the HPS reported they would

engage in activities and behaviours to avoid depression significantly more often than those

in the lowest quartile of the HPS (Morrison, Peyton, & Nothard, 2003). Knowles, Tai,

Christensen & Bentall (2005) assessed response styles in a sample of 528 undergraduate

students and found that rumination and risk taking were both associated with depression

and hypomania scores. Risk-taking in response to depressed mood was also elevated for

participants with BD in a manic mood in comparison to bipolar depressed, bipolar euthymic

and healthy control participants (Thomas, Knowles, Tai, & Bentall, 2007). Individuals with BDI

have been found to be significantly less likely to accept advice on a computer-based task following a positive, but not a negative, mood induction compared to individuals with remitted UD and healthy controls (Mansell & Lam, 2006), which was suggested as evidence that individuals with BD may be less likely to follow advice from others when in a positive mood state, potentially due to negative beliefs regarding how they are perceived by others when mood is elevated. However, this requires further research. There are a limited number of studies exploring descent behaviours in BD, although rumination in response to depressed mood is associated with both depression and mania (Knowles et al., 2005; Thomas et al., 2007; Van der Gucht et al., 2009).

2.6.6 Extreme appraisals linked to outcome in BD

Dodd, Mansell, Sadhnani, Morrison & Tai (2010) found that the HAPPI was predictive of hypomanic symptoms at a three month follow-up point in an analogue sample. However, after controlling for other psychometric measures, only activation was positively predicted by the HAPPI longitudinally. In addition, DAS scores predicted increased conflict and depression, HPS scores predicted self-reported mood symptoms, and BAS dysregulation was also predictive of depression (Dodd et al., 2010). A later study also using analogue participants employed a diary method to record mood and behaviour over a four day period (Dodd, Mansell, Bentall & Tai, 2011a). The HAPPI was found to be predictive of bipolar-relevant internal states and behaviours after controlling for BIS/BAS scores, baseline measures, age and gender (Dodd et al., 2011a). In particular, the HAPPI was positively predictive of activation, depression and conflict on the ISS and also predicted ascent but not normalising behaviours. Finally, a study which aimed to validate the HAPPI with a clinical sample found that total scores were independently and positively predictive of conflict and activation over a four week period when controlling for baseline mood and other extraneous variables, and individual HAPPI factors were also associated with depression over time (Dodd

et al., 2011a). Other research in clinical samples is limited, although overly-positive cognitions about the self have been linked to worse outcomes in response to cognitive therapy (Lam, Wright & Sham, 2005).

2.6.7 The role of catastrophic appraisals and anxiety in the ICM

The ICM highlights the role of catastrophic appraisals of changes to internal state as a key factor in the maintenance of mood swings. Specifically, that catastrophic appraisals lead to the selection of unhelpful self-regulation strategies, which may have the unintended consequence of exacerbating or maintaining mood symptoms (Mansell et al., 2007). This aspect of the model is influenced by cognitive conceptualisations of a number of emotional disorders, including ADs. The role of catastrophic appraisals of internal (e.g. intrusive thoughts) and external cues (e.g. other's facial expressions) have been well documented in the development and treatment of several ADs. For example, catastrophic health appraisals in PD (Clark, 1986; Clark et al., 1997) or the anticipation of negative outcomes in social situations in SoP (Clark & Wells, 1995). Catastrophic appraisals have also been found to be highly prevalent in BD with regards to feared outcomes related to mood fluctuations (Dodd et al., 2011; Kelly et al., 2011; Mansell et al., 2011). In addition, extreme negative appraisals, but not extreme positive appraisals, have been found to significantly predict the experience of BD when entered into regression models concurrently (Kelly et al., 2011). This indicates that it is the combination and interaction of positive and negative appraisals about activated states, as opposed to extreme positive appraisals alone, which interact to predict BD. As such, it appears that catastrophic appraisals are a transdiagnostic cognitive risk factor which is central to the experience of mood instability and anxiety. However, research regarding extreme appraisals in BD has not assessed the presence and impact of anxiety symptoms on attributions, and this is an area for future research.

2.6.8 Interventions based on the ICM

A primary focus of CBT for BD is the recognition of early warning signs and implementation of coping strategies to avoid relapse. CBT assumes individuals are able to distinguish between normal fluctuations in internal states and problematic clinical symptoms, and take action appropriately to control mood. Mansell et al. (2007) suggest that individuals with BD may not feel confident to make this distinction, and therefore may become hypervigilant to changes in internal state, triggering unnecessary ascent and descent behaviours in attempts to control mood. These behaviours are proposed to result in mood episodes and reinforce extreme appraisals and beliefs that mood swings are dangerous and all changes in internal states must be monitored and controlled. An adapted CBT approach suggested is the Think Effectively About Mood Swings (TEAMS) intervention, which attempts to challenge extreme positive and negative appraisals of internal states and widen the range of mood states individuals with BD are able to tolerate without engaging in ascent or descent behaviours to modify their mood (Mansell et al., 2007). A pilot case series with seven individuals with BD who received 12 sessions of TEAMS therapy found that this was acceptable and feasible to deliver, and positive effects were observed on mood symptoms, extreme self-appraisals and functioning post-treatment and at one month follow-up points (Searson, Mansell, Lowens, & Tai, 2012). A controlled trial is currently underway to assess the ability of this approach to prevent relapse longitudinally in a larger sample.

2.6.9 Summary and limitations

The ICM synthesises research from existing psychological models to improve on limitations and provide a holistic description of the development and maintenance of mood swings in BD. Emphasis is placed on the role of cognitions and behaviour in response to changes in internal states and the ICM provides an explanation for why the same changes may trigger

high, low or mixed mood states and episodes due to the potential existence of multiple and conflicting appraisals. The ICM also provides a coherent framework through which current CBT interventions can be adapted and potentially improved for individuals with BD, although longitudinal data from a large trial are pending. Whilst this model is encouraging, there are a limited number of studies which have explored this to date. In particular, research regarding beliefs about mood swings is preliminary, and a large amount of current research using the HAPPI involves analogue samples which, although mood swings are proposed to lay on a continuum, may have limited generalisability to clinical populations. Finally, HAPPI scores have been reported to account for a significant but relatively small proportion of variance in outcomes, and therefore, like previous models, extreme and conflicting appraisals and subsequent behaviours are likely also mediated by a number of other processes in BD already discussed within this chapter.

2.7 Overview and synthesis of current research

Based on the current research it appears that BD likely develops and is maintained by a complex interaction of genetic, psychological, physiological and environmental factors. Early models of BD suggest individual differences in the BAS underlie mood instability, a trait neurobiological motivational system which underlies reward-seeking, impulsivity, extraversion and positive affect. Specifically, the BAS dysregulation model proposes that the BAS is over-sensitive in BD, reacting to life events and stressors with excessive activation or deactivation and leading to the experience of depressed or manic symptoms. There is a large body of research which links BAS dysregulation to both the vulnerability to and expression of BD. However, this model has methodological limitations in terms of measurement and evidence linked to prospective outcomes. In addition, BAS activation has not been found to be reliably linked to depression in BD, and therefore may not be able to account for the complex range of experiences observed for individuals with BD including anxiety, but instead

may be one of many risk factors to mood instability. Subsequent models have taken a predominantly cognitive approach to the conceptualisation of mood instability. The cognitive-vulnerability model of BD based on Beck's (1967) theory of depression has proposed that DAs interact with stressful life events and are appraised either negatively or positively, resulting in depression or mania. Whilst there is evidence for DAs linked to mood symptoms and relapse in BD, these results are inconclusive. Other studies have found no difference between individuals with BD and healthy controls on measures of DAs and other negative cognitive styles, and whilst there is evidence that DAs are linked more often to depression in BD and are therefore important, negative cognitive styles alone have not been found to be sufficient to explain manic experiences. Research has since progressed to attempt to identify cognitive styles which may be unique to BD and therefore unique to the experience of manic symptoms. One example is the adapted SPAARS model proposed by Jones (2001) which suggests that extreme positive appraisals of relevant internal states triggered by life events and disruptions are responsible for escalating and maintaining manic symptoms due to an individuals' desire to sustain those experiences. Evidence suggests that disruption to circadian rhythms as observed via disruptions in sleep, eating and activity patterns are elevated in BD compared to clinical and non-clinical controls, both between, prior to and during mood episodes. In addition, emerging evidence suggests that the interpretation of these events is also important in the development of mood episodes, with measures such as the HAPPI and the HIQ found to distinguish individuals with BD from healthy controls and to predict past, current and future bipolar mood symptoms in clinical and analogue samples. However, research in this area is limited and requires further replication, in particular with regards to the longitudinal application of this model to mood experiences over time. Finally, to account for the apparent inconsistencies and discrepancies in the current literature, Mansell et al. (2007) propose the Integrative Cognitive Model of BD. In brief, the ICM suggests that BD is characterised by extreme appraisals of internal states, as

the cognitive model and Jones (2001) have suggested, but propose that multiple appraisals are likely to occur which can escalate manic and depressed symptoms and which are in conflict with one another. For example, appraising low motivation highly negatively and so feeling compelled to increase activity to avoid depression, and at the same time valuing increased activation as highly positive. Mansell et al. (2007) suggest that these appraisals will vary across the life span and between people, but will always be extreme in nature, will be both negative and positive, will relate to beliefs about the self and others, and will link to themes of catastrophizing and lack of control. Whilst this is a logical and promising progression of the research, evidence to support this model is limited and further research is required, in particular ongoing research which evaluates a novel treatment approach to BD which is underpinned by this model.

2.8 Defining the aims and directions of the current thesis

Despite a growing body of research highlighting anxiety as a predominant experience in BD and linking this to poorer outcomes, anxiety is noticeably absent from current models of BD, which primarily focus on depressed and manic experiences. Whilst these are the two defining features of BD, research suggests that both depression and mania encompass a diverse range of emotions and characteristics, with most manic states found to be mixed states (Cassidy et al., 1998). Based on the information presented in this review, there is evidence to support all models as potential explanations of mood instability in BD. However, there does not appear to be one particular model which is dominant in its ability to account for mood swings in BD. As such, there also does not appear to be one model which is dominant in its ability to account for the experience of anxiety in BD at this stage. Therefore, this thesis does not attempt to test a causative model of anxiety in BD, but instead attempts to explore the experience of anxiety in BD in detail and using a range of methodologies, with the aim of eliciting a more holistic view of these experiences which can then be considered in

the context of these existing psychological models. In particular, the ability of these models

to account for anxiety experiences, and adaptations which may be required to do so in light

of new information generated in the course of this thesis, are considered in the final

discussion (Chapter 8). Considering the evidence described in this chapter with that

presented in Chapter 1, there are some key gaps in the existing evidence base which this

thesis aims to address. The current absence of qualitative research to understand the

interplay of anxiety and other mood experiences in BD in a more detailed way is a key

ommision in the literature. In addition, the use of symptomatic outcomes may be a more

promising approach to explore anxiety and outcome in BD. Finally, research to explore the

temporal relationship between anxiety symptoms and mood in BD is also currently absent

and may be beneficial to highlight specific interactions and processes underlying anxiety and

mood fluctuations. The specific aims and methodologies of this thesis are outlined in Chapter

3.

Chapter 3: Aims and Methodology

3.1 Rationale for the current research

A review of the current literature (see Chapter 1, Sections 1.3 and 1.4) found that there are

several studies which document the prevalence of anxiety in BD and the association with

clinical outcomes retrospectively. However, there is a lack of prospective research which

explores whether anxiety is a significant predictor of outcome longitudinally and a lack of

information regarding the temporal relationship between anxiety and mood in BD. In

addition, there is no current qualitative research which explores the experience and

significance of anxiety in BD as opposed to the diagnosis of ADs. As such, this thesis is

concerned with addressing these current gaps in the knowledge.

3.2 Aims of the current research

3.2.1 Objective 1: To explore the nature of the relationship between anxiety and bipolar mood experiences

This thesis aims to provide information regarding whether anxiety should be conceptualised

as a separate, comorbid experience as much of the literature suggests, or if anxiety is more

appropriately conceptualised as an integral part of BD. Qualitative interviews with individuals

with BD (Study 1) address this question based on subjective perceptions of the relationship

between anxiety and BD. Two quantitative studies (Study 2, Chapter 6 and Study 3, Chapter

7) also explore the interaction between anxiety and mood symptoms over time and assess to

what extent these experiences are related.

3.2.2 Objective 2: To explore the subjective experience of anxiety in BD

Qualitative research in this area is invaluable to increase understanding of the nature of

anxiety in BD and the impact this may have on mood and other important life domains. A

Meta-synthesis described in Chapter 4 and qualitative interviews reported in Study 1 (Chapter 5) aim to explore these experiences in detail.

3.2.3 Objective 3: To assess anxiety as a prospective indicator of depression and mania

Study 2 (Chapter 6) is a longitudinal analysis assessing anxiety as a predictor of depressive symptoms, manic symptoms and functioning. This aims to establish a greater understanding of the association between anxiety, bipolar mood symptoms and clinical outcomes in BD. A secondary aim is to assess the predictive validity of anxiety defined by diagnostic criteria, observer-rated anxiety symptoms and self-reported symptoms of anxiety.

3.2.4 Objective 4: To explore the temporal interaction of anxiety and mood experiences

Whilst Study 2 aims to explore anxiety as a predictor of outcome over time, Study 3 aims to explore real-time interactions between anxiety and mood in BD, and the context in which fluctuations may occur. In addition, this involves the comparison of individuals with a diagnosis of BD and healthy controls and aims to explore both risk factors and protective factors to mood instability. Specifically, contextual factors including thought content, activity and social context are assessed for their role in mood fluctuations. The qualitative aspects of this thesis also provide insight into subjective perceptions of the interaction and significance of mood and anxiety experiences in BD.

3.3 Overview of methods

A mixed methods approach was used in this thesis, with quantitative and qualitative data being collected separately and the results discussed together in Chapter 8. This aimed to answer the primary research questions about the nature of the relationship between anxiety and mood in BD by bringing together evidence from different approaches which have different strengths and weaknesses. Qualitative methods were used to explore potential relationships between anxiety and mood fluctuations in BD which are indicated in previous

research. Quantitative methods were used to measure anxiety symptoms as a predictor of outcome in BD and to assess more subtle interactions between anxiety and affect. Although not always viewed as compatible, a paradigm shift occurred around the 2000s where qualitative and quantitative methods were combined and mixed methods were viewed as a formal research discipline, providing a comprehensive format through which research questions can be investigated in a rigorous and holistic way (Lund, 2012). The most recent guidelines published by the Medical Research Council (MRC) also advocate the used of mixed methods approaches in health research (MRC, 2008). This is particularly useful when a research area or topic is relatively under researched, as mixed methods provide a broad subjective and objective analysis through which hypotheses can be generated and tested. This is highly applicable to the current thesis, where anxiety in BD has been documented extensively in terms of prevalence and associated outcomes, but lacks in-depth qualitative research to identify potentially unknown yet important aspects of the relationship between anxiety and mood fluctuations, and where more stringent quantitative research regarding outcomes and temporal interactions between anxiety and mood are required. This approach also allowed the opportunity to assess if results from different methodologies converged within this thesis (Polit & Beck, 2004). However, there are some fundamental differences in the philosophies which underlie qualitative and quantitative approaches which need to be considered. Quantitative approaches are based on a positivist paradigm, which assumes that phenomena can be reduced to empirical indicators and that there is only one objective reality that exists, which is independent of individual perceptions and experiences. In contrast, qualitative approaches are most often based on the paradigms of interpretivism (Altheide & Johnson, 1994; Kuzel & Like, 1991) and constructionism (Guba & Lincoln, 1994), where by it is assumed that there are multiple realities and truths which are socially constructed and therefore dynamic (Berger & Luckman, 2008). As these methodological approaches are based on different views of reality, they will inevitably measure different

views of the phenomena of interest (Sale & Brazil, 2004). As a result, findings from

qualitative and quantitative methodologies cannot be reliably integrated via cross-validation

or triangulation as they are essentially studying different phenomena (Sale, Lohfeld & Brazil,

2002). A more appropriate method of bringing together the data from these methodologies

has been suggested by Sale et al. (2002) who propose that results should be discussed

together for complimentary purposes, which increases understanding of an area of interest

and builds on the strength of each approach, whilst being mindful of these inherent

philosophical differences. A complementary approach to integration was adopted within the

current thesis, and results are discussed together in the general discussion (Chapter 8) to

explore similarities and differences within the findings.

All methods are described fully in each empirical chapter and therefore only a

summary of the methods used is presented here. The meta-synthesis and empirical studies

in this thesis are presented sequentially, with results from each individual section

summarised prior to presenting the next. The results from all chapters are synthesised in the

final discussion (Chapter 8) and conclusions encompassing these findings are presented. All

studies include participants with a research diagnosis of BD assessed using the Structured

Clinical Interview for Diagnosis IV – Research Version (SCID-DSM-IV; First, Gibbon, Spitzer,

Williams, & Benjamin, 1997) and recruited from mental health services and the community.

Chapter 4 is a meta-synthesis which integrates existing qualitative research within

the BD literature where experiences of anxiety are reported within the results. Fifteen

studies were found to be relevant for inclusion and the results were synthesised and used to

inform the topic guide and structure implemented in Study 1. Study 1 (Chapter 5) used semi-

structured interviews to explore the experience and impact of anxiety in BD directly.

Individuals with a diagnosis of BD were interviewed about their personal experiences of

anxiety, with participants sampled purposively to ensure that a range of perspectives and

experiences were represented. Data were analysed using thematic analysis. Study 2 (Chapter

6) reports an analysis of anxiety, mood and functioning data collected as part of the PARADES (Psychoeducation Anxiety Relapse Advance Directives Evaluation and Suicidality) research program, a National Institute for Health Research funded grant (grant reference RP-PG-00407-103899). Data were collected as part of the PARADES Psychoeducation study over a period of up to 96 weeks. Analysis was carried out using mixed regression analyses to explore anxiety as a prospective indicator of outcome. Finally, Study 3 (Chapter 7) describes an experience sampling methodology (ESM) study which explores the temporal relationships and interactions between self-reported ratings of anxiety, negative affect (NA) and positive affect (PA) over a seven day period. Study 3 recruited individuals with a diagnosis of BD and a non-clinical control group to allow for both between and within-group comparisons. Thoughts, activities and contextual factors associated with mood and anxiety ratings were also explored in this study. Analysis was carried out using multi-level modelling to account for the nested structure of the data.

A service-user researcher was involved in the collection of data for Study 1 and completed half of the qualitative interviews, with the remaining interviews completed by the author. The data for Study 2 was collected by eight research assistants employed on the PARADES program, including the author. Study 3 was completed in collaboration with two other doctoral researchers, Heather Robinson and Faye Banks, with recruitment and data collection being equally shared. All quantitative and qualitative analyses in this thesis were completed by the author.

3.4 Qualitative meta-synthesis

There are currently no qualitative studies which explore the experience of anxiety in BD as the primary research question. However, there are a number of existing qualitative studies which explore the subjective experience of BD in the context of important life domains including occupation, recovery, medication and diagnosis. A qualitative meta-synthesis is the

amalgamation of a group of qualitative studies, with the intention of understanding and explaining phenomena (Walsh & Downe, 2005). This method was employed in the current thesis to explore themes related to the experience of anxiety in BD in existing qualitative research and to generate provisional theoretical relationships which could inform subsequent stages of this research, specifically the design of Study 1.

3.5 Qualitative methods

NICE guidelines for the treatment and management of BD (NICE, 2006) state that "treatment and care should take into account people's individual needs and preferences". In order to identify areas of need and targets for treatment, qualitative research which consults directly with individuals who have those experiences is vital. Study 1 aimed to explore the subjective experience of anxiety in BD to understand how anxiety may influence mood fluctuations and other outcomes, which is relevant for clinical practice and intervention. Qualitative research is one of the most effective ways to gain insight into neglected issues and experiences (Gill, Stewart, Treasure, & Chadwick, 2008) and allows for the exploration of the 'what', 'how', 'when' and 'where' of experience, capturing subtleties, complexities and atypical views which may be missed in quantitative designs (Peters, 2010). Primary qualitative methods used in psychological and health research include grounded theory (GT; Glaser & Strauss, 1967), interpretative phenomenological analysis (IPA; Smith, 1996) and thematic analysis (TA; Braun & Clarke, 2006), although several other qualitative methods also exist. TA, IPA and GT share many similarities and all methods seek to find patterns within qualitative data, with all themes and interpretations being 'data-driven' (Braun & Clarke, 2006). However, TA was chosen as the most appropriate method for this thesis for a number of reasons. Unlike GT, TA is not committed to the development of a complete theory (Holloway & Todres, 2003), which is beyond the scope of this thesis and the current literature regarding anxiety in BD at this stage. However, TA does allow for the generation of theoretical interpretations

and understanding of the data, which was crucial for this thesis. In addition, although Study 1 aimed to answer questions about experiences within a phenomenological framework, IPA maintains an idiographic focus on lived experiences within a homogenous sample. In contrast, TA focuses on patterned meaning across data from individuals sampled to gather a range of perspectives (Braun & Clarke, 2006). This was felt to be an important distinction due to the current lack of experiential data regarding anxiety in BD. It has previously been suggested that thematic analysis is primarily a technique of 'thematising meanings' which is employed across all qualitative methods (Holloway & Todres, 2003). However, more recently formalised guidelines on the conduct of TA have been developed (Braun & Clarke, 2006), establishing this as a valid qualitative method. TA provides a flexible yet structured framework within which consistent and contrasting patterns and themes from subjective accounts can be identified, and attempts not only to describe subjective phenomena, but also to interpret and explain experiences to better understand their context and underlying processes (Boyatzis, 1998). Whilst flexibility is an advantage of TA relative to other qualitative methods, decisions were still made prior to analysis in Study 1 regarding the coding and organisation of data into themes to ensure consistency throughout (Braun & Clarke, 2006). A theoretical, rather than an inductive analytic approach was chosen, with coding of data directed by the primary research question regarding the nature and experience of anxiety in BD, although the content of themes and sub-themes were data-driven. Themes were identified as related topics or issues which were judged by the author to occur consistently across the sample and where a range of views and experiences could be elicited to provide detailed perspectives. Purposive sampling was employed to ensure a range of participants for whom the research question was meaningful were included (Patton, 1990), defined by their current, past or absent experiences of anxiety. In particular, contrasting experiences were probed and explored. Data were analysed at the interpretative and constructionist level, with the aim of going beyond description and

conceptualising the relationship between anxiety and mood fluctuations in BD. This thesis

employed the use of semi-structured interviews which were not restricted to specific

questions but did enable the interview to remain focused on the primary research question.

A constant comparative approach was adopted to allow the direction and focus of the

interviews to be adapted between participants as new data emerged (Glaser & Strauss,

1967). Disadvantages with qualitative research lie mainly with the potential for researcher

bias as data are actively interpreted and understood. The possibility for potential bias is

acknowledged and made explicit at the outset in Study 1, and researcher triangulation was

employed to minimise bias. This included the discussion and agreement of themes within a

multi-disciplinary team which comprised the author (KH), two academic clinical psychologists

(SJ & FL), an academic with expertise in qualitative research (SP) and a service user

researcher with a diagnosis of BD (PB). Members of the research population were also

consulted regarding the final themes to ensure they were accurate reflections of

participant's experiences.

3.6 Prospective designs

There are a limited number of longitudinal studies exploring anxiety as a predictor of

outcome in BD and many have focused on anxiety disorders, neglecting the potential

importance of anxiety symptoms which have been indicated to be a better predictor of

outcome in BD elsewhere (e.g. Coryell et al., 2009). Prospective designs have the advantage

of exploring whether anxiety symptoms and disorders are reliable and valid predictors of

outcome, whilst controlling for potentially confounding variables which may otherwise bias

results, such as sociodemographic and illness variables. This has implications for therapy and

research, as understanding factors which mediate or moderate outcome are important for

determining likely risk factors for relapse and targets for treatment. Study 2 is an analysis of

partial data from the PARADES Psychoeducation study, a pragmatic randomised controlled

trial intended to determine whether structured group psychoeducation is more effective at

reducing relapse and improving well-being for individuals with BD than collaborative group

peer support sessions. The full protocol for this study is described elsewhere (Morriss et al.,

2011) and is explained in more detail in Chapter 6. Study 2 involved the analysis of data from

an opportunistic sub-sample of 259 participants, which lies within the mid-range for sample

sizes used in previous research to assess anxiety disorders and symptoms longitudinally (see

Table 3.1). However, almost half of existing prospective studies have follow-up periods of 12

months or less. Those with the longest follow-up periods have often collected data via

structured clinical interviews, with minimal analysis of self-report data. In addition,

frequency of follow-up rates have been variable, with data collected bi-weekly or monthly

during the first 12 months, but annually or semi-annually thereafter (e.g. Coryell et al., 2012;

Perlis et al., 2006). Sala et al. (2012) had a single follow-up point at three years post baseline

only. Study 2 examines data collected quarterly over a 96 week follow-up period and

includes observer-rated and self-reported anxiety data as covariates. Sociodemographic

factors, other psychiatric disorders and important illness characteristics are also controlled

for in Study 2 to assess the strength of anxiety correlates associated with outcome. Finally, a

number of studies have included individuals with historical and current anxiety disorders in

the 'anxiety' group (e.g. Sala et al., 2012; Perlis et al., 2006), whilst others have assigned

individuals with current anxiety disorders only, often not defining if those with historical

anxiety diagnoses were excluded or assessed as part of the comparison group (e.g.

MacQueen et al., 2003; Otto et al., 2006). This has often been done with no clear rationale or

discussion regarding the impact this may have had on the overall results. Study 2 aims to

improve on previous longitudinal research and although the sample size was medium in

comparison to existing studies the analysis was more rigorous in terms of the issues

discussed above. Specifically, Study 2 considered differences between those with current,

historical and no ADs to determine the most appropriate method of analysis. Extraneous

variables were also included in regression models to assess the impact of anxiety over and above other predictors of outcome longitudinally.

Table 3.1 *Overview of longitudinal studies exploring the impact of anxiety on outcome in BD (n=11)*

Author	N	Anxiety symptoms or disorders	Follow-up period
Prisciandaro et al., 2011	30	Disorders	8 weeks
Gaudiano & Miller, 2005	92	Disorders	28 months
Das et al., 2013	102	Disorders	45 days
Feske et al., 2000	124	Symptoms	~ 24 weeks
Macqueen et al., 2003	138	Disorders	3 years
Coryell et al., 2012	335	Symptoms	16.7 years (mean)
Coryell et al., 2009	427	Symptoms	17.4 years (mean)
Tohen et al., 2007	833	Symptoms	8 weeks
Perlis et al., 2006	858	Disorders	94.5 weeks (mean)
Otto et al., 2006	1000	Disorders	12 months
Sala et al., 2012	1600	Disorders	3 years

3.7 Experience Sampling Methodology (ESM)

Whilst longitudinal research provides a good estimate of the impact of anxiety in BD over time, it does not allow for the assessment of more subtle interactions between anxiety and mood and the context in which these interactions may occur. In addition, longitudinal data relies on participant recollection of symptoms and experiences over weeks or months, which is open to distortion and bias. ESM involves the collection of self-report data in repeated, real life situations by asking participants to complete paper or electronic diaries several times a day for a six or seven day period. ESM was developed to provide a more accurate means of measuring and understanding subjective experience and phenomena in psychological research. Using this method, the need for retrospective recall is minimised and the interaction of variables such as affect, anxiety, thoughts and behaviour can be assessed, allowing underlying mechanisms and process variables, rather than trait variables, to be observed (Ebner-Priemer, Eid, Kleindienst, Stabenow, & Trull, 2009). ESM also has advantages over traditional diary methods, generally having significantly increased data

points and collecting data over a longer period of time, increasing the validity of observations. Established ESM diaries typically provide momentary self-reported assessments of thoughts, feelings, activity and context and have been found to be sensitive to change in clinical samples including BD (Havermans, Nicolson & deVries, 2007; Myin-Germeys et al., 2003). Repeated assessments in ESM also allow for the identification of patterns of experience, the detection of fluctuations in measurements and the assessment of reactivity, specifically the likelihood that one variable will change in response to a change in another (Wenze & Miller, 2010). Current research suggests that cognitive and behavioural reactivity to life events and daily stressors may trigger mood fluctuations in BD (see Chapter 2, Section 2.3.6). As such, ESM was used in the current research to assess variations in mood, associated fluctuations in anxiety, and cognitive, behavioural and environmental triggers to those changes.

Whilst the publication of experience sampling research has gradually increased over the past 20 years, a recent review highlighted that the majority of ESM research exploring mood disorders has been focussed on participants with a diagnosis of UD (aan het Rot, Hogenelst, & Schoevers, 2012). More recently, ESM research with bipolar samples has begun to emerge, providing information about the dynamics of affect in BD. Existing ESM research suggests that euthymic participants with BD show little difference in the overall level of reported symptoms of positive affect (PA) or negative affect (NA) compared to controls, but do show greater variability of affect (Knowles, Tai, Jones, Highfield, Morriss & Bentall, 2007; Kwapil et al., 2011). Non-ESM research has found similar increased variability in activity levels compared to control participants also (Jones et al., 2005). To our knowledge, there are no existing ESM studies exploring the momentary interaction of anxiety and affect in BD.

Whilst holding many benefits, ESM also has limitations. Specific methodological issues relevant to this thesis, and steps taken to reduce these, are described fully in Study 3. In general, ESM may be vulnerable to technical problems due to relying on signalling devices

to prompt response, resulting in the loss of data. However, regular contact with participants throughout studies means issues can be resolved early and minimal data points lost. Repeated assessments over a relatively short time frame in ESM are associated with perceived increased burden to participants compared to longitudinal studies with less frequent assessments (see Ebner-Priemer et al., 2009 for a review). However, recommendations regarding the optimum number of responses per day have been provided from previous research to maximise compliance and minimise potential burden (Myin-Germeys et al., 2003). ESM has been found to be a feasible and acceptable methodology when measuring thoughts, mood and behaviour in bipolar samples, with low attrition rates and no prominent fatigue effects found in existing ESM studies (Depp et al., 2010; Husky et al., 2010; Myin-Germeys et al., 2003).

3.8 Measures

3.8.1 Measures of bipolarity, mood symptoms and functioning

All primary outcome and assessment measures used in this thesis were well-established, validated tools which have been used previously with BD and control participants. The SCID-DSM-IV (First et al., 1997) was used throughout this thesis to assess presence or absence of BD and other psychiatric disorders in clinical and control samples. Despite the limited inter-rater reliability of the SCID in clinical practice (see Chapter 1, Section 1.2.2), inter-rater agreement in research studies is much more promising and shows higher validity for BD diagnoses (Skre et al., 1991; Williams et al., 1992). All researchers received specialist training and supervision from experienced clinicians in the use of the SCID in this thesis and inter-rater reliability was assessed and reported where possible. Bipolar mood symptoms in all studies were assessed using the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Bech-Rafaelsen Mania Scale (MAS) (Bech, Rafaelsen, Kramp, & Bolwig, 1978), which are considered gold standard assessments and are widely used in BD research (Cusin, Yang,

Yeung & Fava, 2009; see Bech, 2002 for a review). Self-reported anxiety symptoms were assessed in Studies 1 and 2 using the anxiety sub-scale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983). This measure was relatively quick for participants to complete and there is good evidence for validity of the HADS sub-scales across a range of clinical samples (Bjelland, Dahl, Haug, & Neckelmann, 2002). Current anxiety symptoms were assessed in Study 3 using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). This is a well validated and reliable observer-rated interview which was delivered in a standardised format using the Structured Clinical Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear et al., 2001), which has been shown to increase accuracy and inter-rater agreement. Functioning outcomes in Study 3 were measured using the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman, Skodol, & Lave, 1992), which has been found to have better concurrent and predictive validity in clinical samples than other functioning measures including the Global Assessment of Functioning Scale (GAF) (Hay, Katsikitis, Begg, Da Costa, & Blumenfeld, 2003). All secondary outcome measures are described within individual chapters.

3.8.2 Novel measures

As ESM is a relatively new methodology for BD research, adaptations were made to existing ESM diaries to facilitate collection of data in Study 3. These are described in detail in Chapter 7, with a brief overview and introduction of important issues provided here. Previous research has collected mood data for 'positive mood' and 'negative states' (e.g. Myin-Germeys et al., 2003), where negative states have included facets of negative affect corresponding to anxiety *and* depression. Whilst anxiety and negative affect are regularly found to be moderately correlated (Nima, Rosenberg, Archer, & Garcia, 2013), research has shown that it is possible to distinguish aspects of negative affect which link to low mood (depression) and anxiety respectively (Sears & Kraus, 2009), and so items were generated to

measure positive affect, negative affect and anxiety independently to allow for the assessment of interactions and variability in all three scales. However, this was done whilst bearing in mind the potentially inherent association between anxiety and other affect domains.

Written data recording thoughts and activities were coded using pre-determined categories in Study 3. Although previous research has used open questions and coded responses, there is no available data on the reliability or validity of those coding schemes (Havermans et al, 2007; Maser & Cloninger, 1990; Myin-Germeys, Nicolson, & Delespaul, 2001). Correspondence with the authors found that this was due to codings assumed to require prior knowledge and context of participants to categorise accurately. As this implies a high level of researcher-interpretation and assumptions to assign category codes, the present study developed a novel coding scheme which was based on previous research but which was amended to ensure that this could be implemented systematically and reliably across raters, allowing for inter-rater assessments and checks. This is outlined fully in Study 3. Copies of the ESM diary and the novel coding schedule are provided in Appendix 9. Copies of all other measures used in this thesis are available from the author on request.

3.9 Patient and public involvement

This thesis was developed in consultation with service users with experience of BD at all stages, from inception to analysis and interpretation of findings. The interview schedule for Study 1, a qualitative study, was discussed with a Service User Reference Group (SURG), which included individuals with a diagnosis of BD, and the interview was piloted with two members of the group prior to beginning the study. This was to assess the appropriateness and relevance of the questions, and the usefulness of the study in general. A service user researcher was involved in the collection and analysis of the qualitative data, and the final themes extracted from the data were reviewed within a focus group with individuals with

experience of BD and anxiety. The PARADES program (Study 2) included a service user

researcher as a grant holder who was involved in the design of the Psychoeducation RCT.

Study 3 was also developed in consultation with a SURG with experience of BD who advised

on methodological and ethical issues. This included the content of the diaries, the number of

data points, and the use of appropriate incentives. This study was also piloted with

individuals with BD and control participants to gain feedback on the practicalities and

acceptability of ESM methodology prior to beginning the study. Feedback was used to refine

the final ESM.

3.10 Summary

This thesis employed a mixed methods approach to explore the nature and experience of

anxiety in BD, the interaction of anxiety and affect in BD and the impact of anxiety on mood

and other outcomes. A combination of qualitative and quantitative methods was used to

collect data in parallel and the results were combined to achieve the primary objectives

outlined in Section 3.2. This allowed the strengths of both methods to be integrated in the

final discussion (Chapter 8) and for the convergence of results across data sets from a range

of methodologies to be observed.

Chapter 4: The Experience of Anxiety in BD - A Qualitative Meta-Synthesis

4.1 Introduction

BD is associated with high rates of other psychiatric disorders, one of the most common

being co-occurring ADs, with up to 93% lifetime (McIntyre & Keck, 2006) and 32% current

ADs (Otto et al., 2006) reported for individuals with BD. Anxiety in BD has been associated

with poorer outcomes in retrospective, cross-sectional and, more recently, longitudinal

research (see Chapter 1, Section 1.4). The majority of current research has compared

individuals with ADs to those without. However, studies which have assessed the impact of

anxiety symptoms on outcomes in BD have found that diagnostic approaches may

underestimate the prevalence of anxiety in BD, and that exploring anxiety as a continuous

process is more beneficial (see Chapter, Section 1.4.4). Taken together, current research

indicates anxiety may be an inherent part of BD, involved in both the development and

expression of bipolar mood swings. However, a recent review highlighted that research in

this area is largely descriptive and is heavily biased towards clinical outcome and prevalence

rather than process or treatment (Provencher et al., 2012). As such, little is known about

anxiety in BD as an experience as opposed to a diagnostic category. Currently it is unclear

how anxiety experiences may impact on important life domains, the temporal nature of the

relationship between mood and anxiety symptoms, or whether the experience of anxiety is

something which requires specific attention in terms of future research and treatment. To

begin to answer these questions, there is a need to first review and clarify the existing

qualitative research to determine the next logical steps to progress this area of study. This

review used a meta-synthesis approach to examine relevant qualitative studies, as this

methodology generates new perspectives, directions and understanding from existing

research (Walsh & Downe, 2005).

4.2 Method

4.2.1 Overview

The findings from existing qualitative studies with individuals with BD were synthesised to

identify themes, patterns and inconsistencies related to the experience of anxiety. This was

done following the core principles of meta-synthesis: 1) identification and inclusion of

relevant research; 2) analysis of eligible studies, including classification and coding key

themes in the data; 3) aggregation of findings across relevant studies; and 4) synthesis and

interpretation of key themes and concepts (Thorne, Jensen, Kearney, Noblit, & Sandelowski,

2004). Although there are no existing qualitative studies specifically designed to target the

experience of anxiety in BD, a preliminary search of the literature revealed that a number of

existing studies investigating wider topics in BD did report anxiety-related themes and

experiences. This review synthesised existing qualitative research into BD and its associated

problems, focusing on papers in which the experience of anxiety was discussed.

4.2.2 Search strategies and study selection

Figure 1 illustrates how eligible studies were selected for review. Potential studies were

identified via a full search of abstracts published between January 2000 and July 2012 in

Psychinfo, MEDLINE, PubMed, CINAHL, AMED, Web of Science and Biomed Central. To

ensure quality, papers were only included if they were published in peer-reviewed journals.

In addition, only those written in English and using qualitative analytic methods were

included. Initial search terms were those commonly associated with BD (*BD, BPD, BD, manic*

depression, cyclothymia, affective psychosis, mania, hypomania) and cross referenced with

anxiety-related terms or ADs (*stress, worry, fear, generalised anxiety, panic, phobia,*

posttraumatic stress, obsessive compulsive disorder ,OCD, agoraphobia). However, this was

found to be too restrictive and returned no search results. The search criteria were modified

and search terms instead included the original BD terms cross referenced with qualitative research methods (*qualitative, interview, focus group, thematic analysis, grounded theory, phenomenological analysis*). This search yielded 312 studies and reference lists from all studies identified in this search were also reviewed. Any studies which included only carers and health professionals were excluded as the focus of this review was the direct experience of anxiety for individuals with BD specifically. Studies with child and adolescent samples (age 17 or younger) were also excluded as childhood anxieties are likely to differ in many areas from those experienced in adulthood (Beesdo, Knappe, & Pine, 2009). Finally, studies including participants with psychiatric diagnoses other than BD were excluded where the data were not analysed and reported separately for each clinical group. This was to allow the exploration of the experience of anxiety in BD specifically, as opposed to the experience of anxiety in any severe and enduring mental illness.

Of the remaining eligible studies, only those which discussed the experience of anxiety were included for review. As anxiety in BD has not been a primary focus of existing qualitative research, studies in which anxiety or anxiety-related terms, correlates or themes were discussed or explored were classified as meeting criteria for inclusion. Correlates of anxiety were determined by consulting the existing diagnostic literature on anxiety and core anxiety symptoms (First et al., 1997; Hamilton, 1959; McNaughton, 1996). Terms identified for inclusion were: *anxiety, stress, concern, worry, and fear*. Anxiety has been defined as "unresolved fear" or, synonymous to the definition of anxiety itself, "as a state of undirected arousal following the perception of threat" (Ohman, 2000). Core features of "anxious apprehension" are worry and concern about the future and what could happen (Barlow, 1991). Stress was also included as the psychological symptoms of stress have been defined as including anxiety and fearfulness (Dion, Tohen, Anthony, & Waternaux, 1988). In addition, stress is a term often used by respondents when asked to describe their experiences of anxiety (Melincavage, 2011), and likewise anxiety is a term used regularly when asked about

stress (Pietilä & Rytkönen, 2008), suggesting a close relationship between the two in terms of experience. For the purpose of this review where papers exploring anxiety in BD were relatively scarce, included papers were assessed as meeting criteria where anxiety was discussed at least once, provided this was accompanied by some description about the nature or impact of anxiety in relation to BD. However, the majority of studies included in this review each described several anxiety-related experiences.

Fifteen studies met full criteria and were included in this analysis (see Figure 4.1). These centred on 5 main research topics: the experience of living with BD, from initial diagnosis through to recovery (n = 7); medication and treatment adherence (n = 2); employment and work functioning (n = 3); reasons for substance use in BD (n = 2); the experience of receiving mindfulness as a treatment for BD (n = 1). The quality of each study was appraised by the first author (KH) using the Critical Appraisal Skills Program guidelines (CASP; Public Health Resource Unit, 2006), although studies were not excluded based on CASP scores. All studies met the screening criteria on the CASP for clear statement of aims and the appropriateness of using qualitative methods. CASP scores were based on the remaining eight questions regarding the design and execution of the research. As in previous qualitative meta-syntheses (Duggleby et al., 2010), a three-point rating system was adopted and each study was awarded a score of 1 (weak), 2 (moderate) or 3 (strong) for each criteria assessed. Each study received a total score out of 24, with higher scores representing better quality of research (see Table 4.1). In line with qualitative meta-synthesis methods, each paper was read several times and initial themes, issues and experiences related to anxiety in the original research were extracted (see Table 4.2). These were then collated into potential themes and sub-themes for the current meta-synthesis, and the original papers were revisited regularly to ensure that the emerging themes were reflective of the original data. All studies were reviewed by KH. Potential themes were discussed and reviewed regularly at supervisory meetings with co-authors SJ and FL to ensure reliability of extraction. Finally,

themes from each paper were synthesised to provide an integrative account of the

experience of anxiety in BD. These are summarised in Table 4.3. An overview of the studies

which contributed to each theme, and the themes within relevant studies which make up

each theme in the present study, is also provided (see Table 4.4).
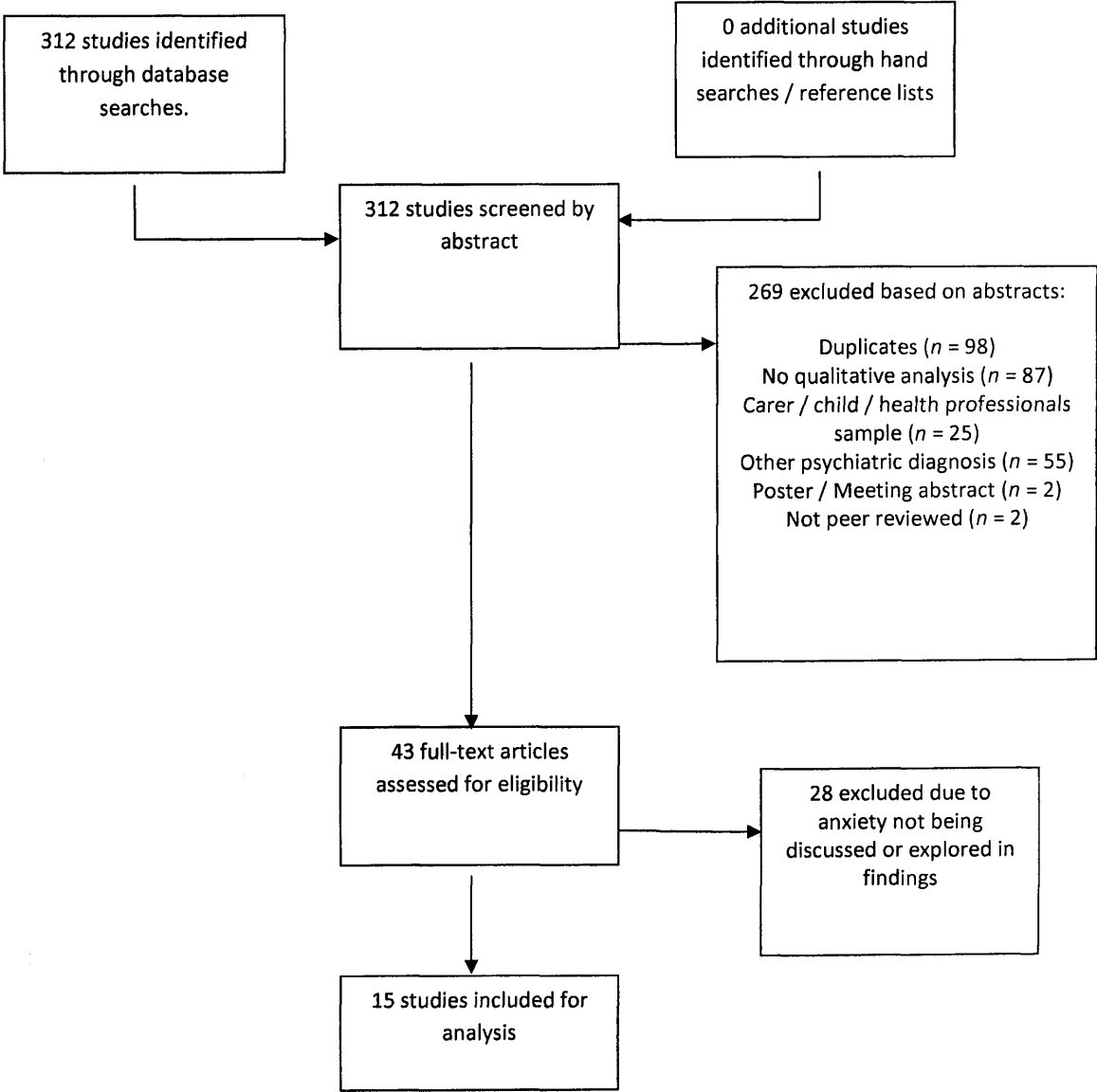
Figure 4.1. *Study selection process*

Table 4.1. *Quality appraisal of individual studies using the CASP guidelines*

Study	Research design	Sampling	Data collection	Reflexivity	Ethical issues	Data analysis	Clarity of findings	Value of research	Total CASP score
1. Tse & Yeats (2002)	3	2	2	3	1	2	3	2	17
2. Jones (2005)	1	2	1	1	1	1	1	2	10
3. Michalak et al. (2007)	1	3	3	1	2	2	3	3	18
4. Proudfoot et al (2009)	2	2	3	2	3	2	2	2	18
5. Michalak, Yatham, Kolesar & Lam (2006)	1	2	3	1	2	2	3	2	16
6. Jonsson, Wijk, Skarsater & Danielson (2008)	2	2	2	1	3	2	3	2	17
7. Rusner, Carlsson, Brunt & Nystrom (2009)	3	2	2	3	3	2	2	3	20
8. Michalak, Livingston, Hole, Suto, Hale & Haddock (2011)	3	3	3	1	1	2	3	2	18
9. Russell & Browne (2005)	1	2	2	1	1	2	2	2	13
10. Mansell et al. (2010)	3	2	2	3	2	2	3	3	20
11. Clatworthy, Bowskill, Rank, Parham & Horne (2007)	1	2	3	1	1	1	3	3	15
12. Sajatovic, Jenkins, Cassidy & Muzina (2009)	2	2	2	1	2	1	2	2	14
13. Healey, Peters, Kinderman, McCracken & Morriss (2009)	3	3	3	1	2	3	3	3	21
14. Ward (2011)	3	2	2	2	3	2	2	3	19
15. Chadwick, Kaur, Swelam, Ross & Ellett (2011)	2	3	3	3	2	3	3	3	22

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Table 4.2. *Initial coding of individual studies*

Reference	Research Topic	Participant Characteristics & Recruitment Source	Analysis used	Anxiety: Content & Triggers	Impact of anxiety	Management of anxiety
16. Tse & Yeats (2002)	Vocational outcome	N= 67, BD diagnosis; Mental health services & research database	Grounded Theory	Work stress; disclosure	Increased stress; inability to work	Structure; flexible working; supportive relationships
17. Jones (2005)	Employment	N = 11; BD diagnosis; Non-statutory mental health services	Grounded Theory	Work stress; lack of control; impact of mood symptoms; lack of support	Reduced work functioning	Work as positive distraction; structure & routine; support
18. Michalak et al (2007)	Occupational functioning	N= 35 (clinical sample); Bipolar I, II & spectrum; Inpatients & outpatients	Thematic analysis	Mood symptoms at work; fear of relapse; inability to work; restricted career prospects; disclosure; finances	Avoidance of occupational routine; avoidance of work commitments	Reduction of work stress: flexible working; support
19. Proudfoot et al (2009)	Diagnosis	N = 26; Recent BD diagnosis	Phenomenology & lived experiences framework analysis	Medication side effects; managing symptoms; fear of relapse; ability to identify early warning signs; BD as a chronic illness; future; fear of disclosure; work stress; familial relationships	Non-adherence to medication; fear; confusion; uncertainty about the future	n/a
20. Michalak, Yatham, Kolesar & Lam (2006)	Quality of life	N= 35 (clinical sample); Bipolar I, II & spectrum; Inpatients & outpatients	Thematic analysis	Employment; Lack of routine; social situations; lack of financial independence	Reduced quality of life	Routine; flexibility; support to achieve independence
21. Jonsson, Wijk, Skarsater & Danielson (2008)	Living with BD	N = 18; BD diagnosis; Outpatients	Qualitative content analysis	Fear of relapse; fear of failure; employment; education; finances; relationships; stigma	Reduced self-confidence; avoidance of planning & goal setting	Creating safe & manageable situations; reduction of stress; planning; routine; support; medication; time for self
22. Rusner, Carlsson, Brunt & Nystrom (2009)	Experience of BD	N = 10; BD diagnosis; Outpatients	Phenomenological philosophy	Anxiety as a changeable & constant state; fear of relapse; BD as a chronic illness; the future; new relationships; inability to work & study; medication; disclosure & loss of support	Decreased self-confidence; constant struggle to self-monitor; reduced income & financial difficulties; isolation	n/a

Reference	Research Topic	Participant Characteristics & Recruitment Method	Analysis used	Anxiety Content & Triggers	Impact of anxiety	Management of anxiety
23. Michalak, Livingston, Hole, Suto, Hale & Haddock (2011)	Internalised stigma	N = 32; Bipolar I & II; Voluntary organisations & general population	Thematic analysis	Stigma; Disclosure	n/a	Judicious disclosure
24. Russell & Browne (2005)	Staying well	N = 100; BD diagnosis; ≥ 24 months episode free; General community	Thematic analysis	Stress; sleep deprivation; work	Misdiagnosis; reduced work functioning	Managing symptoms; control over illness; flexible working
25. Mansell et al. (2010)	Recovery	N = 11; Bipolar disorder; General population	Interpretative Phenomenological Analysis (IPA)	Fear of relapse; medication side effects; disclosure; being defined by the illness	Avoidance; reduced socialising; over-compensation; 'comfort zone'	Stress reduction; acceptance of illness; social support
26. Clatworthy, Bowskill, Rank, Parham & Horne (2007)	Treatment adherence	N = 16; BD diagnosis; Outpatients	Thematic analysis	Stress; consequences of non-adherence; medication side effects; addiction	Triggered onset of BD; medication non-adherence; disengagement from services	n/a
27. Sajatovic, Jenkins, Cassidy & Muzina (2009)	Medication	Synthesis of results from 3 studies; N = 90; Bipolar I; Outpatients & inpatients	Thematic analysis	Medication side effects; addiction; long term damage	n/a	Medication
28. Healey, Peters, Kinderman, McCracken & Morriss (2009)	Reasons for substance use	N = 15; Bipolar I; Outpatients	Grounded Theory	Stress (work, home & trauma); anxiety as a result of drug & alcohol use; anxiety as a result of depression	Self-medication with substances; sleep disturbance	n/a
29. Ward (2011)	Substance use	N = 12; BD diagnosis; Outpatients	Phenomenological analysis	Finances; shelter; bipolar symptoms	Self-medication	n/a
30. Chadwick, Kaur, Swelam, Ross & Ellett (2011)	Mindfulness	N = 12; BD diagnosis; Participants in mindfulness group	Thematic analysis	Worry about relapse; the future	Less able to manage mood changes; increasing cycle of anxiety; sleep disturbance; fear of relapse triggers mood episodes	Mindfulness; learning not to dwell on worries; relaxation

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Main Theme	Subthemes	Description
1. Anxiety as a direct impact of living with BD	**Anxiety as a clinically and personally relevant experience**	The impact of anxiety on BD and well-being
		Anxiety as difficult to control
	BD & Identity	Being defined by illness
		Stigma & loss of self-identity
		Acceptance of diagnosis
	Living with BD & the fear of relapse	Fear of relapse & lack of control
		Anxiety as a trigger to mood episodes
		Reduced self-confidence
		Learning to manage symptoms reduces fear of illness
	Anxiety as a result of taking long-term medication	Side effects - physical & psychological
		Ambivalence towards medication
2. Living with BD increases anxiety about everyday stressors	**Anxiety about maintaining employment and financial independence**	Ability to support oneself
		Restricted career prospects & reduced work functioning
		Anxiety & guilt as a result of unemployment
		Fear of relapse
		Disclosure & stigma
		Managing stress is key to maintaining employment
	Anxiety linked to relationships and social support	Pressure on existing close relationships
		BD as a barrier to new relationships
		Support to monitor mood
	Fear of disclosure	Behaviour interpreted in terms of illness & impact of this
		Positive and negative experiences of disclosure
3. Managing anxiety as an integral part of managing BD	**Conflicting strategies to manage anxiety and stress**	Using substances to manage anxiety
		Removal of stressor
		Avoidance of stress - Balancing act
	Managing anxiety successfully	Structure & routine
		Psychological treatment

Main Theme	Subthemes	Contributing Studies	Original Themes
1. Anxiety as a direct impact of living with BD	Anxiety as a clinically and personally relevant experience	Chadwick et al. (2011) Clatworthy et al. (2011) Jonsson et al. (2008) Michalak et al. (2007) Rusner et al. (2009) Russell & Browne (2005)	Reducing impact of mood state; Relating differently to negative thoughts Illness perceptions An uncertain future Illness management strategies in the workplace; Loss A struggle to understand Identify trigger factors; Managing sleep and stress
	BD & Identity	Chadwick et al. (2011) Mansell et al. (2010) Michalak et al. (2006) Michalak et al. (2007) Michalak et al. (2011) Proudfoot et al. (2009)	Acceptance Medication; Sense of identity; Understanding; Avoidance of mania Identity Loss Expectations and experiences Questions of identity
	Living with BD & the fear of relapse	Chadwick et al. (2011) Healey et al. (2009) Jones (2005) Jonsson et al. (2008) Mansell et al. (2010) Michalak et al. (2007) Proudfoot et al. (2009) Rusner et al. (2009) Russell & Browne (2005) Sajatovic et al. (2009) Tse & Yeats (2002)	Adopting mindfulness practice to different mood states; Relating differently to negative thoughts Experimenting in the early course of the illness Positive effects of BD on work Being insecure in oneself; An uncertain future Avoidance of mania; Prior illness vs current wellness An illness that is intertwined with one's whole being The impact of bipolar symptoms; Uncertainty about the future Lack of continuity and consistency Stay well concept; Recognise warning signs Hopes / best-case scenario expectations of medications Factors related to my health
	Anxiety as a result of taking long-term medication	Clatworthy et al. (2011) Mansell et al. (2010) Proudfoot et al. (2009) Sajatovic et al. (2009)	Beliefs about medicines; Illness perceptions Medication; Prior illness vs current wellness Ambivalence about taking medication Expressed fears or concerns regarding medications

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Main Theme	Subthemes	Contributing Studies	Original Themes
2. Living with BD increases anxiety about everyday stressors	**Anxiety about maintaining employment and financial independence**	Jones (2005) Mansell et al. (2010) Michalak et al (2006) Michalak et al. (2007) Rusner et al. (2009) Tse & Yeats (2002)	Experiencing BD symptoms Life-style fundamentals Independence; Identity Loss An illness that is intertwined with one's whole being; A struggle to understand Factors related to support in the workplace; Factors related to people's attitude and welfare system
	Anxiety linked to relationships and social support	Mansell et al. (2010) Rusner et al. (2009) Russell & Browne (2005) Tse & Yeats (2002)	Avoidance of mania; Support and companionship An illness that is intertwined with one's whole being Access support; Recognise warning signs Factors related to support from my family, friends and professional people
	Fear of disclosure	Mansell et al. (2010) Michalak et al (2006) Michalak et al. (2007) Michalak et al. (2011) Tse & Yeats (2002)	Support and companionship Stigma and disclosure; Identity Stigma and disclosure in the workplace Judicious disclosure Factors related to my health
3. Managing anxiety as an integral part of managing BD	**Conflicting strategies to manage anxiety and stress**	Healey et al. (2009) Russell & Browne (2005) Tse & Yeats (2002) Ward (2011)	Managing stress; Living with a serious mental illness Managing sleep and stress Factors related to my health Life is hard; Trying to escape
	Managing anxiety successfully	Chadwick et al. (2011) Jones (2005) Jonsson et al. (2008) Mansell et al. (2010) Michalak et al (2006) Michalak et al. (2007) Tse & Yeats (2002)	Reducing and stabilising negative affect Positive effects of being in employment on BD A hopeful future Avoidance of mania; Understanding Routine Illness management strategies in the workplace The nature or structure of the work helped me stay on

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4.3 Results

Three emergent themes relating to the experience of anxiety were found: i) anxiety as a result of BD, ii) anxiety as a result of everyday stressors and iii) the management of anxiety in BD. To show to what extent each theme was represented in the papers included, each paper was numbered in Table 4.1 and studies are referred to in the results by their corresponding number. Quotes from the original papers were included to illustrate the issues and experiences discussed.

4.3.1 Theme 1: Anxiety as a direct impact of living with BD

4.3.1.1 Anxiety as a clinically and personally relevant experience

Before exploring anxiety in BD in depth, it is necessary to first establish whether this is an important experience which has a significant impact on daily life and well-being. In fact, this meta-synthesis found that anxiety, worry and stress were a persistent problem in daily life and, for many, a key aspect of their BD.

"Well, it is the management of my anxiety chiefly...that is one of the key things that I see as a problem in my BD..." [15, p.283]

"Stress is a big trigger for me. To a large extent, managing my illness is about managing my stress" [9, p.191]

Anxiety and stress were identified as specific triggers to relapse[9,11,15], whilst managing stress and worry featured highly in strategies for self-management and staying well[3]. In one study, a third of participants (n =5) felt stress had caused their BD, whilst a quarter (n = 4) felt that a mixture of heritability, physiology and stress was to blame[11]. Anxiety was experienced by many in the early stages of illness and one of the most commonly reported misdiagnoses prior to receiving a diagnosis of BD was clinical anxiety[9]. Having a diagnosis of BD was described as leaving individuals with "a daily life characterised

by worry and fear"[6], and despite recognising that worrying would not change or improve their situation, unsurprisingly this anxiety was often difficult to control[15].

"I can't affect the future by worrying about it, right, and the best thing is to relax about it and not to worry because worry serves no purpose what so ever. It just makes me get into a more and more anxious state, and then I really begin to worry, sleep less well and, um just worrying about the future all the time." [15, p.282]

However, whilst anxiety was clearly a frequent and relevant experience, this was not a constant state for all, and some individuals reported having times where they were completely free of worry and anxiety[7].

4.3.1.2 BD and identity: "My biggest issue is coming to terms with the loss of who I am" [4, p.125]

Receiving a diagnosis of BD for many was synonymous with concern and anxiety that having a mental health problem would mean always being defined by that illness. This was expressed not only in terms of being seen differently by others once they knew about the illness, but also through concern that a person's own sense of self would also change. This was a persistent source of anxiety, described at the time of initial diagnosis and beyond[3,4,10]. The potential consequences of these perceptions were an altered self-image, a loss of self-identity and the notion of no longer being the person they had once been[4,5,10]. There was also a concern regarding stigma as a result of the portrayal of BD in the media, and that this negatively affected the way society viewed the person and the illness[8]. However, not all studies included in this review discussed anxiety in the context of stigma, even when stigma emerged as a main theme[5]. Therefore the strength of this association is unclear.

Although regaining a sense of self-identity was not discussed directly as a way of reducing anxiety, this was explored due to loss of identity being reported as an 'anxious

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trigger'. To begin regaining a sense of self and identity, the first step for many was to accept their diagnosis and to see this as a part of who they are, rather than as everything they are[4,5].

"I am beginning to be able to live with BD and accept this as part of myself" [15, p.281]

This acceptance was an important part of recovery, and those who had been able to do so reported being better able to utilise pro-active, preventative strategies such as reducing stress levels to avoid relapse[10]. Strategies included attending local self-help groups, consulting professionals, accessing formal therapy, and subjective experience of 'trial and error' to find out what helps. On the whole, taking steps to learn more about BD and to understand the illness appeared to alleviate concerns about identity and restore a more positive sense of self[9,10]. In turn, this facilitated the ability to cope with a common anxiety expressed by many - the fear of living with BD and the possibility of relapse.

4.3.1.3 Living with BD and the fear of relapse: *"...at the back of my head there is always the worry that it might go a little too far...."* [10, p.204]

One of the most prominent triggers to anxiety was the unpredictable nature of BD and the constant fear of becoming unwell[3,4, 6,7,9,10]. The knowledge that BD was a recurrent and chronic condition was a significant concern at the time of diagnosis, when individuals were 'terrified' by the possibility of an oncoming episode[4]. However, this fear of relapse persisted long after initial diagnosis. For many there was a feeling of inevitability that a relapse would occur, which resulted in worry about the future and the ability to have a 'normal' life[4]. Whilst these worries were reported as a product of the unpredictable nature of BD, and of individuals being unsure of how to get help or manage their illness, the impact of this anxiety was that individuals felt unable to make long term plans or have dreams for the future[6].

"The fear is that your mood might soar or that you might become depressed and unable to do what you have to...you don't dare have long-term goals and dreams because you know that you are totally chaotic. You do not dare to dream" [6, p.1229]

Although symptoms associated with high mood could be experienced as enjoyable, any feelings of either high or low mood would often result in feeling scared or worried that this would develop into a full episode[4,10]. Some respondents felt that the potential occurrence of a manic episode was actually more worrying than early warning signs of depression, as the motivation to reduce positive symptoms in the early stages was much lower.

"Initially my worry was catching it when I am high.......when you're having a good feeling and you're thinking why stop it?" [15, p.281]

"Yeah, I think I worry more about the sudden bursts of energy than I do about the depression........the worry that it might go a little too far and I'll go manic" [10, p.204]

"...the mania terrifies me, the thoughts run through my mind like a speed train and I hate it." [4, p.124]

For others the prospect of a manic episode was feared because it was perceived to be inevitably linked to a subsequent spiral into depression.

"...I started to feel really good but became scared that a high was coming on and it would only be followed up with another bout of depression, and it is that that scares me the most" [4, p.124]

Even when individuals were relatively stable and free of relapse for two years or more, any feelings of positive or negative mood were often accompanied by a worry regarding their ability to control symptoms, fearing that it would 'go too far' and develop into a full episode[12]. As is often the case, despite being able to identify that worrying

persistently about relapse actually increases the likelihood it will happen, not doing so was very difficult.

"Being over-concerned and being worried about an onset of an episode, actually reinforces it and increases the likelihood of it becoming bad...so your attitude can evoke a very bad episode because of this kind of fearing" [15, p.283].

Conversely, despite fear of relapse being a key concern for many, some participants would at times attempt to prolong their positive mood symptoms through certain activities or the use of substances[13]. This was particularly true when experiences had positive consequences such as feeling good or increased productivity and work functioning[2]. This indicates that whilst the instability of mood change is undoubtedly a cause of worry and concern, in some circumstances this change is not problematic. However, despite enjoying the experience of positive mood symptoms, few individuals actually wanted to experience a full manic episode[12].

Overall, anxiety regarding relapse resulted in reduced self-confidence in an individual's ability to manage their illness, to make plans, or to succeed. Many reported a fear of failure in important life domains where planning ahead and making commitments might be important, for example work or relationships[4,6,7]. In particular, anxiety regarding managing BD seemed to stem from the fact that early warning signs of mood change were difficult to recognise subjectively, and that subsequently trying to manage behaviour was difficult due to being unaware of what needed to be managed or modified[4]. For some this lead to a tendency to avoid thinking about their illness when well, leaving no opportunity for preventative strategies to be put in place[6]. This itself had negative consequences as it prevented learning from previous episodes and subsequently managing future changes in mood[6]. In order to reduce anxiety about relapse, individuals reported the importance of understanding what caused their mood changes, gaining more individualised knowledge

about their own experiences and having confidence in their ability to positively influence their own situation. In turn, this increased motivation to be pro-active in response to fluctuations in mood[1,6,9].

"One of the best things I can say about my illness now is that I am not scared of it anymore. I believe that I have the power to control it. I have learnt how to manage my symptoms" [9, p.189]

4.3.1.4 Anxiety as the result of taking long-term medication

Two papers focussed on the experience, adherence and perception of taking medication, however worry and concern about medication was not limited to these studies alone[4,10,11,12]. Many participants had either experienced physical side effects, or worried about potential physical side effects of their medication, such as earache, nausea and weight gain[10,11]. Specific fears were also reported about the toxicity of psychiatric medication and the potential development of physical diseases, such as diabetes and organ damage[11,12]. Concern was expressed about having to take medication on a long term basis, both with regards to fear about the potential for becoming addicted to medication, and worries about withdrawal effects when medication was stopped[11].

"What worries me is the side effects of coming off. It is more the withdrawal of it than the taking of it that worries me" [11, p.661]

Concern was also expressed about the psychological effects of medication and the way it made respondents feel, or to be more precise, the way it stopped them from feeling. Blunting creativity, reducing energy levels and dulling the senses were all side effects that had been experienced and which lead to dissatisfaction, worry and non-adherence[4,10,11].

"I chose a therapist because I was afraid of the drugs. I ended up a drugged out zombie anyway..." [4, p.124]

"...and the problem is that they all put you into zombie mode....you have got no drive, no drive to do anything whatsoever" [11, p.661]

It was felt that medication took away feelings of normality and fundamentally changed a person's sense of identity, with individuals feeling unsure if how they felt was the 'real them', 'the medicated them', or a combination of the two[4,10]. For those who were very worried about side effects, discontinuing medication or reducing dosages without professional advice was the most common outcome[11,12].

Despite these concerns, medication was still reported as being one of the central factors to remaining well and stabilising mood[10]. Generally, individuals felt that the negative side effects and concerns about medication were bearable if they felt that, overall, their medication was beneficial in terms of affording them stability in their mental health and allowing a feeling of 'normality' in comparison to being ill[4]. Positive effects of medication were also reported with regards to anxiety, with medication helping to relieve anxious and depressive symptoms, and aiding individuals to relax, calm down and sleep[12].

Worries about medication in part stemmed from a hope, and subsequently a disappointment, that medication would manage symptoms, provide a cure or ensure normality[11,12]. As one would expect, anxiety was reduced if participants had taken medication for a period of time without experiencing any feared negative side effects[12]. It is interesting to note that participants in one study said that they had never before been asked about their own feelings regarding their illness or their treatment[12].

4.3.2 Theme 2: Living with BD increases anxiety about everyday stressors

In addition to illness-specific stressors, living with BD inevitably led to worry and anxiety about daily life stressors and activities. These were separated into three main subthemes and are discussed below.

4.3.2.1 Anxiety about maintaining employment and financial independence

Anxiety related to work and the ability, or inability, to have financial independence was experienced by those both in and out of current employment. Like most people, there was a desire to be self-reliant and to earn enough money so as not to be a burden to others[5,7]. For some, anxiety had resulted from the perception that they had never really had the option to be financially independent because illness had prevented attempts to study and work, which resulted in a sense of loss of control over one's own life, impacting negatively on identity and self-esteem[5,7]. From initial diagnosis there was a fear that having BD would mean being unable to achieve ones potential or have a career which is meaningful and fulfilling[3]. During the early stages of diagnosis, worry centred mainly on immediate financial problems, whilst those further on in the recovery process reported anxiety regarding long term goals, such as the ability to secure and maintain an occupation and apprehension about progressing in a chosen career[1]. Although some felt that securing employment was possible, the positions considered attainable following diagnosis were often those which held little interest or ambition[3].

"When I was diagnosed with BD I was very afraid that the illness would disable me to the point that I either couldn't work, or I'd have to work at something that I thought was below my original potential...so that I would be a housecleaner, but it wasn't what I wanted to do and it didn't give me meaning" [3, p.134]

Perhaps an even greater barrier to employment related back to the fear of relapse, and as a result there was a reluctance to make work commitments due to a constant worry that something would 'go wrong', that an episode would develop and that this would end in failure[3,7].

(In the context of talking about employment).... "The other thing that really makes me afraid is that I can't make a commitment, you know? And I, I can't commit to anything because it's always in the back of my mind that, when's this going to hit?" [3, p. 133]

This was particularly true for younger people with BD[6]. In addition, re-entering employment was prevented by the worry that this would mean the loss of government or state benefits, and, ultimately, all financial income if unsuccessful once in post[1,3].

"I feel really handcuffed because if I went out to do another job, and wasn't successful, I would fear losing my LTD (Long Term Disability benefit) *, and then be left with nothing"* [3, p.134]

These worries were often grounded in lived experience of relapse which had negatively impacted on the ability to hold down a job[3,5,7]. Whilst symptoms of mania or hypomania could lead to an increase in productivity and creativity, this was by no means an entirely positive experience. Hypomania at work was associated with increased feelings of anxiety, which was often due to individuals taking on more than they could manage or tasks which were not their responsibility, leading to inter-personal problems with colleagues[3]. Unsurprisingly, depression at work could also lead to anxiety and reduced performance.

"....I couldn't take any decisions, I saw everything in terms of worries, rather than problems that come up in the course of things." [2, p.72]

The impact of these anxieties was a feeling of reduced ability to find paid work and a loss of confidence about the ability to maintain employment[1]. Nevertheless, there were exceptions and not all experiences were negative. In some cases it was felt that BD had actually helped in career development, especially where personal experience had been used to pursue a related occupation in mental health or education[3]. An integral part of staying well and maintaining employment was managing stress. This included, when necessary,

reducing workloads, taking on a less stressful position, maintaining work day routines, taking

time out of work to cope with stress and making use of emotional and practical support from

colleagues[1,3,10]. Having the flexibility to put these measures in place was a worry for those

thinking about entering into employment.

"I worry about how my quality of life will change once I'm no longer a student and I

enter into the workforce and have to be at a certain place at a certain time every day, and

doing something at a certain time every day" [3, p.135]

It seems that providing support to find flexible employment and supportive work

environments may go some way to reducing anxiety and helping individuals to regain

independence.

4.3.2.2 Anxiety linked to relationships and social support

Relationships with family, friends and partners were identified as an important part of daily

life. Relationships were often key in both the cause and prevention of anxiety and relapse[1].

In terms of existing, close relationships, anxiety about social events and situations due to low

mood or reduced self-confidence was common. As a result, situations which involved

socialising with family and friends were often avoided, leading to worry about being

inconsistent with loved ones and putting strain on close relationships[10].

"I feel sometimes that I'm not consistent with my friends....if I'm maybe feeling a bit

down I may not be in contact with them or if I'm feeling quite anxious" [10, p.204]

For those looking to start new relationships, past experience lead to worry that

having a diagnosis of BD, and the ups and downs that go along with this, may cause

problems.

"I now have a relationship with a girl and I'm worried if I'll start doing too much or be depressed and that it will ruin things in my life again as it has done several times before" [7, p.165]

These concerns could result in closing oneself off to the possibility of new relationships, or making such relationships more difficult[7]. However, once stable, trusting relationships had been established, family and friends were more often identified as having an integral role in supporting self-management and staying well, with those closest often being relied upon to feedback changes in mood and behaviour[9,10]. Those who reported having supportive family relationships also reported decreased stress and increased confidence about their ability to find employment[1]. Similarly, those who confided in loved ones and colleagues ultimately allowed those around them to become more involved in their lives, bringing them closer together and strengthening these relationships[10].

4.3.2.3 Fear of disclosure

A common theme relating to living with BD, engaging in employment and establishing and maintaining relationships was anxiety about disclosure of bipolar diagnosis and the consequences of this. There was concern that being open about diagnosis would result in being appraised differently, no longer being seen as an equal, being perceived as someone who is unable to cope and that 'having a bad day' would be over-interpreted in terms of illness and becoming unwell[1,3]. The experience of disclosure was mixed; on the one hand, many were reluctant to tell anyone about their diagnosis. For those who chose not to share, this impacted upon their ability to make new friendships, feeling that new friends were only really ever 'surface friends' and feeling guilty about their lack of honesty[5]. For others the opposite was true, disclosing their diagnosis whilst unwell to too many people and later regretting the decision to do so, leading to feelings of "worry and angst"[8]. For those who were employed, anxiety regarding their ability to succeed in employment was linked not only

to relapse, but also to concerns about colleagues being informed of their diagnosis. For the most part, as with other triggers to anxiety, it was past negative experiences of disclosure and fear regarding negative responses from others which seemed to mediate this anxiety and the decision regarding whether or not to disclose[5].

Despite clear negative implications and experiences of disclosure, when done in the right way and with people who were trusted, confiding in others could actually be a very positive experience which ultimately reduced anxiety. Once out in the open, the need to worry about what others would think or about appearing ill in front of others when unwell was gone[8].

"It (being unwell at work) *was the best thing that ever happened to me...because now I could be sick in public and not worry about it"* [8, p.218]

"I used to worry about stigma coming up and, honestly, whenever I've disclosed...it's been more of an empowering thing because it's something you've come through and become stronger by" [8, p.218]

Rather than confirming the fear of being rejected, the ability to be open was actually reported to increase social networks, opening up access to additional help and support[10].

4.3.3 Managing anxiety as an integral part of managing BD: "managing my illness is about managing my stress" [9, p.191]

Managing stress and anxiety was repeatedly highlighted as a key factor in managing BD, and individuals reported various strategies which had been used to manage anxiety.

4.3.3.1 Conflicting strategies to manage anxiety and stress

A common reason for the use of alcohol or substances was to control anxiety and as a means of relaxation[13,14]. Alcohol in particular was used to manage day to day stressors such as work,

family life, parenting, emotional instability and ineffective socialisation, as well as major traumas such as bereavement[1,13,14]. Substances were also used in response to fear of relapse and worry about medication, and changes in mood symptoms led to use of drugs or alcohol in an attempt to self-regulate and 'feel normal' again, without the sedative effects of prescription medication[13]. In particular, feeling anxious when depressed led to substance and alcohol use.

"Well I drink two or three times a week now. I drink to quell my anxiety when I am in a depressive mode and get anxiety" [13, p.122]

However, it was often the case that using substances actually increased anxiety rather than reducing it[13]. Individuals often found themselves trapped in a difficult cycle, where substances and alcohol were used when daily stress and symptoms were too much to deal with. The result was that anxiety and mood symptoms worsened, in turn making life even harder to cope with[14]. In this way, these strategies had mixed effects, being effective in the short term but doing little to address the underlying anxieties over time. To break this cycle, and to manage stress and anxiety effectively, learning to manage the stressor often removed the urge to use alcohol or drugs.

"But luckily cause I don't have that stress I don't have that craving now" [13, p.123]

4.3.3.2 Managing anxiety successfully

To manage anxiety successfully, and to maintain mood stability, situations that were perceived as too stressful or taxing were often avoided in an attempt to control both manic and depressive symptoms[6,10]. Whilst effective in the short term, avoidance as a strategy meant that individuals never had the opportunity to test out or disprove their anxious thoughts or concerns, and so finding successful ways to manage daily life and stress were helpful. Having structure, better planning and clear routines were particularly useful in

reducing stress and maintaining "order in the chaos"[1,2,3,5,6]. Social support, having someone

to talk to, accepting help, taking medication and making time for oneself were also cited as

useful strategies for stress reduction[6]. Despite work stressors being identified as a cause of

anxiety, employment was also highlighted as a protective factor for keeping well and was

said to reduce the likelihood of depressive symptoms by providing distraction from negative

and anxious thoughts[2]. However, these strategies were not universally helpful. For example,

50% of respondents in one study exploring quality of life found that very rigid routines, such

as a set working day, were too structured and inflexible, having the opposite effect[5]. It

seemed that whilst having a routine was important, having the power to control and change

that routine to meet individual needs was even more so.

Whilst dealing with stress and anxiety was clearly an integral part of illness

management, a down side to this was that individuals felt that controlling stress often

resulted in overcompensating and over-regulating mood and behaviour. A common

experience was the feeling that mood was monitored excessively and behaviour was over-

controlled, resulting in the exclusion of enjoyable activities such as socialising due to the fear

of triggering mania[10]. Avoiding stress completely is impossible, and one participant described

the ability to manage stress and symptoms, but still enjoy life, as a "balancing act"[10]. In terms

of psychological treatments for anxiety in BD, a specific outcome of mindfulness therapy was

the reduction of anxiety.

"It (mindfulness)*has certainly helped me to manage mood changes I think....just*

reducing the amount of anxiety and worry in my life is one of the key benefits" [15, p. 282.]

However, only mindfulness was explored in the papers reviewed here, and so the

potential benefits of other psychological therapies for anxiety in BD is unknown and requires

further exploration.

4.4 Discussion

4.4.1 The interaction between anxiety and mood in BD

To illustrate the results of this meta-synthesis, a tentative model of the potential interaction between anxiety and mood in BD is presented (see Figure 4.2). Anxiety was reported as an important subjective experience across studies and was hypothesised by many respondents to be a causal factor in both the development and, even more so, the maintenance of extreme mood swings (Figure 4.2, box 3). This suggested a potential underlying vulnerability to dysregulation of anxiety and mood as a precursor to the development of BD (Figure 4.2, box 1 and 2), and anxiety as a trigger to subsequent bipolar episodes. This is consistent with current conceptualisations of BD in the literature, where anxiety has been proposed as both a precursor to and mediator of bipolar mood episodes (see Chapter 1, Section 1.6). Once established, the diagnosis of BD and the experience of extreme mood fluctuations had two main consequences for anxiety (Figure 4.2, box 6); specific illness-related worries, in particular fear of relapse, and worries related to other life stressors which were heightened as a result of living and coping with BD (Figure 4.2, box 4 and 5). Although these themes of anxiety were presented here separately for ease of description, these worries were intrinsically linked, with increased worry about relapse leading to increased anxiety about other stressors, which in turn increased anxiety about reoccurrence and reinforced the likelihood that a mood episode would occur. This is consistent with current research suggesting anxiety is linked to more severe outcomes, including increased number of episodes (see Chapter 1, Section 1.4). This suggests a potential vicious circle linking anxiety and mood symptoms in BD.

The mechanism by which worry about relapse led to mood episodes was not fully explored or well-defined in those studies included for review. However, there were

indications that this may be mediated to some extent by appraisals of mood swings and

subsequent behavioural responses.

| 1. Potential vulnerability to anxiety / stress | ←————————→ | 2. Potential vulnerability to BD |

3. Mood episode

(Depression / mania)

4. Diagnosis - Specific Stressors:
- Diagnosis
- Fear of relapse
- Medication side effects
- Disclosure / stigma

5. Enhanced life stressors:
- Obtaining and maintaining employment
- Finances and independence
- Relationships
- Planning and achieving goals

6. Anxiety

7. Ineffective or short-term coping strategy:
- Extreme appraisals / Constant worry / preoccupation
- Isolation
- Self-medication with drugs / alcohol
- Lack of knowledge about BD
- Avoidance of thinking about BD when well
- Increased symptoms of high or low mood
- Over-monitoring and modification of behaviour

8. Effective coping strategy:
- Increased understanding of mood experiences
- Management of anxiety
- Reduction of stress
- Structure & routine (flexible)
- Professional support
- Social network
- Ability to recognise early warning signs
- Feeling of confidence & control over mood

- **9. Reduced Anxiety**
- **Stability of mood**
- **Improved quality of life**

Figure 4.2. *Model of anxiety and mood in BD*

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Existing models of BD such as the cognitive therapy model (Beck, 1967) and the ICM (Mansell et al., 2007; see Chapter 2, Sections 2.4 and 2.6) propose that extreme and potentially conflicting appraisals about mood swings and oneself lead to behaviours which attempt to regulate mood but unintentionally exacerbate symptoms, leading to relapse. Anxieties were often characterised by extreme negative appraisals of the consequences linked to both depressed and manic episodes, and beliefs that mood should be monitored and controlled to avoid relapse. However, individuals also recognised that worry led to hypervigilance regarding any change in mood, limiting positive experiences as a way to avoid mania, but also reducing protective factors such as social support, meaningful occupation and the chance to challenge extreme appraisals (Figure 4.2, box 7). These are potentially conflicting, as thoughts about having to control mood and avoid relapse co-exist with beliefs that monitoring mood and behaviour is restrictive. Behavioural responses were also implicated, with short term, but ultimately ineffective, coping strategies often used to manage mood and anxiety, including rumination, use of drugs and alcohol and failure to plan ahead or think about mood when well. This description of anxiety about relapse as a potential driver to attempts to control mood swings which ultimately exacerbate mood symptoms fits well within the ICM of BD (Mansell et al., 2007). This also links to other related psychological theories of human behaviour and control, for example perceptual control theory (PCT; Powers, 1973; adapted by Mansell, 2005). PCT proposes that people continually compare their current state to their desired state, and take action to reduce any discrepancy that is perceived between the two. PCT suggests that psychopathology, such as extreme mood swings in BD, occurs when behaviour attempts to modify the same quantity, in this case mood, based on two or more conflicting desired states or goals, which interrupts the achievement of all goals (Mansell, 2005). For example, in this meta-synthesis PCT would propose that an individual's desired internal state would be the image of the self as a stable

and successful person, and that this is the internal concept which is driving attempts to control mood when changes in internal state are detected. However, the concept of ideal self has two conflicting goals here - to be successful at avoiding relapse by strictly monitoring and controlling mood, and to have positive experiences and be successful in achieving life goals by engaging in relevant activities. As it is impossible to resolve this conflict, no control is maintained and the individual is left fluctuating between the two goals, which leads to distress, such as lack of positive experiences, anxiety, depression and mania. In particular, attempts to avoid relapse are unstable, as they involve moving away from feared negative outcomes but do not provide a clear goal to head towards (Mansell, 2005). Conflict is resolved by the re-organisation and prioritising of goals. In the case of the TEAMS treatment approach (Mansell et al., 2007), it is suggested that the primary goal could be adapted to focus instead on being able to tolerate fluctuations in internal states without engaging in behaviours which attempt to control mood. This would potentially reduce the exacerbation of mood symptoms and associated anxiety and hypervigilance regarding early warning signs.

4.4.2 Clinical implications

In terms of helping people with BD, it is possible that supporting people to manage their mood would go a long way to reducing anxiety, whilst being able to tolerate and manage anxiety would likely have a positive impact on the experience of mood symptoms and fluctuations. Current psychological interventions such as IPSRT (Frank et al., 2002) and CBT tend to focus on identifying early warning signs of illness and advocate taking action straight away to prevent escalation of symptoms. However, this may actually be unhelpful to some people as this may induce hypervigilance and anxiety. Whilst existing psychological approaches such as CBT do try to help people normalise their mood experiences rather than over-control them, this may not be as effective for individuals with BD who have very extreme appraisals of any fluctuation in mood and who may be unable to differentiate

between normal and problematic mood changes (Mansell et al., 2007). As such, it has been suggested that helping people to accept and tolerate a greater degree of mood change without taking action to control mood may be an important adaptation to current psychological treatments, in particular those for BD.

NICE (2006) currently recommends additional, rather than combined treatment for anxiety in BD where anxiety is problematic (see Chapter 1, Section 1.7), however this does not appear logical or even possible due to the apparent inseparable nature of the two experiences described here. In addition, problems exist for this client group in that standard pharmacological therapies for anxiety, mainly serotoninergic antidepressants and benzodiazepines, are often contraindicated in BD due to the potential for interaction with mood stabilising medications and being linked as a possible trigger to mania, especially when used as long term treatments (El-Mallakh & Hollifield, 2008). Concern about medication side effects was also found to be a significant source of anxiety in this meta-synthesis, and so providing a range of therapeutic options, such as psychological therapies informed by service-user preference, may be key to managing mood and anxiety effectively.

Individuals were able to report clear sources of anxiety and worry, all of which are potential targets for therapy. In particular, lack of knowledge about BD, lack of confidence to prevent or cope with relapse, lack of social support and lack of meaningful occupation and financial security were all highlighted as key areas of concern. To some extent many of these issues are covered in existing CBT interventions for BD, however perhaps not optimally. Ensuring psychological interventions for BD focus on these as important issues and in relation to bipolar mood experiences and anxiety may be beneficial. Whilst anxiety was often felt to be a difficult experience to control, individuals did report positive coping strategies for mood and anxiety. Unsurprisingly, these were generally the opposites to sources of anxiety and included increased knowledge about BD, supportive relationships and structured routines. However, the latter strategy came with a caution, with some individuals finding

very rigid and inflexible routines counter-productive or even harmful. This has potential

implications for existing treatment approaches such as IPSRT (Frank et al., 2002), which

attempts to prevent relapse by stabilising social rhythms and routine. IPRST has so far

received mixed results (Frank et al., 2005), which may be due to the possibility that strict

routines are not universally helpful. Mindfulness was reported to reduce anxiety specifically

and to provide the skills needed to manage both anxiety and mood. It is therefore possible

that other psychological treatments may be helpful in reducing anxiety in BD, and exploring

which methods and techniques are most effective for which people is imperative in

developing more effective treatments.

4.4.3 Limitations and areas for future research

Participants in all studies were recruited via convenience sampling and were

inpatients or outpatients of mental health services or self-referred members of the public. As

a result, it is possible that these participants may differ from those who are not supported by

services or actively participating in research, by being more motivated to seek treatment,

better at managing their illness, or more accepting of a medical model, their diagnosis and

psychiatric and / or psychological interventions. For this reason, strategies which have been

highlighted as useful in the self-management of mood and anxiety, such as psychoeducation

and acceptance of diagnosis, may not be as relevant to those outside of this arena. Future

research which recruits participants from outside of services and in the wider general

population would likely include important accounts from individuals with BD which may have

been missed. However, even then research would only include participants who are willing

and motivated to participate, and so likely this will always bias results to some extent.

In order to explore the link between anxiety and BD, assumptions were made about

anxiety-related constructs and correlates. These were drawn from widely accepted research

and clinical descriptions of anxiety and so allow the exploration of relevant issues. However,

it was not possible to comment on the level of anxiety generated by each of the themes or sub-themes. With the exception of one study, all respondents were assessed as being outside any full mood episode, although it is possible participants may have experienced sub-syndromal symptoms. For this reason it cannot be said that the worries and anxieties reported are influenced by, or are purely the product of, extreme mood states, and suggests that the anxieties reported persisted even during periods of relative euthymia. Future research should report the current mood of participants to provide the context in which experiences are reported.

4.4.4 Conclusion

This meta-synthesis provides an initial insight into key triggers of anxiety for individuals with BD, how this can impact on daily life, and begins to explore the complex relationship which exists between anxiety and mood symptoms and how this may lead to worse outcomes. However, this is a preliminary review of the existing research, none of which focuses directly on anxiety and BD. Future qualitative research is required which asks more direct questions regarding not only what triggers anxiety, but how and why this impacts on daily life, and what help, if any, do individuals want to manage anxiety. Similarly, further research exploring the strategies used by those individuals who are able to manage anxiety alongside their mood and day to day stressors seems integral in developing solution-focused interventions.

Chapter 5: Study 1 – A qualitative study exploring the lived experience of anxiety in BD

5.1 Introduction

High levels of anxiety in BD have been well documented, as has the potential role anxiety may play in determining poorer clinical outcomes (see Chapter 1, Section 1.3 and 1.4). A limitation of current research is that anxiety has been explored only quantatively with a focus on prevalence and clinical outcome. Consequently, little is known about the meaning or significance of anxiety for individuals with BD, or about the underlying processes which may explain the relationship between anxiety and mood. A review of the literature in Chapter 4 found no existing qualitative studies which have explored the experience of anxiety in BD directly, however there are several qualitative studies which have explored other key issues and which have discussed anxiety in the context of those experiences. A qualitative meta-synthesis integrating data from these studies (Chapter 4) found that individuals with BD reported anxiety as an important subjective experience, with worries related to living with BD but also worry about normal daily stressors which were amplified by having a diagnosis of BD. In particular, anxiety was cited as a trigger to the onset and maintenance of mood episodes. In general, fear of relapse and negative beliefs about mood swings resulted in behavioural responses aimed at controlling mood, but which often had the undesired outcome of exacerbating mood symptoms. However, as previous research has not explored anxiety in BD directly, the mechanisms which underpinned these processes were not well-defined and did not differentiate from interactions between anxiety and depression, and interactions between anxiety and mania. The present study aims to expand on current research and the results of the meta-synthesis in Chapter 4 by exploring the subjective experience of anxiety in BD directly.

5.2 Method

5.2.1 Design

Thematic analysis (TA) was used to explore the data. This was the most appropriate method

for the primary research question, as TA is not restricted by any one theoretical framework

and allows themes to be grounded in and driven by the data, which is key when exploring a

relatively under-researched area such as the experience of anxiety in BD where qualitative

data are scarce (Braun & Clarke, 2006). TA provides a flexible yet structured framework

within which consistent and contrasting patterns and themes from subjective accounts can

be identified, and attempts not only to describe but to interpret experiences to better

understand associated contexts and processes in the setting of daily life (Boyatzis, 1998). TA

recognises the active role of the researcher in the interpretative process (Holloway & Todres,

2003) and therefore the authors documented their assumptions and expectations regarding

the results of the study prior to analysis. The research team was multi-disciplinary and

included the author (KH), a research assistant and doctoral student completing a thesis

exploring the experience and processes underlying anxiety in BD, two academic clinical

psychologists (SJ & FL) with a focus on psychological processes and interventions in BD, an

academic with expertise in qualitative research (SP), and a service user researcher with a

diagnosis of BD (PB). Based on the current literature and clinical experience, the primary

expectation of the research team was that anxiety would be an important experience in the

expression of mood episodes and that anxiety would be an integrated experience within BD.

5.2.2 Recruitment

As a formal power analysis is not appropriate in a qualitative study, sample size is generally

accepted as being the point at which no new themes or information are observed in the data

(Tuckett, 2004). A review of the literature found that thematic saturation generally occurs

between 12 and 24 interviews (Guest, Bunce, & Johnson, 2006), and so the recruitment

target for this study was set within this range. There is a debate regarding whether thematic

saturation can ever truly be achieved, and it has been suggested that while ever a researcher

is examining and analysing a dataset, there is always the potential for new themes and

information to emerge (Strauss & Corbin, 1998). As such, thematic saturation was defined in

this study as the point at which new information no longer added anything novel to the

overall theoretical understanding of the experience of anxiety in BD. This study was reviewed

and approved by the Lancaster NHS Research Ethics Committee (reference: 10/H1015/5).

Recruitment was largely focused in mental health and primary care services and service user

groups in the North West of England from March 2010 to July 2010. Self-referrals were also

encouraged through advertisements in the local media. Potentially eligible individuals were

invited to take part in a study to talk about their experience of anxiety in BD. Interested

individuals obtained more information about the study from their health care professionals

or by contacting the research team directly. Participants were required to meet criteria for

primary BDI or II confirmed using the SCID-DSM-IV (First et al., 1997). To avoid restricting

participant's responses during the qualitative process, likelihood of meeting criteria for BD

was assessed initially using the Mood Disorders Questionnaire (MDQ; Hirschfeld et al., 2000)

as a screening tool, and diagnosis was confirmed on completion of the qualitative interviews.

Individuals were excluded if experiencing a major depressive or manic episode, currently or

within the previous four weeks, or if experiencing current suicidal ideation or suicidal intent.

Participants were not excluded based on the presence of sub-syndromal symptoms of

depression or mania, which were expected in this client group. However, to understand

reported experiences in the context of current mood state, symptoms were assessed at the

time of interview using the Bech-Rafaelsen Mania Scale (MAS) (Bech et al., 1978) and the

Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Current level of anxiety was

measured by self-report using the anxiety subscale of the Hospital Anxiety and Depression

Scale (HADS-A) (Zigmond & Snaith, 1983). All participants were required to give written, informed consent prior to participation, to speak English to a level to enable them to complete the interviews and questionnaire measures independently, and to be aged between 18 and 65 years of age. Purposive sampling (Patton, 1990) was employed to ensure the final sample comprised individuals who had a range of scores on the anxiety spectrum (HADS-A), a variety of ages (18 – 65), and both male and female respondents. Recruitment continued until thematic saturation as defined in Section 5.2.2 was achieved. In total, 33 participants were referred to the study. Nine participants were excluded at pre-screen for the following reasons: aged > 65 years (n = 2); meeting only sub-threshold criteria for BD (hypomania without depression or hypomania < 4 days with depression) (n = 3); meeting criteria for schizoaffective disorder (n = 1); experiencing a current episode of depression or mania which did not remit before the end of the study (n = 3). A further three participants were excluded prior to analysis due to having missing MAS and HAM-D data, making it impossible to determine to what extent their reported experiences may have been influenced by their current mood state. Twenty one participants were included in the final analysis.

5.2.3 Procedure

A semi-structured interview allowed the interviewer to ask key questions specific to anxiety in BD, whilst also allowing flexibility to diverge and explore any important or unexpected ideas or responses in more detail (Britten, 1995). A basic topic guide was developed by the research team in consultation with a service user reference group (SURG), including several members who had personal experience of anxiety and BD (see Appendix 1). Following this, the interview was piloted in full with two individuals with BD and feedback was sought from respondents regarding the appropriateness, clarity and relevance of the interview to the

research question. The final topic guide included, but was not restricted to, the following issues:

1. An opening question asking if the participant had experienced anxiety, now or in the past. Participants were asked to recall an example of a recent or memorable anxious experience if possible. The language used by the participant to describe anxiety (e.g. stress, worry, agitation) was then adopted by the interviewer.

2. The context in which anxiety may occur and how this is managed

3. If and how the person felt their anxiety and mood were related to each other.

4. If there were any consequences (positive or negative) linked to anxious experiences

5. Additional questioning to explore and expand on important issues raised in relation to anxiety and mood

At the end of the interview participants were given the opportunity to raise any other important issues in relation to their experience of anxiety in BD that had not already been discussed. All interviews were conducted in person, either at the participants' homes or at a University site, according to individual preference. Interviews were completed over one or two appointments depending on participant preference and lasted between 29 and 110 minutes (mean: 66 minutes, SD: 18 minutes). Participants were interviewed by either a research assistant (KH, n = 10) or a service user researcher with a diagnosis of BD (PB, n = 11). Participants were informed prior to interview which researcher they had been assigned.

5.2.4 Analysis

The data were analysed according to the key principles of TA (Braun & Clarke, 2006). All transcripts were analysed as soon as possible after completion using a constant comparative approach in order to inform subsequent interviews (Glaser, 1965). This involved the constant comparison of all codes, categories and themes identified in the first and then subsequent

interviews. This allowed the topic guide to be amended prior to each interview so that common experiences were explored in more detail and unexpected or unusual issues could be discussed with future participants to understand contrasting experiences. Each transcript was read and coded firstly by the interviewer (KH or PB) and all transcripts were coded independently in the first instance and then compared to check and refine the coding frame and to ensure this was being applied in a structured and consistent way. The initial codings were discussed within the wider research team, who provided consultation and training during the planning, analysis and interpretative stages of the analysis. In order to ensure the analysis was carried out consistently, the research team met regularly to refine the specifics of the identified themes, to re-categorise and re-order themes as new data were collected and to generate clear and comprehensive definitions for each. Particular attention was also paid to data which the themes did not capture. The overarching themes were consistently related back to the data corpus to ensure that these were reflective of the individual experiences reported and were relevant to the main research question. Final themes were determined by clustering connected themes which most strongly reflected participant's views and experiences of anxiety in BD. As part of a follow-up study all participants were invited to participate in a focus group to review the identified themes and discuss potential ways of helping people with a diagnosis of BD who experience anxiety. Three participants who completed the qualitative interviews attended these focus groups (two male, one female) and confirmed that the final results of Study 1 were reflective of their own experiences. Two additional participants with personal experience of BD who had not completed the interviews also attended the focus group and agreed the identified themes were a true representation of their experiences of anxiety and mood.

5.3 Results

5.3.1 Participants

Sociodemographic and clinical characteristics of the final sample (see Tables 5.1 and 5.2) show that individuals included in this study were generally representative of BD populations reported in other research (Kessler et al., 2005), with the exception of ethnicity, as all participants were white British, and diagnosis, as all except one person met criteria for BDI. The median age of respondents was 44 years (range 25 – 62 years). Whilst this sample had mainly completed tertiary education, the majority were out of work and had a range of marital and living circumstances. Experience of mood episodes varied greatly and ranged from one to thirty or more episodes of depression and mania. All except two individuals had been hospitalised for a mood episode at some point in their lives. Participants were found to have a range of scores on the HADS-A, from no or minimal anxiety to severe anxiety symptoms. Over half of the sample had scores within the moderate anxiety range. Mean scores were calculated for current mood symptoms on the HAM-D and the MAS. On average, participants had minimal manic symptom scores but mild symptoms of depression. Fourteen participants (66.7%) met criteria for one or more current AD and nine participants (42.9%) met full criteria for at least one lifetime AD. Three participants had a current substance use or eating disorder. Information about ADs and other psychiatric disorders was missing for one participant who declined to complete the SCID interview beyond the mania, depression and psychosis modules. Participants included those both in and out of mental health services. Eight participants were recruited as self-referrals from the community (n = 1) and local peer support groups (Bipolar UK; n = 7) and three participants came from a university participant database of individuals who had taken part in previous research and consented to being contacted. The remaining 13 participants were referred to the study by health professionals working in primary (n = 7) or secondary care services (n = 6).

Table 5.1. *Sociodemographic and clinical characteristics of the final sample included for analysis (n = 21)*

Sociodemographics:	N (%)	Clinical characteristics:	N (%)
Age	44	Bipolar diagnosis:	
Age (range)	25 – 62	BDI	20
Ethnicity: White British	21	BDII	1
Gender		Age 1st mood disorder diagnosis	25.71(10.65)*
Male: 8			
Female: 13		Age at bipolar diagnosis	34.14 (9.83)*
Highest level of education:		HAM-D	9.81 (7.43)*
Secondary	3	MAS	1.57 (2.27)*
Further	9	HADS-A:	11.19 (4.59)*
Higher	9	0-7 (normal)	4
Employment status:		8 - 10 (mild)	3
Employed (paid)	5	11 - 15 (moderate)	12
Employed (voluntary)	2	16 - 21 (severe)	2
		No. current anxiety disorders:	
Retired	4	0	6
Student	1	1	5
Unemployed	9	2	5
Marital status:		3	2
Married / cohabiting	7	4	2
Divorced / separated	7	Missing	1
Never married	7	Current anxiety disorders:	
Family:		Social Phobia	7
Children < 16 years	4	Agoraphobia	2
Children > 16 years	12	GAD	9
Living arrangements:		PTSD	3
Spouse / Partner	5	Panic with /without Ago	3
Spouse / partner & children	2	OCD	3
Relatives & children	1	Specific phobia	2
Relatives	4		
Alone	9		

Where ages or symptom scores are reported these refer to the group mean and standard deviation

Table 5.2. *Additional clinical characteristics of the final sample (n = 21)*

Clinical Variable	N	Clinical variable	N
No. depressed episodes:		No. (hypo)manic episodes:	
0	1	0	0
1 – 6	2	1 - 6	3
7 – 11	2	7 - 11	5
12 – 29	5	12 - 29	9
30+	**10	30+	4
No. past anxiety disorders:		Past anxiety disorders:	
0	11	PTSD	4
1	7	Specific phobia	2
2	2	Panic with /without Ago	4
Missing	1	Missing	1
No. previous hospitalisations: 0	2	OCD	1
1 – 6	14	Other current psychiatric disorders:	
7 – 11	4	Substance abuse / dependence	1
12 – 29	1	Eating disorder	2

5.3.2 Findings

Participants taking part in this study reported that they were pleased to have the

opportunity to talk about their experiences of anxiety in more detail. In general participants

were able to remain focused on anxiety as the key issue for discussion and unless otherwise

stated the quotes presented relate directly to the experience of anxiety in BD. Where quotes

relate to the broader experience of BD or other relevant issues, this is highlighted. Many

people stated that they had never been asked about their experiences of BD or anxiety in

depth before and talked about their experiences at length, providing a large amount of data.

As such, the decision was made to report the data in two parts. The present study reports

four key themes related to the experience of anxiety in BD, the interaction of anxiety with

mood symptoms and the consequences of these experiences. Participants also discussed

self-management of anxiety extensively together with both positive and negative

experiences of accessing treatment for anxiety. The analysis of this data is presented

elsewhere (Jones et al., in prep). The number of participants contributing to each theme is quoted in brackets after each theme title.

5.3.2.1 Theme 1: "Which came first?" The temporal relationship between anxiety and bipolar mood episodes (n = 18)

This theme captures the temporal relationship and interaction between anxiety and mood, from first experience to post-diagnosis. Many participants perceived a clear link between early anxiety and the later onset of mood episodes. Several people described themselves as always having been an "anxious person" or being someone who was "wired that way", suggesting a susceptibility to stress and anxiety from an early age.

"I think I have always been an anxious person, I was always a worrisome child probably from about the age of 6 or 7, and I have had bouts of it ever since, of anxiety, stress, worry, agitation, yes it's definitely been there for as long as I can remember."(Participant 8)

Early anxiety in childhood and adolescence was often linked to traumatic life events, such as assault or physical and emotional abuse. Trauma was identified by some as the trigger to bipolar mood episodes and anxiety, however it was difficult to identify from the data exactly how trauma had led to mood instability. Unresolved feelings following traumatic experiences were highlighted as the main reason for persistent anxiety following trauma, often due to a lack of support or intervention at the time. Not addressing traumatic experiences at the time of occurrence was linked to difficulties in processing experiences and emotions later on.

"Part of difficulty in describing feelings and emotions is that to cope over the years, I have kind of shut them down. Resulting from a really bad experience about 10 years ago, just over 10 years ago.....well it was an assault and that generated sort of crippling anxiety.....

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If that hadn't have happened, you know things might have gone a lot better 10 years ago and

it probably set me back 10 years." (Participant 13)

In contrast, some participants felt that their problems with anxiety had come only

following their diagnosis of BD and being told they had a chronic illness. However, once

anxiety had begun it often continued as a persistent problem, even after having time to

adjust and achieving periods of mood stability.

"The anxiety started with the breakdown. The anxiety started with the realisation

once I suppose when you think about it, when you get realisation when somebody is telling

you [that you have BD] *and telling you and everybody is telling you and telling you, the*

anxiety started coming in then because I was panicking and I knew there was something

wrong." (Participant 10)

Some participants were unable to pinpoint whether bipolar mood episodes or

anxiety had come first, but still felt that anxiety was a fundamental part of their mood

instability. For some the experience of depression, mania and anxiety were so closely

intertwined that being able to dissociate anxiety and mood was very difficult.

"...it's difficult to know whether it's the bipolar that brought it on or, the other way

round, whether the anxiety brought the bipolar on." (Participant 3)

Overall, there was a general consensus that, whether linked to mood or anxiety,

participants had always been quite 'up and down' in terms of affect, experiencing

fluctuations in all mood states from an early age, and prior to any formal diagnosis of mood

or anxiety disorders. Some reflected that anxiety and mood may actually be two features of

the same phenomenon, with anxiety being a facet of BD rather than a distinct or separate

experience.

"Not really sure, I don't know how long I have had bipolar. I know I have always been up and down, even in third year secondary school I had a lot of problems.....even though people said I was just an awkward teenager but even then I used to get panic attacks......I can't really say, whether that is just part of me or part of the bipolar" (Participant 19)

5.3.2.2 Theme 2: The specific interaction of anxiety with symptoms of depression and mania (n = 20)

Theme 2 explores the interactive relationship between anxiety and symptoms of high and low mood. Anxiety was described as both a persistent experience and an episodic phenomenon both within and between participants. Whilst participants often reported consistent, low level anxiety, there were also times where 'bouts' of extreme anxiety occurred. These were very much linked to changes in mood, and anxiety could act as a trigger to episodes of depression and mania, co-occur within a mood episode of either type, or be the consequence of experiencing a severe mood episode.

"...I think with the extreme highs and the extreme lows, the anxiety was extreme as well, so where in the past, the anxiety has been little, not a lot, the highs have been quite high, the lows have been quite low, they were all the highs were extreme, the lows were extreme and the anxiety was extreme at that time..." (Participant 10)

Anxious experiences were regularly described as being synonymous with feelings of depression and mania observed in mixed episodes. Racing thoughts, agitation and restless energy were central to the experience of anxiety but were also accompanied by simultaneous feelings of a lack of energy, loss of appetite and decreased motivation.

"I got what I describe....as the Christmas tree light effect in my head. If you can imagine.. a Christmas tree with, with the little lights that flash on and off, and you attach...a light going on to..a thought. Or even not sometimes a thought but.. a word, right? ....So like

you're, you're running round trying to.. swat flies because these lights are coming on and going off and you, and you think- and, and it, it really does sort of send you..mentally insane." (Participant 2).

Sleep disruption was a frequent problem when feeling anxious and linked to worry about becoming depressed or manic, and to the exacerbation of mood symptoms. Participants described the mind being constantly filled with worries and the body with an influx of nervous energy. This would lead to insomnia and longer term disruptions in regular sleep patterns, ultimately having two main outcomes: worry about the consequences of prolonged loss of sleep on mood, or triggering an episode of high or low mood.

"And then the anxiety'll feed into....the anxiety component is like erm....it, it, it's the breeding ground it's where where the ruminations starts. And that again triggers....a mania. The rumination affects the sleep...erm....the mania...it, it's almost as if it starts with anxiety really..." (Participant 6)

There was a clear bi-directional pattern to mood and anxiety, with each being identified as both a product of, and a trigger to, the other. In particular, the anxiety-depression link was highlighted, with participants citing persistent, low level, daily anxiety which, if left unresolved, gradually culminated in a depressive episode. This relationship was also reversed, with depression seen as a trigger to anxious feelings. As mood became low, this led to a reduction in self-esteem and confidence, which in turn resulted in increased anxiety.

"...obviously in the depression your self-esteem goes down and you're feeling worthless so therefore your anxiety...there's a lot of anxiety around that.......if you're mood's down you can be anxious about everything..." (Participant 3)

The link between anxiety and mania was also discussed, although this experience was more variable. For some, mania was a time of relief from anxiety, although anxiety would often return following a high episode if individuals had behaved impulsively or acted out of character. For others, the agitation and restlessness that came with being anxious was a trigger to elevated moods and impulsive behaviour, and anxiety was viewed as an early warning sign to manic episodes.

".....yes I would say anxiety is a precursor [to high moods] *and now I tend to think of it as being sort of a warning sign, if I am getting unduly anxious or something, and it's probably time to get some fresh air and exercise and camomile tea and perhaps avoid too many stimulating things or whatever"* (Participant 13)

For some, there was a sense of unpredictability linked to anxiety, with this being as much a trigger to depression as it was to mania, often with little warning of which way it would go.

"If I get anxious it will trigger me into a depression or into mania and it doesn't matter what I am being anxious about, if you know, work completely screws me up, it's not the clients, it's the environment, it's the noise, and if I am anyway tense or anxious it will push me one way or the other" (Participant 11)

Overall, having BD was seen to amplify all emotional experiences, including anxiety. Anxiety was generally linked to day to day stressors which are familiar to most people such as work, relationships and the future. However, these worries were intensified due to the added worry of becoming unwell and the consequences of this. As such, daily stressors were perceived as being even more stressful than they might otherwise be.

"I think probably the bipolar...impacts on the anxiety. In that everything you feel even when you're relatively stable I, I think is like magnified by, by bipolar.....yeah I'm , I'm sure that the

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bipolar made, helped make anxiety seem.....far worse than...than it, it was at times. Therefore made situations more difficult to handle" (Participant 9)

5.3.2.3. Theme 3: The consequences of anxiety in BD (n = 19)

This theme describes the impact of being anxious in the context of living with BD, focusing on the specific consequences of anxiety on important life domains. People were able to clearly identify a number of ways in which anxiety had impacted on important areas of their lives. Overall, anxiety was described as a barrier to achievement and enjoyment in life. Anxiety was seen to have restricted opportunities to get a good education or progress within a chosen career. Increased sensitivity to anxiety meant any stress linked to occupation was magnified, such as being on time or feeling under pressure to always be "well enough" to go to work. Being anxious had a negative impact on cognitive performance and concentration, with people feeling that their mind was so full of anxious thoughts there wasn't room for anything else. As a result, concentrating at work or school was very difficult or even impossible, impacting on education, career progression and financial security.

"I'd go to work to distract myself and... which can you imagine the effect you know it didn't do my career prospects a lot of good because you were just thinking about the anxiety rather than the work" (Participant 3)

Loss of concentration due to anxiety extended to a loss of enjoyment in other areas of life. This included being unable to relax and read a book, watch TV or take part in hobbies or interests due to feeling restless and distracted. Lack of motivation was also cited as a consequence of anxiety as it was such a draining experience, making it difficult to start new projects or see things through to the end. Being unable to concentrate or focus on activities was especially problematic in terms of coping with anxiety as people found it difficult to do things which effectively distracted them from anxious thoughts.

"It [anxiety] just kind of jams you up from doing other things, yes and difficult to get back into hobbies and interests and things like that, and projects I might have got involved in, maybe just languish" (Participant 13)

In particular, anxiety was felt to impact significantly on relationships and interpersonal skills. Being anxious led to over-dependence on friends and family, with people often needing to seek regular reassurance or support. This placed extra pressure on relationships, often changing dynamics where partners adopted the role of carer or became the main provider for the home where previously they were not. This appeared to be over and above changes in roles which were more generally associated with having BD. Arguments occurred due to relatives not understanding what it's like to feel severely anxious and losing patience. This lack of independence resulted in reduced confidence and self-esteem. Many people reported that they actively prevented others from getting "too close", and avoided establishing romantic relationships or friendships due to fear of rejection and simply not knowing how to work through interpersonal problems. Social situations were also frequently avoided when feeling very anxious, with people worrying about becoming too easily upset should something go wrong. This often meant that the opportunity to socialise and form relationships was limited even when participants were open to this.

"Relationships.....it's just a no-go area, area for personal, you know, finding a partner or owt like that. I don't, I don't know how to cope with it....Yes, I, this is a big, big area for me. I do get really anxious over relationships. I keep everyone at a distance" (Participant 12)

In addition, worrying about letting others down and fear of failure often resulted in not making plans or avoiding thinking about the future altogether. Despite the overwhelming majority of experiences of anxiety being negative, one participant did identify a positive aspect of anxiety, feeling that being anxious motivated him to keep on top of things such as work and managing finances. Overall though, the impact of anxiety was associated with

feelings of regret and frustration at the barriers this presented and at the way life had turned

out as a result.

"It kills your, it kills your life off bit by bit. I just think it's so sad, it's so sad but it's true

that anxiety can take your life. It doesn't take the breath out of your body it takes the drive

out of your soul, and that in a nutshell basically, it's so powerful it can rob of you of

everything that you can go and get" (Participant 21)

5.3.2.4. Theme 4: The perception of anxiety in BD (n = 15)

Theme 4 brings together the experiences of anxiety and BD discussed so far and explores

how these experiences are perceived subjectively. Participants frequently described their

anxious thoughts as 'irrational' or 'silly', and there was a sense of helplessness and

embarrassment linked to the belief that they should be able to cope with anxiety and a sense

of failure when this wasn't the case. For many, anxiety was a mixed experience in that it was

reliably persistent but largely unpredictable in terms of how the person would respond or

manage when feeling anxious. Because anxiety was seen as a trigger to mood change, this

unpredictability was associated with a lingering feeling of having a lack of control over both

anxiety and mood episodes, constantly waiting for something to happen or for the next thing

to go wrong.

"you can n-never ever smugly say I'm cured or I'm completely under control. Cos'

there's always some nasty little Achilles heel that sneaks up and gets you" (Participant 9)

In general, there was a difference in the way anxiety and bipolar mood experiences

were perceived. Whilst anxiety was more readily conceptualised as a permanent, intrinsic

state, BD was more often described as "the illness" or as "having the bipolar". This was

consistent with quotes in earlier themes where BD was seen as an external object. This gave

the impression of BD as a separate entity to be dealt with and treated, whilst anxiety was

viewed as a more static personality trait. As a result, there was a sense of resignation and hopelessness for some people that there was nothing that could be done to resolve anxiety.

"....but at the end of the day I think there are some people that you are just wired that way, you know, there is some people that just are naturally anxious people and I don't think there is any amount of tablets or therapy that will change it, you just have to manage it" (Participant 12)

Despite anxiety being such a persistent and at times overwhelming experience, for many it had also become an almost 'hidden' problem. People were often so well practised at disguising their anxiety that even those close to them didn't realise quite how much they were struggling. As such, anxiety was a problem that could frequently go unrecognised and underestimated by family, friends and health professionals.

"...what makes me anxious a lot is I have gone through a lot of my life being terribly, terribly broken and something being horribly wrong and I could not let anybody know, and so I have, I am a huge pretender you know ....I always used to get misunderstood, because I present together, I am not" (Participant 11)

This was in part due to a fundamental belief that others may not take anxiety as seriously as depressed or manic episodes. In addition, bipolar mood episodes were seen as more tangible, with others being able to see clearly how they felt and how they were affected when feeling depressed or high, but this was less obvious when a person was feeling anxious. As such, it was felt that anxiety was all too often dismissed as an irrelevant or less important experience.

"...then it gets put down to oh well, it's just anxiety, well it's not just anxiety, because anxiety can be one of the worst things in the world..." (Participant 8).

Despite the sense of hopelessness for some regarding the possibility for anxiety to improve, many participants felt that anxiety was a neglected area in life and in treatment, and that this was something that they would like to receive more help with, in addition to support to manage mood. Participants felt that recognising anxiety as an integral part of BD was an important step forward in getting the help they needed and that treatment should not focus solely on mood symptoms.

"But yes anxiety is, is a controlling thing. If you could take the anxiety away you would cure the problem I think..." (Participant 14)

5.4 Discussion

5.4.1 Interpretation of key findings

A summary of key themes and their implications for theory and clinical practice are presented in Table 5.3. A number of potential conceptualisations of the interaction between anxiety and mood in BD have been proposed at the beginning of this thesis (see Chapter 1, Section 1.6). Primarily, research appears to point to anxiety and mood as transdiagnostic features of a fundamental dysregulation of emotion, with anxiety as both a precursor to, and consequence of, mood fluctuations and poorer outcomes in BD. Consistent with this hypothesis, there was a general inherent instability of affect reported by most people in this study, with extreme fluctuations in anxiety and mood reported from an early age (Theme 1). Perhaps the most striking finding was the integration between anxiety and bipolar mood experiences, which were intertwined for many participants.

Consistent with the findings of the meta-synthesis in Chapter 4, anxiety was described as a consequence of BD and frequently persisted during periods of euthymia due to worry and concern about relapse. In addition, having BD, or 'being bipolar', was itself felt to impact on the experience of all emotions, with feelings being heightened and more intense compared to people without BD. Previous research exploring the positive aspects of

BD has suggested that heightened emotional experiences can be seen as a benefit (Lobban, Taylor, Murray, & Jones, 2012). However, in this context amplification of emotion resulted in anxiety also being heightened, with life stressors and situations perceived as more difficult to cope with. This appeared to create a cycle of anxiety and mood fluctuations. Consequences of this heightened sensitivity to anxiety were explored in Theme 3. Perhaps most significantly, anxiety was reported to be a barrier to achievement in many areas of life including occupation, leisure and self-management. In addition, inter-personal difficulties related to forming and maintaining close relationships were reported as an important consequence of anxiety. This is consistent with previous research which has reported a link between early trauma and related anxiety and later inter-personal difficulties which may perpetuate mood instability (See Chapter 1, Section 1.5.1).

There is a lack of research which reports the temporal relationship between anxiety and mood symptoms. Subjectively these experiences were diverse, with anxiety reported prior to, during, and as a consequence of mood episodes (Theme 2) both within and between participants. As with many emotional disorders (see Chapter 1, Section 1.2.2), symptoms of anxiety, depression and mania overlapped. Anxiety was reported to be low level and chronic generally, but also severe and episodic, mirroring the cyclical profile of BD characterised by sub-syndromal mood symptoms and extreme mood fluctuations. In particular, the link between depression and anxiety was quite clearly defined, whilst the anxiety-mania link was less clear. Anxiety was a reported as a frequent trigger to and consequence of depression, whilst anxiety during mania was less common. More frequently anxiety was cited as a precursor to mania, with physiological symptoms of anxiety such as agitation and restlessness being recognised as early warning signs of elevated mood. Anxiety was also a consequence of manic episodes, linked to embarrassment and shame about actions when unwell. This pattern is consistent with current longitudinal research, where anxiety has been found to be a consistent predictor of depressive relapse over time, whilst

associations between anxiety and mania are variable (see Chapter 1, Section 1.3.4). It may be that these inconsistencies simply mirror the reality of a range of individual and changeable presentations, and highlights the importance of exploring individual experiences.

Anxiety has previously been highlighted as a trigger to mood episodes (see Chapter 4), although the mechanisms which underpin this have not been well defined. In depth exploration of mood and anxiety experiences in this study generated potential hypotheses regarding how anxiety may be linked to poorer outcomes in BD. Traumatic experiences in childhood and adolescence were identified as one trigger to subsequent problems with mood and anxiety. In particular, unresolved feelings and a lack of support at the time of trauma were proposed to lead to later difficulties with the expression of emotion. This was linked to using avoidance to cope with negative emotions at the time of trauma and is consistent with research which shows emotional processing is significantly impaired for individuals with BD with anxiety compared to those without (see Chapter 1, Section 1.5.2). Anxiety has also been linked to emotional suppression and suicidality in existing research (Simon et al., 2007). This may be important for explaining anxiety as a predictor of relapse in BD, with individuals being more anxious and less able to cope with emotions following trauma. However, anxiety preceding BD was not universally reported and for some anxiety was triggered only following diagnosis.

Sleep was also indicated in the present study as a potential link between anxiety and mood swings. Anxiety was reported to be a precursor to sleep disruptions, and resulted in subsequent anxiety about impending relapse, or the actual occurrence of a mood episode. Disruptions in circadian rhythms, and the appraisal of these changes in internal states, have been linked to the onset of bipolar mood episodes (see Chapter 2, section 2.5). It may be that anxiety increases disruptions in sleep, and these disruptions are appraised as catastrophic (e.g. if I don't get more sleep, I will have a relapse), which leads to rumination about sleep loss, which disrupts sleep further and perpetuates increases in mood symptoms.

A final potential link between anxiety and mood fluctuations in BD was anxiety as a barrier to goal achievement. Participants also reported negative appraisals about anxiety and mood swings, with beliefs that anxiety in particular was difficult or impossible to recover from (Theme 4). A large body of research has found there may be increased sensitivity to goal attainment and failure for individuals with BD (Chapter 2, Section 2.3.6). Mania has been found to occur as a result of striving for achievement and when goal-directed behaviour is excessive, whilst there is evidence that depression may occur in the event of failure, potentially due to the negative way in which these events are appraised (See Chapter 2, Section 2.4.2). Specifically, anxiety was cited as disrupting engagement in meaningful employment, education and important relationships. This may result in frustrative-non-reward or appraisals that goals may be achieved if an individual tried harder, possibly resulting in manic experiences. Alternatively, this could also lead to failure and negative appraisals that trying is hopeless as anxiety is impossible to overcome, leading to a reduction in activity and depression. In addition, reduced activity and experience of failure may result in a lack of protective factors such as positive experiences and social interactions, which are likely to be a source of self-esteem and self-efficacy.

Table5.3. *Overview of themes and sub-themes*

Theme	Key points	Implications for theory	Clinical implications
1. Which came first? The temporal relationship between anxiety and bipolar mood episodes	Early experiences of anxiety, mood fluctuations and trauma linked to later anxiety and BD	Anxiety and trauma as a risk factor for mood lability and the development of BD for some people	Importance of asking about anxiety during initial treatment and addressing early anxiety and trauma as it occurs
	Others experience anxiety following diagnosis of BD which then persists even during periods of euthymia	Anxiety is a consequence of experiencing severe mood episodes and living with a diagnosis of BD	There is a need to offer more information and support at time of diagnosis and beyond
	Anxiety and mood are so closely linked that they are inseparable	Potential inherent instability of affect	
2. The specific interaction of anxiety with depression and mania	Anxiety is both persistent and episodic, with periods of extreme anxiety linked closely with mood change	Bi-directional pattern between anxiety and mood episodes	Importance of addressing anxiety as part of treatment, and especially during periods of euthymia
	Unresolved, low level anxiety as a trigger to depression, and reduced confidence when depressed as a trigger to anxiety	Anxiety is a trigger to depression and mania	Support to manage anxiety around life stressors linked to illness is needed
	The variable experience of anxiety in mania - a time of relief from anxiety, anxiety as an early warning sign to mania and anxiety as a consequence of impulsive behaviour	Anxiety is the result of depression and mania	Importance of exploring individual experiences
	Having BD means emotions are more intense, and anxiety in particular is amplified due to the added worry of becoming unwell		

Theme	Key points	Implications for theory	Clinical implications
3. The consequences of anxiety in BD	Anxiety effects concentration and cognitive performance, interfering with occupation, education and leisure activities	Anxiety as a barrier to goal attainment and positive experiences	Anxiety is a clinically significant experience
	Anxiety associated with sleep disruptions and a lack of motivation	Anxiety as a mediator to mood fluctuations via disruption of sleep patterns and associated appraisals	Support to address problems within relationships and more information for family and friends to increase understanding
	Being anxious linked to inter-personal problems and increased pressure on relationships	Anxiety as a barrier to protective factors	
4. The perceptions of anxiety in BD	Feeling of helplessness and embarrassment at being unable to control anxiety and mood changes	Extreme appraisals about mood swings	Changing perceptions regarding anxiety as permanent and uncontrollable may be key
	Anxiety perceived as permanent and innate whilst BD was perceived as separate and treatable	Extreme appraisals regarding others perceptions of self when anxious	Need to validate both anxiety and mood as important experiences
	The significance of anxiety is often underestimated by others and people would like help for anxiety to be included as a part of treatment for BD		

5.4.2 Therapeutic implications

Receiving a diagnosis of BD was a critical time which was linked to the onset of chronic anxiety for many. Provision of increased support and information at this early stage and beyond may be important to reduce anxiety and increase confidence to live successfully with bipolar experiences. Participants reported a desire for more help with anxiety and for the focus of BD treatment to be less rigid in its consideration of depression and mania alone. Many people felt that treatment for anxiety was of equal or greater importance than help to manage mood. As mentioned previously (Chapter 1, Section 1.7), this is in contrast to current NICE guidelines for BD which recommend the prioritisation of medication and therapy for mood symptoms, with help for anxiety offered separately should this persist (NICE, 2006). The need to address and provide early intervention for initial anxiety was also identified. In terms of psychological treatment for anxiety and mood, the reported experiences of these as shared, overlapping phenomena potentially underpinned by the same psychological mechanisms suggest that treatment should address them as such. Therapeutic interventions which focus on triggers and consequences to both anxiety and mood fluctuations would therefore likely be helpful in achieving improvements with regards to both mood instability and anxiety. However, as highlighted previously (Mansell et al., 2007), care must be taken not to maintain excessive hypervigilance to normal mood swings. This suggests the importance of continuing to explore anxiety as a key part of BD treatment.

Deficits in treatment guidelines may not be the only barrier to accessing help for anxiety. Theme 4 goes beyond the descriptive experience of anxiety and explores the perception of anxiety as an unchangeable and permanent experience. This was potentially due to the perceived familiarity of anxiety and the sense that being anxious was an inherent part of a person's personality. However, in contrast to this perceived sense of hopelessness about anxiety, many people did report that this was something they would like more help with. However, there was a sense of shame and embarrassment attached to being unable to

cope with anxiety, which was described as 'irrational thoughts' about 'silly things'. This perception was often externalised and it was felt that others saw anxiety as a less severe experience than depression or mania. The ICM (Mansell et al., 2007) identifies beliefs about mood and beliefs about others as drivers of cognitive appraisals and behavioural responses to changes in internal states. In-line with this model, beliefs about anxiety and beliefs about the response from others when a person was anxious appeared to be a barrier to accessing help and support. This has direct clinical implications for practice and indicates that asking about anxiety during therapy may be important to allow clients the space to talk about anxiety and feel validated in considering this as an important issue. Challenging appraisals regarding the permanence of anxiety may also need to be a key part of treatment.

The experience of trauma had clinical implications for the experience of anxiety and mood swings in this study. In particular, the timing of support following trauma was perceived to be crucial, with participants reporting that failure to have support at the right time led to problems with emotional processing later on. There have been mixed findings regarding the benefits of psychological help very soon after a traumatic event in the current literature. A meta-analysis found that psychological debriefing, which generally involved one session of psychological and emotional support immediately after a traumatic event, was associated with increased PTSD symptoms relative to no psychological support (Van Emmerik et al., 2002). It was suggested that debriefing may have interfered with the natural recovery process following trauma, but may also have been due to the provision of support by a range of professionals with varying levels of skills and qualifications. Brief trauma-focused CBT (TF-CBT) has been found to be more effective at reducing symptoms of post-traumatic distress in comparison to supportive counselling and waiting list controls in a systematic review of the literature (Roberts et al., 2010), although findings require replication on a larger scale. Overall, it seems that the provision of structured, psychological support by appropriately trained therapists following a traumatic event may help to prevent later problems with

anxiety and mood instability as described in this study. However, this requires investigation to assess if this is effective in practice and it will likely depend on the nature of the trauma and the needs of the individual as to how effective this help may be and when.

5.4.3 Implications for future research

Current research suggests that early experiences such as anxiety may be important in the development and onset of BD due to individuals being vulnerable to their environment and traumatic experiences in childhood and adolescence (Alloy et al., 2006b). This may be due to a general underlying vulnerability to these experiences, as suggested by biological models of BD and theories such as the BAS hypersensitivity model (see Chapter 2, Sections 2.2 and 2.3). Participants in this study identified that a lack of resolution or support following early trauma may be linked to subsequent mood instability, however it is not yet known specifically what influences the transition from early anxiety to BD, or indeed if early anxiety may be a marker of a generalised dysregulation of emotion rather than anxiety as a mediator to later mood episodes. Future research is required which explores in more detail the progression from early anxiety and potential sub-threshold mood fluctuations to later bipolar mood experiences in order to focus early treatment and interventions.

5.4.4 Limitations

Participants in this study had a limited range of BD diagnoses and ethnic backgrounds, as all but one of the participants had a diagnosis of BDI and all were white British. As such, the experiences reported here may not be universally applicable to those individuals of other ethnicities or who have not experienced manic episodes. In terms of ethnicity, experiences are embedded in the culture and beliefs of one's environment and society (Fernando, 2012), and so understanding these experiences across a range of cultural contexts relevant to the

wider population is important and necessary to progress both research and individualised treatment (Fernando, 2012; Oishi, Diener, Napa Scollon, & Biswas-Diener, 2004).

5.4.5 Conclusion

The subjective experience of anxiety and mood in BD is undoubtedly complex and there is still a long way to go to understand the specific mechanisms which underlie anxiety and mood interactions. As much of the current literature exploring anxiety and mood is retrospective in nature and explores ADs as a primary outcome, research which explores the real time relationship between anxiety and mood may be helpful in contextualising some of the experiences described in this study further and highlighting specific patterns in interactions. Exploring the same processes in individuals without a diagnosis of BD would also be valuable for highlighting shared processes and differences which may confer vulnerability to, or protection from, BD.

Chapter 6: Study 2 - Anxiety as a predictor of outcomes over 96 weeks - An analysis of data from the PARADES Psychoeducation study

6.1 Introduction

Previous studies in this thesis have explored the qualitative experience of anxiety in BD (see Chapters 4 and 5). Taken together with the current existing literature (see Chapter 1, Section 1.6) anxiety has been hypothesised as a trigger to depressed and manic symptoms and relapse, although experiences linking anxiety and mania are diverse and appear to vary both within and between participants (see Chapter 5, Section 5.4). Most previous research has found anxiety is linked to poorer outcomes in BD based on retrospective and cross-sectional reports (see Chapter 1, Section 1.4). More recently anxiety has been explored as a predictor of outcome longitudinally, although several of these studies have focused on categorical diagnoses of ADs (e.g. Otto et al., 2006; Sala et al., 2012). Current and lifetime ADs have been linked to poorer outcomes over time (Otto et al., 2006; Perlis et al., 2006; Sala et al., 2012), although studies have not distinguished whether there are differential effects of current and lifetime experiences (e.g. MacQueen et al., 2003; Otto et al., 2006). Research has also assessed the association of individual ADs with illness course in BD, and significant effects have been suggested as examples of bipolar subtypes linked to specific anxiety experiences such as panic and OCD (e.g. Magalhaes et al., 2010; Pini, Dell'Osso, Amador, Mastrocinque, Saettoni & Cassano, 2003). However, these effects have not been found to retain significance when controlling for illness severity and sociodemographic characteristics (Simon et al., 2007), indicating that it is the global experience of anxiety which may be important. Anxiety symptoms assessed on a continuum have been found to be more robust predictors of outcome over lengthy follow-up periods compared to ADs or symptoms of depression at baseline (Coryell et al., 2012). Qualitative research within this thesis has also indicated the importance of a continuum approach to anxiety, with participants reporting

anxiety experiences across the spectrum (see Chapters 4 and 5). Understanding the impact of anxiety on outcomes in BD is key to exploring how best to help people who experience anxiety and mood fluctuations, and whether or not this should be done through integrated therapeutic approaches which address all mood experiences including anxiety. One potential limitation of the current research is that the consistent link between anxiety and depression (see Chapter 1, Section 1.4) which means that there may be a high degree of multi-collinearity between these variables. As such, anxiety may not add anything in terms of predictive validity in longitudinal analyses per se. The present study aimed to assess and compare anxiety diagnoses and symptoms as predictors of outcome over a 96 week period, whilst controlling for baseline assessments of mood symptoms and functioning to assess the extent to which anxiety is a useful independent predictor of illness course.

6.2 Aims and hypotheses

The present study aimed to explore the impact of anxiety on depressive symptoms, manic symptoms and functioning over time. To do this anxiety was assessed in two ways; firstly as a categorical diagnostic variable and secondly anxiety experiences were assessed on a continuum using anxiety symptom scores. Specifically the following hypotheses were tested:

1. Diagnosis of any current AD would be associated with increased depressed and manic symptoms and reduced functioning at all follow-up points

2. There would be no difference in the predictive validity of individual ADs related to mood and functioning outcomes when controlling for other relevant clinical and sociodemographic variables

3. Anxiety symptoms would predict increased depressed and manic symptoms, and reduced functioning longitudinally

4. Anxiety symptoms would be a better predictor of prospective outcomes than ADs

6.3 Method

6.3.1 Overview of the PARADES Psychoeducation study

The PARADES program (Chief Investigator Jones; grant number: RP-PG-0407-10389) is the largest psychological bipolar research program carried out in the UK to date and comprises five linked projects which aim to reduce harm and risk in BD. The present study is a secondary analysis of partial data from the PARADES Psychoeducation study, a pragmatic randomised controlled trial intended to determine whether structured group psychoeducation is more effective at reducing relapse and improving well-being for individuals with BD than collaborative group peer support sessions. This study was reviewed and approved by the Nottingham NHS Research Ethics Committee 2 (reference: 09/H0408/33). The study was a single blind RCT which provided participants with 21 weeks of either psychoeducation group therapy or a peer support group. Groups met weekly and were co-facilitated by two health practitioners and one service user. Outcomes were assessed by telephone and face to face interviews at 16 week intervals from baseline to 96 weeks. The full protocol for this study is described elsewhere (Morriss et al., 2011). Issues such as power and sample size which have already been addressed for this study in the methodology chapter (Chapter 3, Section 3.6) are not repeated here.

6.3.2 Participants

In total, 304 individuals with a diagnosis of BDI or II disorder were recruited to the Psychoeducation study from mental healthcare services, voluntary services and the wider community across the North West of England and the East Midlands. Participants were aged between 18 and 65 years and assessed as being at increased risk of relapse, defined by the experience of a bipolar mood episode (depression or mania/hypomania) in the 24 months prior to study entry. Exclusion criteria included experience of a depressed or (hypo)manic episode in the four weeks prior to baseline, current suicidal intent or ideation at study entry,

and being unable or unwilling to provide written informed consent. This was a single blind study and the trial was still on-going at the time of data analysis in the current investigation. For this reason, participants from both treatment arms were included, with no information regarding group allocation known. Although the psychoeducation and peer support groups discussed anxiety as part of their group sessions, this was not the specified main focus of any of the sessions in either arm of the trial. Participants were followed up every 16 weeks post-randomisation up to a maximum of 96 weeks.

6.3.3 Measures

Interviews and assessments were administered by trained researchers based at each site, all of whom had received structured training in the delivery of all assessments and using the relevant standardised training materials for specific measures where appropriate. Training was supervised by the Chief Investigator at each site (Lobban, Morriss and Jones), all of whom were clinically trained academics working extensively in bipolar research. In addition, monthly supervision was held for researchers from all sites to ensure comparable standards of training and to discuss queries or discrepancies to be agreed by the wider research team. Following randomisation, participants completed a baseline assessment followed by six follow-up assessments at intervals of 16 weeks. Follow-ups alternated between face to face interviews (32, 64 and 96 weeks) and telephone interviews (16, 48 and 80 weeks). The primary outcome measures for the study are described in the original protocol paper (Morriss et al., 2011). The present analysis focused on a sub-set of secondary outcomes from the Psychoeducation study and explored AD diagnosis and anxiety symptoms at baseline as longitudinal predictors of symptoms of depression, mania and functioning outcomes. The relevant measures are described below and Table 6.1 illustrates the schedule of data collection.

Table 6.1 *Schedule of data collection for all measures*

Time-point	Method of data collection	SCID	Primary SCID anxiety symptoms	HADS-A	HAM-D	MAS	SOFAS
Eligibility	Face to face	+	-	-	-	-	-
Baseline	Face to face	-	+	+	+	+	+
16 weeks	Telephone	-	+	-	+	+	+
32 weeks	Face to face	-	+	-	+	+	+
48 weeks	Telephone	-	+	-	+	+	+
64 weeks	Face to face	-	+	-	+	+	+
80 weeks	Telephone	-	+	-	+	+	+
96 weeks	Face to face	-	+	-	+	+	+

6.3.3.1 Measures to confirm diagnosis

SCID-DSM-IV (First et al., 1997)

To be eligible for the study participants were required to meet criteria for a primary

bipolar I or II disorder diagnosis using the SCID-DSM-IV interview. Participants were also

assessed for other current or lifetime axis I psychiatric disorders. Presence of seven current

or lifetime ADs were assessed at baseline: panic disorder (PD), panic disorder with

agoraphobia (PD_Ago), agoraphobia (Ago), social phobia (SoP), specific phobia (Sp), post-

traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD). The SCID-DSM-IV

assesses the presence of generalised AD (GAD) in the past 6 months only, and so only

presence or absence of current GAD was recorded at baseline.

6.3.3.2 Self-reported and observer rated measures of anxiety

Experience of anxiety symptoms – anxiety module screening questions from the SCID-DSM-IV (First et al., 1997)

Participants were asked at baseline and all follow-up interviews if they had experienced any primary symptoms associated with six ADs commonly reported in BD (see Table 6.2). Questions were taken from the SCID screening overview for each type of AD and responses were recorded as present or absent. Symptoms of PTSD were not included here as there was no single primary screening question or symptom for this disorder. Baseline SCID anxiety symptoms were entered as a predictor variable in the final analysis, however experience of SCID anxiety symptoms across all follow-ups was also reported.

Table 6.2 *SCID screening questions asked at baseline and follow-up to indicate the presence or absence of any anxiety symptoms*

AD	Primary symptom assessment (all questions prefixed by "since I last saw you / spoke to you.....")
PD	Have you had a panic attack, when you suddenly felt frightened or anxious or suddenly developed a lot of physical symptoms
Ago	Have you been afraid of going out of the house alone, being in crowds, standing in a queue, or travelling on buses or trains?
SoP	Is there anything that you have been afraid to do, or felt uncomfortable doing in front of other people, like speaking, eating or writing?
Sp	Are there any other things that you have been especially afraid of since I last saw you, like flying, seeing blood, having an injection, heights, enclosed places, any animals or insects?
OCD – compulsions	Have you been bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them?
OCD – obsessions	Were there things that you had to do over and over again and couldn't resist doing, like washing your hands again and again, counting up to a certain number, or checking something several times to make sure that you'd done it right?
GAD	Have you been particularly nervous or anxious since I last saw you?

Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A) (Zigmond & Snaith, 1983)

This is a 14-item self-report questionnaire completed at baseline to assess depression and anxiety in clinical samples with good evidence for validity of sub-scales across a range of clinical samples (Bjelland et al., 2002). Only the anxiety subscale (HADS-A) was analysed in the present study, which included seven items to assess the presence, frequency and severity of anxious symptoms in the week prior to interview. Items on the anxiety scale were: 1) I feel tense or wound up; 2) I get a sort of frightened feeling as if something bad is about to happen; 3) Worrying thoughts go through my mind; 4) I can sit at ease and feel relaxed; 5) I get a sort of frightened feeling like butterflies in the stomach; 6) I feel restless and have to be on the move; 7) I get sudden feelings of panic. Each item was scored from 0-3, with a total score calculated out of a possible 21. Where baseline HADS-A questionnaires were incomplete, total scores were pro-rated if only one item was missing, in-line with NHS guidelines for handling missing data in services (IAPT, 2011). Pro-rating was done using the formula 'total score of completed items*(total number of items on scale / number of items rated)'. This was done for 9 assessments in total. Incomplete HADS-A questionnaires with more than one item missing were excluded from the analysis (n = 2).

6.3.3.3 Primary outcome measures

Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960)

Administered at baseline and all follow-up interviews to assess the presence and severity of depressed symptoms in the previous seven days. This is a widely used measure in bipolar research and is currently the gold standard for the assessment of depression in clinical studies (Cusin et al., 2009). Some issues have been raised in terms of limited inter-rater and re-test reliability for some items on the scale (Bagby, Ryder, Schuller, & Marshall, 2004) and so the scale was delivered using a semi-structured interview format which has

been found to increase inter-rater reliability (Morriss, Leese, Chatwin, & Baldwin, 2008). The HAM-D contains two items which are based on observer ratings of behaviour. As these could not be assessed over the telephone at alternate follow-ups these items were not rated in 50% of interviews. To ensure comparable scores across follow-ups an attempt was made to pro-rate the missing items by running a univariate regression analysis based on time points where all data had been collected. This found that the behavioural items of the HAM-D and the total score of all other items had little or no association (B = 0.007, SE = 0.005, p = 0.15, CI -0.003, 0.2). In addition, there is evidence that these items are not the most sensitive to change over time when using the HAM-D as an outcome measure (McIntyre, Kennedy, Bagby, & Bakish, 2002). Therefore the decision was made to exclude the behavioural items from the HAM-D at all time points prior to analysis and so final scores are based on the remaining 15 items.

Bech-Rafaelsen Mania Rating Scale (MAS; Bech et al., 1978)

Administered at baseline and all follow-up interviews to assess the presence and severity of (hypo)manic symptoms based on 11 items evaluating mood and behaviour linked to high mood over the previous week. The MAS is a well validated, observer-rated interview which is used regularly in research with individuals with a diagnosis of BD (Bech, 2002).

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

This scale provides an assessment of an individual's social and occupational functioning, which does not only consider impairments due to psychological symptoms but assesses overall functioning in these areas irrespective of reasons for impairment. Using the SOFAS, participants are assigned a functioning score rated on a continuum from 0 to 100, where 0 represents persistent inability to care for self or to maintain personal safety, employment or relationships, and 100 represents good functioning across all relevant activities. The SOFAS was used in the present study to rate current level of functioning at

baseline, and was re-assessed at every time point to assess level of functioning since the previous interview.

6.4 Data analysis

6.4.1 Analysis of baseline data

Differences between participants with (ANX+) and without (ANX-) current and lifetime ADs at baseline were explored. Between group comparisons of HAM-D, MAS, SOFAS and HADS-A scores were performed using two-sided independent samples t-tests, with the mean difference (MD) reported to indicate effect size. To compare groups on other sociodemographic and clinical characteristics, Pearson chi square tests were applied to categorical variables (gender, marital status, employment, education, ethnicity), whilst independent samples t-tests were applied to continuous variables (age, days since last episode, number of previous episodes, primary SCID anxiety symptoms).

6.4.2 Associations between anxiety and prospective outcomes

The primary aim of this analysis was to assess anxiety as a longitudinal predictor of mood symptoms and functioning. The impact of ADs and anxiety symptoms was assessed using linear mixed effects regression analyses where fixed and random effects were included. The outcome variables of interest were HAM-D, MAS and SOFAS scores, with anxiety entered as a predictor in four ways, all analysed in separate statistical models:

1. Presence of a current AD, evaluated firstly using the variable 'any AD' to identify participants meeting criteria for one or more ADs at study entry.

2. Specific ADs were also examined individually to assess their significance in predicting longitudinal outcomes. Each AD was coded as a binary variable to denote presence or absence of each disorder at baseline. All individual AD variables were then added to the model together, to control for the confound that over a third of the ANX+ group had 2 or more AD diagnoses.

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3. Self-reported HADS-A symptoms at baseline were assessed as predictors of outcome for the entire sample.

4. Observer rated primary SCID anxiety symptoms were assessed as predictors of outcome for ANX- participants only.

As most outcome variables were collected at six prospective assessments, the mixed effects regression assessed outcome across all time points (16, 32, 48, 64, 80 and 96 weeks) in a model that included 'time point' entered as a categorical covariate to examine trends (upwards or downwards) in outcome over time. Where there were significant main effects of anxiety on depression, mania or functioning, interaction effects between time point and anxiety were modelled to assess if effects existed only at specific follow-up points or across all assessments. As this was a multi-site study, 'site' was accounted for as a random effect. Within-participant differences were also modelled as a random effect to control for individual differences and correlations between repeated assessments over time. Alpha was set at 0.01 to partially control for multiple testing and 99% confidence intervals (CI) are reported to show accuracy of estimated effect sizes. More conservative correction options for multiple testing, such as Bonferroni corrections, were not adopted due to the exploratory nature of the analysis and the risk of not detecting potential areas of interest.

To determine relevant covariates to be included in the model alongside anxiety diagnosis or symptoms, preliminary analyses were run. Individual variables were entered into the model independently, to be retained in the final model only if individually predictive of depression, mania or functioning outcomes. Based on previous research indicating factors associated with outcome in BD (see Chapter 1, Section 1.2.4) the following variables were assessed: age at consent, gender, bipolar type, number of previous episodes and other current axis I psychiatric disorders (full output data are reported in Appendix 4). Number of previous episodes was entered as a categorical variable to encompass total number of depressed and (hypo)manic episodes where categories were defined as ≤ 7 episodes, $8 - 19$

episodes, or 20+ episodes. Previous research suggests that relapse is three times more likely

for individuals experiencing 20+ past episodes compared to those who have experienced <7

previous mood episodes (Lobban et al., 2007).

6.5 Results

6.5.1 Participant characteristics

Of the 304 participants consented into the PARADES Psychoeducation study, two were

excluded from the present analysis due to failing to provide AD data at SCID interview. Three

additional participants did not complete a baseline appointment or provide any other data

beyond the initial assessment and were also excluded. One final participant was excluded

from the analysis due to meeting eligibility criteria for BDI or II. The remaining 298

participants were grouped according to anxiety status: any current AD (ANX+, n = 127), any

lifetime AD but no current AD (ANX-lifetime, n = 39) and no current and lifetime AD (ANX-, n

= 132). Preliminary analyses found that the ANX- group were significantly less anxious than

the ANX+ group at baseline, however the ANX-lifetime group were not significantly different

to either the ANX- or the ANX+ group at baseline (see Appendix 3). As such, it was felt that

individuals with lifetime ADs only could not reliably be assigned to either participant

category and were excluded from the current analysis. The final sample included 259

participants, of whom 49.03% (n = 127) met criteria for one or more current AD (see Table

6.3). The remainder had no historical or current AD. All participants met criteria for BDI or II

disorder according to the SCID-DSM-IV (First et al., 1997). At study entry, participants in the

ANX+ group were slightly younger and had a higher proportion of female participants

compared to the ANX- group, although this was not significant. Groups did not differ

significantly on any other sociodemographic variables. Participants from both groups were

predominantly single, white British and, despite both groups being well educated over all, all

participants were more likely to be retired or unemployed than in current employment. GAD

was the most prevalent AD in the ANX+ group (46.46%), followed by SoP (26.77%) and Sp

(21.26%). Approximately 40% of ANX+ participants met criteria for two or more ADs. ANX+ participants reported a more severe illness course retrospectively at baseline, with current AD diagnosis associated with an earlier age of onset of first mood episode and increased number of previous depressed and (hypo)manic episodes. Participants with current ADs were at increased risk of meeting criteria for any current eating disorder diagnosis (anorexia, bulimia or binge eating disorder) and any current personality disorder (borderline or anti-social personality disorder). There was no significant difference in current rates of alcohol disorders or substance abuse or dependence, which were low for both groups. ANX+ participants had significantly elevated HAM-D, HADS-A and MAS scores and lower functioning scores on the SOFAS at baseline. Participants in the ANX+ group reported more primary SCID anxiety symptoms occurring in the four weeks prior to baseline than ANX- participants (74.05% vs. 32.74%). However, AD diagnosis was not a reliable estimate of the actual experience of anxiety symptoms. A quarter of the ANX+ group did not experience any primary anxiety symptoms in the four weeks prior to baseline. In particular, this was true for those participants meeting criteria at SCID interview for GAD (n = 59 criteria met, n = 48 symptoms), SoP (n = 34 criteria met, n = 32 symptoms) and Sp (n = 27 criteria met, n = 24 symptoms). In contrast, a number of participants not meeting criteria for specific ADs in the ANX+ group still reported experiencing primary anxiety symptoms at baseline. This was true for PD and PD_Ago (n = 30 criteria met, n = 43 symptoms), Ago (n = 13 criteria met, n = 50 symptoms), OCD (n= 25 criteria met, n = 35 symptoms). Similarly, a third of the ANX- group reported having experienced one or more primary anxiety symptoms in the four weeks prior to baseline, despite not meeting criteria for any AD. In particular, excessive worry (GAD) and Ago were the most frequently reported symptoms in the ANX- group. This suggests that anxiety symptoms were inaccurately estimated in both groups using categorical diagnostic data alone.

Table 6.3 Participant demographic characteristics

	Anx+ (n = 127)	Anx- (n = 132)	Test statistic	MD	P
Age at consent: mean (SD)	43.33 (10.98)	46.62 (11.46)	t (257) = 2.36	3.29	0.02
Age at 1st mood episode: mean (SD)	22.09 (10.38)	24.68 (11.94)	t (257) = 1.86	2.59	0.06
Gender: female n (%)	79 (62.20)	68 (51.51)	x^2 (1) = 3.01	-	0.08
Ethnicity: White British n (%)[a]	117 (92.86)	119 (92.25)	x^2 (1) = 0.03	-	0.85
Occupational status: Working n (%)	29 (22.83)	39 (29.55)	x^2 (1) = 1.51	-	0.22
Education: n (%)					
Primary	13 (10.24)	9 (6.81)	X^2 (3) = 4.99	-	0.17
Secondary	28 (22.05)	22 (16.67)			
Further	43 (33.86)	39 (29.55)			
Higher	43 (33.86)	62 (49.97)			
Marital status: Married / cohabiting n (%)	53 (41.73)	40 (30.30)	X^2 (2) = 3.70	-	0.16
Bipolar type: BDI n (%)	100 (78.74)	110 (83.33)	x^2 (1) = 0.89	-	0.35
Number of depressed episodes mean (SD)	16.86 (20.49)	10.23 (11.39)	t (219) = -3.01	-6.62	<0.01
Number of (hypo)manic episodes mean (SD)	13.79 (18.39)	8.01 (6.19)	t (224) = -3.25	-5.78	<0.01

[a] Ethnicity data missing for n = 4 participants (ANX+ n = 1, ANX- n = 3)

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Table 6.4 *Participant clinical measures*

	Anx+ (n = 127)	Anx- (n = 132)	Test statistic	MD	P
HADS-A mean (SD)	11.04 (4.68)	8.50 (4.82)	$t(224) = -4.01$	-2.54	<0.01
HAM-D mean (SD)	7.57 (5.20)	5.02 (4.60)	$t(257) = -4.20$	-2.56	<0.01
MAS mean (SD)	2.43 (2.83)	1.58 (2.05)	$t(257) = -2.80$	-0.86	0.01
SOFAS mean (SD)	73.04 (12.87)	77.52 (11.53)	$t(243) = 2.87$	4.48	<0.01
Primary SCID Anxiety symptoms[a]:					
Any anxiety symptoms	94 (77.05)	37 (33.33)	$x^2(1) = 45.13$	-	<0.01
Panic attacks	43 (35.25)	7 (6.31)	$x^2(1) = 28.88$	-	<0.01
Agoraphobia	50 (40.98)	18 (16.22)	$X^2(1) = 17.98$	-	<0.01
Social anxiety	32 (26.23)	4 (3.60)	$x^2(1) = 23.04$	-	<0.01
Specific phobia	24 (19.67)	8 (7.21)	$x^2(1) = 7.62$	-	0.01
Obsessions / compulsions	35 (28.69)	12 (10.81)	$x^2(1) = 11.54$	-	<0.01
Excessive worry	48 (39.34)	18 (16.22)	$X^2(1) = 15.98$	-	<0.01
Eating disorder n (%)	11 (8.66)	2 (1.52)	$x^2(1) = 6.93$	-	0.01
Alcohol abuse / dependence n (%)	6 (4.72)	1 (0.76)	$x^2(1) = 3.87$	-	0.05
Substance abuse / dependence n (%)	2 (1.57)	4 (3.03)	$x^2(1) = 0.59$	-	0.44
Personality disorder n (%)	14 (11.02)	1 (0.76)	$x^2(1) = 12.40$	-	<0.01

[a]*Primary SCID anxiety symptom data missing for n = 26 participants (ANX+ n = 5 missing, ANX- n = 21 missing)*

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Table 6.5 *Anx+ AD prevalence at baseline (n = 127)*

AD	n (%)	Number of current ADs		n (%)
PD	5 (3.94)		1	78 (61.42)
PD_Ago	25 (19.69)		2	33 (25.98)
Ago	13 (10.24)		3	11 (8.66)
SoP	34 (26.77)		4	3 (2.36)
Sp	27 (21.26)		5	2 (1.57)
OCD	25 (19.69)			
PTSD	11 (8.66)			
GAD	59 (46.46)			

6.5.2 Missing data and FUP rates

As this analysis involves data from an on-going study, 30 participants had not yet completed the 96 week follow-up (ANX+ n = 19, ANX- n = 11). In addition, primary SCID anxiety symptom data was missing for 26 participants at baseline (ANX- n = 21, ANX+ n = 5), as this was added to the protocol after the start of the study, and was also missing for 20 participants at 96 weeks where this had not yet been entered onto the database (ANX- n = 9, ANX+ n = 11). Participants who did not provide any data beyond baseline (ANX- n = 15, ANX+ n = 13) were excluded from the longitudinal analysis. In total 88 participants (ANX+ n = 31, ANX- n = 57) left the study prior to the final appointment. When compared together, there was no difference between participants who completed the study and those who dropped out with regards to baseline scores on the HADS-A (t (224) = -0.25, MD = 0.17, p = 0.80), HAM-D (t (257) = -1.19, MD = 0.79, p = 0.24) or MAS (t (257) = -1.25, MD = -0.41, p = 0.21). However those who completed the study did have significantly lower functioning scores on the SOFAS (completed SOFAS: mean = 73.53, SD = 12.69; loss to follow-up SOFAS: mean = 78.78, SD = 11.04; t (243) = -3.2, MD = -5.25, p = <0.01), although mean scores for both groups still fell within the range for only slight impairment in functioning and so this difference was not considered clinically significant. Participants who completed at least one follow-up post-randomisation were included in the analysis. Overall, 47.88% of the final sample completed all follow-up assessments, with 77.61% of participants providing data for

at least half of the possible time points. ANX- participants had higher retention rates overall

and completed more follow-ups than did ANX+ participants (see Figure 6.1).
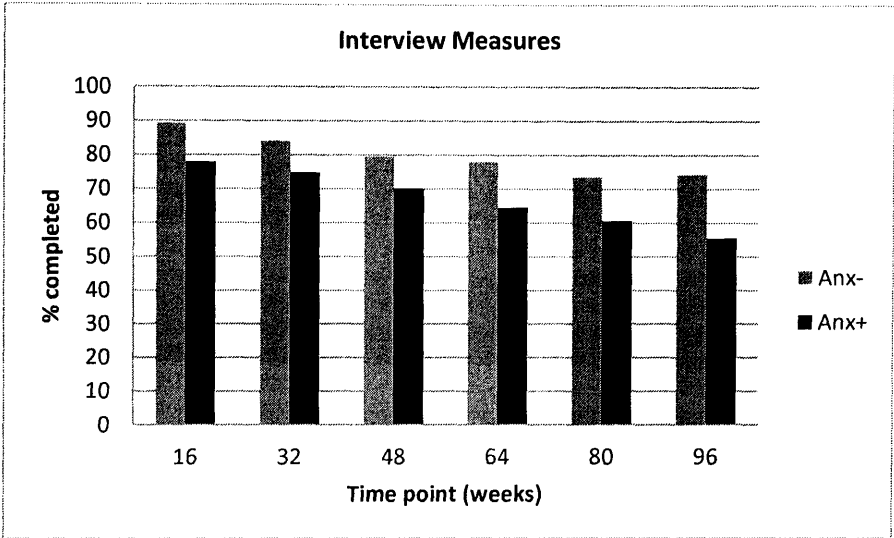
Figure 6.1 *Percentage of participants completing interview measures at each time point per group (ANX+ n = 127, ANX- n = 132)*

6.5.3 Preliminary analyses

When entered into the regression model independently, there were no main effects of age

at consent, gender, bipolar type, current eating disorder diagnosis or current alcohol or

substance abuse or dependence on any prospective outcomes (see Table 6.6). Current

personality disorder diagnosis and number of previous episodes were significantly associated

with HAM-D and SOFAS scores longitudinally and were therefore included as covariates in

the regression models estimating HAM-D and SOFAS outcomes.

Current ADs were found to be significantly associated with HAM-D and MAS scores

at baseline and there was a trend towards reduced SOFAS scores as a function of anxiety at

inception (see Table 6.4). As such, the longitudinal models did not control for baseline HAM-

D, MAS or SOFAS scores in the first instance, as this would likely mean controlling for

variability as a function of anxiety status, which was the focus of this analysis. However, to assess the robustness of the findings, baseline scores for the relevant outcome variable were added to all models and re-analysed to assess the impact this had on any significant findings. For example, any AD as a predictor of HAM-D scores was estimated via three analyses in total: 1) any AD entered in the model alone; 2) any AD entered into the model whilst also adjusting for all other relevant covariates; 3) any AD, all relevant covariates and baseline HAM-D scores entered into the model simultaneously. This process was then adopted for all other analyses.

Table 6.6 *Testing the independent effects of specific covariates on prospective HAM-D, MAS and SOFAS scores for the whole sample*

Covariate	Outcome Variable (n = 259)		
	HAM-D[c]	MAS[c]	SOFAS[c]
Age at consent^	-0.02	-0.02	-0.01
Gender^	1.21	0.18	1.60
Bipolar diagnosis[d]	0.35	0.09	2.48
Current personality disorder	7.71*	1.17	-9.55*
Current eating disorder^	2.68	-0.20	-3.48
Current alcohol abuse / dependence	4.03	0.19	-2.92
Current substance abuse / dependence	-1.36	-0.67	-6.79
Number of previous episodes:			
8-19[a]	3.06*	0.55	-5.23*
20+[a]	4.03*	0.61	-6.8*

*$p < 0.01$; [a] *Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 weeks;* [c] *Refers to the regression coefficient of that specific outcome variable. All outcomes are longitudinal follow-up data;* [d] *Bipolar diagnosis coefficient refers to individuals with BDII compared to those meeting criteria for BDI;* ^*Site removed as a random effect*

As primary SCID anxiety symptoms at baseline were assessed as predictors of outcome for the ANX- group only, preliminary analyses also assessed other covariates as predictors of primary outcome measures in this group alone to inform the final regression models (see Appendix 4). There were no significant effects of any covariates on MAS or SOFAS scores. Only number of previous episodes had a significant effect on HAM-D outcomes for the ANX- group (20+ episodes: B = 2.73, SE = 1.00, p <0.01, 99% CI 0.76, 4.71)

and so number of episodes was adjusted for in the HAM-D analysis alone. As with previous

models, time point was included as a fixed effect, and site and participant were entered as

random effect terms in every model where effects could be estimated. Models were run

with and without the corresponding baseline score for the relevant outcome measure

included as a covariate to assess the robustness of any significant findings and to avoid

controlling out the effects of baseline anxiety symptoms.

6.5.4 Hypothesis 1: Any current AD as a predictor of prospective outcomes

Mean scores and SDs are presented in Table 6.7 for each group at each time point and show

that variability and level of manic symptoms was relatively low for both groups in

comparison to HAM-D and SOFAS scores.

HAM-D

Having a diagnosis of any AD was associated with significantly increased HAM-D

scores at follow-up (B = 2.40, SE = 0.63, p = <0.01, 99% CI = 0.76, 4.04) when entered into the

model independently. However, when adjusting for all covariates, any current AD was no

longer a significant predictor of depressed symptoms prospectively (see Table 6.8). Having a

diagnosis of a current personality disorder was the largest predictor, with those participants

having increased HAM-D scores longitudinally irrespective of anxiety status. Previous

number of bipolar episodes was a significant predictor of HAM-D scores at follow-up. All

significant effects were consistent across assessments, with no significant time

point*covariate interactions found. Adding baseline HAM-D score to the model as a

covariate did not affect the significance level for current personality disorder diagnosis,

which remained at p <0.01, however number of previous episodes was no longer significant.

HAM-D score at baseline was a significant predictor of HAM-D scores at follow-up in the final

model (B = 0.44, SE = 0.06, p <0.01, 99% CI 0.29, 0.58). This suggests that baseline symptom

scores were a better predictor of HAM-D outcome than historical data regarding previous

episodes, however current personality disorder diagnosis remained the largest predictor of HAM-D outcomes prospectively.

MAS

There was no effect of having any current AD on MAS scores across follow-ups (see Table 6.9). Entering baseline MAS scores in the model found that these were a significant predictor of manic symptoms at follow-up, with elevated baseline scores predicting increased manic symptoms at future assessments (B = 0.24, SE = 0.05, p < 0.01, 99% CI = 0.11, 0.38). This suggests that only baseline MAS scores were a reliable predictor of manic symptoms at follow-up in the current study.

SOFAS

There was a significant effect of any current AD on SOFAS scores at follow-up, with participants with current ADs having decreased SOFAS scores across assessments (B = -4.31, SE = 1.33, p = <0.01, 99% CI = -7.76, -0.86). However, when controlling for all covariates, having any current AD was no longer significant, although there was still a trend for reduced functioning for ANX+ participants (see Table 6.10). Similarly, there was a trend for reduced functioning across assessments for those with current personality disorders, and for all participants there was a tendency for better functioning outcomes at 48 week and 80 week assessments (both telephone assessments), although none of these findings reached significance. Only number of previous episodes significantly predicted functioning at follow-up, with participants with a history of 20+ episodes scored as having lower SOFAS scores across assessments. When baseline SOFAS scores were added to the model, number of episodes (20+) was no longer a significant predictor (B = -3.46, SE = 1.90, p = 0.07, 99% CI = -8.39, 1.48). Only baseline SOFAS scores were a significant predictor of SOFAS scores prospectively in the final model (B = 0.36, SE = 0.05, p < 0.01, 99% CI = 0.23, 0.49).

Table 6.7 *Mean scores for primary outcome measures by group and across follow-up points*

Time point	ANX+ mean (SD), n = 127			ANX- mean (SD), n = 132		
	HAM-D	MAS	SOFAS	HAM-D	MAS	SOFAS
16 weeks	7.96 (6.32)	2.16 (3.23)	70.12 (13.82)	5.84 (6.00)	1.83 (2.95)	75.41 (12.51)
32 weeks	8.24 (7.37)	2.00 (3.11)	71.50 (12.12)	6.44 (6.62)	1.33 (2.07)	72.81 (13.66)
48 weeks	8.28 (7.43)	1.61 (2.94)	72.06 (14.73)	5.07 (7.05)	1.70 (2.84)	78.10 (12.41)
64 weeks	8.29 (6.69)	1.70 (2.42)	71.33 (15.97)	5.37 (5.60)	1.94 (3.40)	76.60 (12.63)
80 weeks	6.97 (7.12)	1.56 (2.08)	73.64 (11.98)	5.38 (5.81)	1.41 (2.22)	76.76 (12.34)
96 weeks	6.93 (5.96)	1.92 (3.03)	72.19 (13.91)	5.32 (5.73)	1.61 (4.12)	75.67 (13.69)

Table 6.8 *Estimating the effect of having any current AD on HAM-D scores at follow-up (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Any current AD	1.19	0.62	0.06	-0.43	2.80
Current personality disorder	6.57	1.39	<0.01	2.99	10.15
Number of previous episodes:					
8-19[a]	2.63	0.94	0.01	0.19	5.07
20+[a]	3.24	0.88	<0.01	0.95	5.54
Time point[b]:					
32 weeks	0.39	0.51	0.44	-0.92	1.69
48 weeks	-0.28	0.51	0.59	-1.60	1.05
64 weeks	-0.24	0.52	0.65	-1.58	1.11
80 weeks	-0.61	0.53	0.25	-1.98	0.76
96 weeks	-0.64	0.56	0.25	-2.08	0.80

[a]*Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 week follow-up assessment; * Site has not been included as a random effect in the mixed regression model as random effects could not be estimated accurately. Removing this from the model made no difference to the fixed effect values.*

Table 6.9 *Estimating the effect of having any current AD on MAS scores at follow-up (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Any current AD	0.20	0.25	0.42	-0.44	0.84
Time point[a]:					
32 weeks	-0.35	0.25	0.17	-1.00	0.30
48 weeks	-0.30	0.26	0.24	-0.97	0.36
64 weeks	-0.13	0.26	0.62	-0.80	0.54
80 weeks	-0.42	0.27	0.12	-1.10	0.27
96 weeks	-0.17	0.28	0.55	-0.89	0.55

[a] *Reference time point is 16 week follow-up assessment*

Table 6.10 *Estimating the effect of having any current AD on SOFAS scores at follow-up (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Any current AD	-2.68	1.37	0.05	-6.24	0.88
Current personality disorder	-7.21	3.01	0.02	-15.03	0.61
Number of previous episodes:					
8-19[a]	-4.55	2.08	0.03	-9.96	0.86
20+[a]	-5.63	1.96	<0.01	-10.72	-0.53
Time point[b]:					
32 weeks	-0.54	1.01	0.59	-3.13	2.06
48 weeks	2.48	1.02	0.02	-0.16	5.12
64 weeks	1.55	1.04	0.14	-1.14	4.23
80 weeks	2.52	1.06	0.02	-0.21	5.24
96 weeks	1.27	1.11	0.25	-1.60	4.14

[a]*Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 week follow-up assessment; * Site has not been included as a random effect in the mixed regression model as random effects could not be estimated accurately. Removing this from the model made no difference to the fixed effect values.*

6.5.5 Hypothesis 2: Individual ADs as predictors of longitudinal outcomes

The predictor 'Any AD' was exchanged for individual ADs entered as binary variables into the model simultaneously to represent presence or absence of each disorder, and to control for those participants who met criteria for multiple anxiety diagnoses. Due to the relatively low number of participants meeting criteria for PD (n = 5), PD and PD_Ago were combined as a single category. All covariates in the previous models were retained, and relevant baseline

symptom or functioning scores were added to the model post-analysis to test the robustness of any significant effects. Full output data is provided in Appendix 5.

HAM-D

Individuals with a diagnosis of OCD and GAD had significantly higher HAM-D scores at follow-up after adjusting for current personality disorder and number of previous episodes (see Table 6.11). There were no significant interaction effects with time point for either AD, which suggests this effect was significant across follow-ups. However, when adding baseline HAM-D scores to the model, baseline scores significantly predicted HAM-D scores at outcome (B = 0.42, SE = 0.06, p < 0.01, 99% CI 0.27, 0.57), whilst independent effects of OCD did not (B = 1.09, SE = 1.01, p = 0.28, 99% CI -1.55, 3.72). However, GAD remained a significant predictor of increased HAM-D scores across all follow-ups (B = 1.82, SE = 0.69, p <0.01, 99% CI 0.02, 3.61).

MAS

OCD also predicted increased MAS scores at follow-up compared to those participants who did not have a diagnosis of OCD. In contrast, there was a protective effect of having SoP, with those participants reporting significantly lower manic symptoms prospectively. These effects were found across follow-ups, with no significant AD*time point interactions. When baseline MAS scores were added to the model, SoP retained a significant negative association to MAS scores (B = -1.22, SE = 0.39, p = <0.01, 99% CI = -2.23, -0.20), and OCD remained significantly associated with increased MAS scores at follow-ups (B = 1.25, SE = 0.41, p <0.01, 99% CI = 0.20, 2.31).

SOFAS

There were no independent effects of individual ADs on SOFAS outcomes.

Table 6.11 *Estimating the effect of individual ADs on longitudinal outcomes (n = 259)*

IV	HAM-D[a]	MAS[a]	SOFAS[a]
PD with / without Ago *B*	0.003	-0.71	-3.16
Agoraphobia *B*	0.57	-0.58	-5.45
Social anxiety *B*	-0.84	-1.18*	0.04
Specific phobia *B*	1.11	0.62	2.72
OCD *B*	2.75*	1.39*	-3.46
PTSD *B*	3.16	-0.03	-3.94
GAD *B*	1.95*	0.54	-2.05

Significant at p ≤ 0.01; [B]All regression coefficients refer to the effect of having an individual AD compared to participants in both the ANX+ and ANX- group who do not having a diagnosis of that disorder; [a] All models retain covariates included in the previous models estimating the effects of any AD on outcome

6.5.6 Hypothesis 3: Self-reported anxiety symptoms (HADS-A) as a predictor of prospective outcomes

Exchanging AD diagnoses for baseline HADS-A score showed that anxiety symptoms were a better and more robust predictor of HAM-D outcome overall. Increased HADS-A scores at baseline significantly predicted increased HAM-D scores across follow-ups (See Table 6.12), with no time point*HADS-A interaction effects. HADS-A remained a significant predictor when controlling for baseline HAM-D scores, although the effect size reduced slightly (B = 0.38 to B = 0.20) due to baseline MAS and HAM-D scores accounting for some of the variance in outcome.

There was no significant effect of HADS-A scores on manic symptoms across assessments (see Table 6.13). There was a significant effect of anxiety symptoms on SOFAS scores at follow-up, with increased HADS-A scores predicting decreased functioning across all follow-up points (see Table 6.14). HADS-A score at baseline remained a significant predictor of decreased SOFAS scores longitudinally after controlling for baseline SOFAS scores (B = -0.38, 0.14, p <0.01, 99% CI -0.74, -0.03), indicating that anxiety symptoms predicted reduced functioning.

Table 6.12 *HADS-A scores as a predictor of HAM-D scores at follow-up (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Baseline HADS-A score	0.38	0.06	<0.01	0.22	0.54
Current personality disorder	5.89	1.26	<0.01	2.61	9.18
Number of previous episodes:					
8-19[a]	2.05	0.91	0.03	-0.32	4.42
20+[a]	2.14	0.88	0.02	-0.16	4.43
Time point[b]:					
32 weeks	0.34	0.53	0.53	-1.03	1.71
48 weeks	-0.06	0.54	0.92	-1.45	1.34
64 weeks	-0.22	0.55	0.68	-1.64	1.19
80 weeks	-0.41	0.56	0.46	-1.85	1.02
96 weeks	-0.55	0.58	0.34	-2.06	0.95

[a]*Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 week follow-up assessment;* *Site has not been included as a random effect in the mixed regression model as random effects could not be estimated accurately. Removing this from the model made no difference to the fixed effect values.*

Table 6.13 *HADS-A scores as a predictor of prospective MAS scores (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Baseline HADS-A score	0.05	0.03	0.08	-0.02	0.12
Time point[a]:					
32 weeks	-0.41	0.27	0.13	-1.10	0.28
48 weeks	-0.29	0.27	0.29	-1.00	0.42
64 weeks	-0.12	0.28	0.67	-0.83	0.60
80 weeks	-0.42	0.28	0.13	-1.15	0.30
96 weeks	-0.15	0.30	0.62	-0.91	0.61

[a]*Reference time point is 16 week follow-up assessment*

Table 6.15 *HADS-A scores as a predictor of prospective SOFAS scores (n = 259)*

	B	SE	P	99% CI Lower	99% CI Upper
Baseline HADS-A score	-0.55	0.14	<0.01	-0.65	-0.44
Current personality disorder	-7.17	2.80	0.01	-9.24	-5.10
Number of previous episodes:					
8-19[a]	-3.81	2.05	0.06	-5.33	-2.30
20+[a]	-3.62	1.98	0.07	-5.08	-2.15
Time point[b]:					
32 weeks	-0.62	1.05	0.55	-1.39	0.15
48 weeks	2.06	1.07	0.05	1.28	1.85
64 weeks	1.46	1.08	0.18	0.66	2.26
80 weeks	2.30	1.09	0.04	1.49	3.11
96 weeks	1.53	1.15	0.18	0.68	2.39

[a]*Individuals within the $\leq$ 7 episodes category are the reference group;* [b] *Reference time point is 16 week follow-up assessment*

6.5.7 Hypothesis 3: Observer-rated primary SCID anxiety symptoms and prospective outcomes in the ANX- group

Anxiety symptoms were reported by 33% to 50% of the ANX- group across follow-ups, suggesting that anxiety symptoms were persistent even for individuals who didn't meet criteria for current or past ADs (see Figure 6.1).
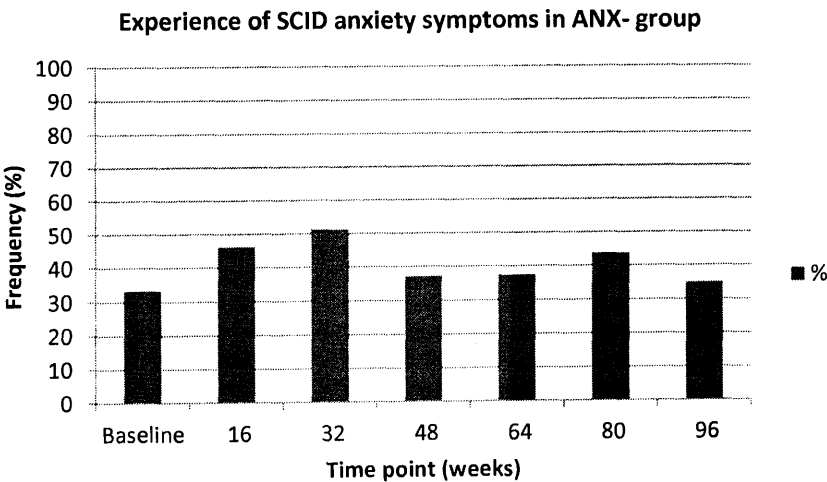
Figure 6.1 *Percentage of participants experiencing primary SCID anxiety symptoms across follow-up assessments (n = 132)*

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When testing for the effect of individual baseline anxiety symptoms on outcome, all

symptoms were entered into the model together to control for participants who reported

multiple anxiety symptoms (see Table 6.16). There was a significant effect of experiencing

any anxiety symptom at baseline which predicted elevated HAM-D scores at follow-up. This

effect remained significant even after controlling for baseline HAM-D scores, although the

effect size was reduced due to baseline HAM-D scores accounting for a proportion of

variance in outcome (B = 4.05 to B = 2.75). There was no significant effect of any individual

SCID anxiety symptom on HAM-D outcomes, and there were no effects of SCID anxiety

symptoms on MAS or SOFAS scores across follow-ups. Full output data is provided in

Appendix 6.

Table 6.16 *Estimating effect of anxiety symptoms on HAM-D, MAS and SOFAS scores at follow-up for participants with no current or past AD at baseline (ANX-; n = 132)*

Baseline Symptom	HAM-D[a^]	MAS[b]	SOFAS[c^]
Any anxiety symptoms	4.05*	0.78	-4.25
Panic attacks	0.93	1.55	1.02
Agoraphobia	1.72	0.62	-2.65
Social anxiety	3.11	0.52	-1.37
Specific phobia	0.40	0.29	-0.77
Obsessions / compulsions	2.56	0.39	-3.44
Worry	2.29	-0.08	-4.32

[a] *Number of episodes is adjusted for as a covariate as there was an independent effect of this variable on outcome;* [b] *Baseline SOFAS score is included as a covariate;* * p < 0.01; ^ *Site has not been included as a random effect in the mixed regression model as random effects could not be estimated accurately. Removing this from the model made no difference to the fixed effect values.*

6.6 Discussion

6.6.1 Interpretation of key findings

Consistent with previous research (see Chapter 1, Section 1.4.1), current ADs were

associated with a more severe illness course retrospectively, including earlier age of onset of

BD, increased number of bipolar mood episodes, and increased psychiatric disorders, with

the exception of substance abuse and dependence, with rates of this being relatively low in

both groups when separated according to AD diagnosis. Also in-line with previous research

(see Chapter 1, Section 1.3.5), there were no significant differences in sociodemographic

variables between those with and without current ADs at baseline, although there was a

trend for ADs to occur more often for women than men.

Previous research has found high levels of anxiety symptoms and experiences for

individuals with BD who fail to meet threshold criteria for AD diagnosis (Contreras et al.,

2010; Frank et al., 2002), questioning the validity of diagnostic assessments of anxiety. This

finding was replicated in the present study. Although AD diagnosis was a significant predictor

of elevated anxiety symptoms at baseline, categorical anxiety diagnoses were not a reliable

predictor of the experience of anxiety for all participants. There were more participants

reporting experience of primary anxiety symptoms assessed using the anxiety SCID-DSM-IV

questions than those meeting criteria for ADs. Likewise, meeting criteria at screening for AD

diagnosis was not consistently associated with experiencing symptoms related to that

disorder in the brief period between screening and baseline assessment. It may be that

validated self-report or observer rated measures which assess a range of anxiety symptoms

would provide a more accurate reflection of anxiety experiences than diagnostic or single

symptom assessments.

As previously discussed in Chapter 1 (Section 1.2.2), diagnoses are only useful if they

are reliable predictors of symptoms over time and allow treatment to be focused

accordingly. Based on the current literature, it was hypothesised that current ADs would

predict increased depressed and manic symptoms and reduced functioning longitudinally.

Although there was a significant effect of any current AD on HAM-D and SOFAS outcomes

when entered into the model independently, current AD status was not found to be a robust

predictor of these outcomes after adjusting for other clinical variables. Current AD did not

predict MAS scores in any model. Baseline symptom and functioning scores were the most

consistent predictors of symptoms and functioning across follow-ups in the categorical

models. Only baseline manic symptoms predicted mania prospectively, although manic symptom scores were relatively low for all participants across follow-ups. Similarly, baseline depression and SOFAS scores were significant predictors of prospective functioning and depression after controlling for all other covariates. Current personality disorder diagnosis was the largest predictor of depressed outcomes, and number of previous episodes predicted depression and functioning scores longitudinally. These findings are in contrast to the original hypothesis for this study and other current existing longitudinal studies which have found significant effects of ADs in relation to outcomes in BD (see Chapter 1, Section 1.4.3). This discrepancy may be due to the current study controlling for a number of baseline measures, in particular baseline symptoms of depression, which may have accounted for the variance in outcomes explained by ADs elsewhere. This study also used symptoms as a primary outcome, compared to previous research which has generally focused on relapse rates.

Hypothesis 2 stated that there would be no significant effect of individual ADs on outcomes, based on previous research which has found that these effects disappear after adjusting for other relevant variables (Simon et al., 2007). However, there was evidence that individual ADs were significant predictors of outcome in this study, even after controlling for all other covariates in the final model. This suggested that a categorical approach to anxiety was more useful when testing the effects of independent ADs on outcome as opposed to testing any current AD. GAD and OCD were associated with increased depression across follow-ups, although the effect for OCD was no longer significant when accounting for baseline HAM-D scores. OCD and SoP were also associated with increased and decreased MAS scores respectively, which remained significant after controlling for all other variables. Evidence regarding the association between anxiety and manic symptoms is currently mixed, and anxiety has been suggested to be both a protective factor and a risk factor to increased manic symptoms and relapse (see Chapter 1, Section 1.3.4). The current investigation

provides support for both sides of this argument, with SoP linked to reduced MAS scores and OCD to increased manic symptoms. This may explain the lack of significant effect of any AD on outcomes, where potentially dissimilar anxiety experiences were grouped together. However, these results may also have been biased due to GAD, OCD, and SoP being over-represented in the current sample compared to other ADs, and due to the relatively small variation in manic symptoms observed throughout the study.

As predicted (Hypothesis 3) anxiety symptoms significantly predicted prospective outcomes. Self-reported HADS-A scores were a significant predictor of depression and functioning scores for all participants after accounting for all covariates, and this was consistent across follow-ups. There was no significant association between manic symptoms and self-reported anxiety symptoms. SCID primary anxiety symptoms were less predictive of outcome than self-reported symptoms when assessed in the ANX- group and were associated only with depression scores prospectively after controlling for all other variables.

These results suggest that assessing only presence of any current AD was not a reliable predictor of outcome in this sample, and that other categorical and symptomatic covariates were more useful clinical predictors longitudinally. Of the anxiety variables, self-reported anxiety symptoms were the most robust predictor of depression and functioning outcomes, as predicted (Hypothesis 4). However, in contrast to the original hypothesis, anxiety symptoms were not a better predictor of mania scores in this study, and only independent ADs (OCD and SoP) reliably predicted prospective experiences of manic symptoms.

6.6.2 Clinical implications and future research

The close association of anxiety symptoms with depressed outcomes longitudinally reinforces previous research which has found consistent links between these experiences (see Chapter 1, Section 1.4.4). The finding that anxiety symptoms were experienced at

relatively high levels by individuals with and without AD diagnoses in this study also supports

the theory that anxiety is an intrinsic part of BD (see Chapter 1, Section 1.6.4). This is useful

in clinical practice, as assessment of self-reported anxiety symptoms in particular could be a

useful indicator of those individuals who may be most at risk of experiencing a depressed

trajectory. Therapeutic interventions which target both anxiety and mood fluctuations in BD

are once again indicated in this study. Current research which has begun to explore

combined treatments have been discussed previously (see Chapter 1, Section 1.7). However,

the present study highlights the need for combined interventions to focus on the

relationship between anxiety and depression in particular to help stabilise mood. This study

is helpful in indicating other variables which may also signpost a likely worse illness course,

including number of previous episodes and current personality disorder diagnosis, which

may be helpful in indicating those people who may be at increased risk and require

additional help and support. As with previous research, the current study does not allow for

the exploration of the interaction between anxiety and bipolar mood symptoms, the

temporal relationship which leads to poorer outcomes or the psychological processes which

underlie this. A study which attempts to explore these interactions in more detail and to

contextualise changes in mood and anxiety in which they occur is presented in Chapter 7.

6.6.3 Strengths and limitations

This study was an analysis of partial secondary outcome data collected within a large scale

RCT, although all but 30 participants had completed the study at the time of analysis. Within

the available dataset, almost half of participants had completed all six follow-up

assessments, and three quarters of participants had completed at least half. Missing

outcome data were not imputed in this study and reasons for missing data were unknown.

Therefore it cannot be concluded that data were missing at random and failure to complete

follow-ups may have been associated with primary outcomes such as depression, mania or

functioning. This may have resulted in bias in the results, potentially excluding people who had high levels of symptoms and felt unable to take part, or those who were well and no longer felt it necessary to take part in the study, although this is speculative. Data regarding depressive and (hypo)manic relapse were the primary outcome measure for the PARADES Psychoeducation study. This data was unavailable at the time of the present investigation but could be used in future analyses to assess if missing data was associated with relapse. However, the present study was an analysis of data from a large scale RCT and the key questions were the internal relationships for which data were available.

Anxiety was assessed in this study as an independent predictor of mood and functioning outcomes, however there is growing evidence in the current existing literature and this thesis for anxiety as in intrinsic part of BD. Given the consistent association between anxiety and depression across studies (see Chapter 1, Section 1.4) it cannot be discounted that there was likely a degree of multi-collinearity between measures of anxiety and depression, and potentially anxiety and manic symptoms also. However, this study accounted for baseline mood and functioning outcomes in all analyses to assess the robustness of anxiety as an independent predictor.

It is unknown which participants in this study were allocated to the psychoeducation condition and the number allocated to the peer support group. As such, the impact of experimental condition on anxiety and outcomes cannot be controlled for in the present study. The application of random sampling, which used number of previous episodes to stratify and which was a factor related to anxiety experiences at baseline in the present investigation, should have led to relatively equal allocation of participants with a range of anxiety experiences at baseline to both study arms, especially in a large scale definitive trial of this sort. However, this would not have controlled for how well either arm of the intervention worked to reduce anxiety across follow-up points, which may have impacted on outcomes.

Data regarding Inter-rater reliability for the primary outcome measures in this study was not reported here as this was not available at the time of analysis. This is potentially important as possible consistent differences between raters cannot be eliminated and there may have been over or under-rating on the scales used. However, the use of standardised, semi-structured interview schedules was employed to minimise inconsistencies, and all raters received identical training and structured supervision throughout the study.

Finally, anxiety symptom measures were pre-determined prior to the beginning of this thesis. As such, anxiety symptoms were not measured using the current gold-standard for observer-rated or self-reported anxiety symptoms. These include the State-Trait Anxiety Inventory (self-report measure; Spielberger & Reheiser, 2004) and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959), which may have provided more comprehensive anxiety assessments. In particular, the use of primary SCID-DSM-IV symptoms as a measure of anxiety symptoms rather than diagnosis has not been validated. However, all measures and questions used to assess anxiety were standardised and the HADS-A has an evidence base showing acceptable validity and reliability elsewhere (see Section 6.3.3).

6.6.4 Conclusion

This study found that anxiety was a significant predictor of mood and functioning outcomes prospectively in BD, and that considering anxiety as symptoms on continua was more useful than diagnostic criteria as predictors for depressive and functioning outcomes. However, individuals ADs, specifically OCD and SoP, were more useful in predicting manic symptoms longitudinally. This study replicates consistent associations between anxiety and depression found elsewhere, and suggests that anxiety may be an inherent part of BD depression. Anxiety and mania were not consistently linked in this study, potentially due to the lack of variability in manic scores. Future research exploring anxiety for individuals with increased levels of manic symptoms would be useful.

Chapter 7: Study 3 - The EMOTE Study (Everyday Momentary Observations of Thoughts and Emotions) - exploring anxiety and mood interactions using ESM

7.1 Introduction

Research regarding anxiety in BD has consistently linked anxiety to poorer outcomes using retrospective, cross-sectional and longitudinal designs (see Chapter 1, Section 1.4). However, these methods often employ the use of interview and questionnaire reports to recall anxiety and mood symptoms over a specified period of time. In addition, outcomes are often focused on categorical clinical outcomes of relapse or recovery from mood and anxiety symptoms. As a result, data may be subject to recall bias from participants and may fail to capture subtle changes in anxiety and mood symptoms or the context in which these occur. A methodology which resolves these issues is the experience sampling method (ESM), which has been used to collect data about psychological phenomena in real time (Larson & Csikszentmihalyi, 1983). ESM involves the collecting of data in real life situations, usually several times a day for a six or seven day period, and was developed to provide a more accurate means of understanding subjective experience in psychological research. Using this method, the need for retrospective recall is minimised and the interaction of variables such as affect, anxiety, thoughts and behaviour can be assessed together over time and in the context in which they occur, allowing underlying mechanisms and processes to be observed (Ebner-Priemer et al., 2009). In particular, the momentary assessment of experiences allows potentially more subtle fluctuations and interactions to be detected than is possible in other longitudinal designs with a longer time lapse between observations.

Whilst the publication of experience sampling research has gradually increased over the past 20 years, a recent review highlighted that the majority of ESM research exploring mood disorders has been focussed on participants with a diagnosis of UD (aan het Rot et al., 2012). More recently, ESM research with bipolar samples has begun to emerge, providing

information about the dynamics of affect in bipolar samples, alone and in comparison to other clinical groups. ESM has been found to be a feasible and acceptable methodology when measuring thoughts, affect and behaviour in bipolar samples, with low attrition rates and no prominent fatigue effects (Depp et al., 2010; Husky et al., 2010; Myin-Germeys et al., 2003). Previous ESM and research using diaries with euthymic participants with BD suggests there may be little difference in the overall level of reported symptoms of positive affect (PA) or negative affect (NA) compared to controls, but that individuals with BD have significantly elevated variability of affect (Knowles et al., 2007; Kwapil et al., 2011). Non-ESM research has found similar increased variability in activity levels compared to control participants also (Jones et al., 2005), suggesting a potential inherent instability and dysregulation of mood and behaviour in BD. To our knowledge, there are no existing ESM studies exploring the momentary interaction of anxiety and affect in BD, although research has explored emotional reactivity in response to stress. A previous study by Myin-Germeys et al. (2003) found that individuals with BD had greater decreases in PA in response to perceived stressors compared to controls. A second study by Havermans et al. (2007) exploring time use and appraisal of events found that whilst there was no difference in the frequency of events reported by bipolar and control participants, individuals with BD with sub-threshold symptoms of depression perceived negative events as more stressful. This gives an insight into the potential impact of environmental stressors on mood, however does not explore anxiety in response to daily life events or the impact this may have on the experience of NA and PA.

Affect refers to the experience of emotion and current research suggests that this experience is made up of two separate, unipolar constructs of positive and negative affect, rather than bipolar opposites of a single continuum (Watson & Clark, 1997; Watson, Clark, & Tellegen, 1988; Zevon & Tellegen, 1982). This is supported by research showing that positive and negative affect often have weak negative correlations (Watson & Clark, 1997) suggesting

that these are independent factors which can occur simultaneously. Based on current research and findings within this thesis, there is a progression towards the conceptualisation of anxiety as a feature of a more general dysregulation of emotion, rather than a separable or independent experience of bipolar mood symptoms. As such, there is a debate regarding whether NA and anxiety can be reliably measured as separate constructs. There is evidence that anxiety and depression are underpinned by shared psychological processes. Bird et al. (2013) found that thought suppression, experiential avoidance and worry were equally predictive of depression, anxiety and stress whether considered separately or as a single latent factor. This was suggested to represent a core process of negative, uncontrollable thinking across anxiety and depression (Bird et al., 2013). Negative thinking has been proposed to differ in content, but not process, in the experience of anxiety and depression (Segerstrom et al., 2000). For example, worry is future-focussed and rumination is past-focussed, but both represent a single process of negative cognitive style (Watkins, Moulds, & Mackintosh, 2005).Whilst NA and anxiety are undoubtedly related, it is possible to have low mood without feeling excessively anxious, and likewise to feel anxious without being low in mood (Maes, Meltzer, Cosyns, & Schotte, 1994). Previous research which has assessed state anxiety and NA independently in non-bipolar samples has found significant moderate correlations (Andreotti et al., 2013; Carrieri-Kohlman, Donesky-Cuenco, Park, Mackin, Nguyen & Paul, 2010), with correlation coefficients of $r = 0.45$ and $r = 0.62$ in these studies respectively. Raghunathan & Pham (1999) differentiated undergraduate participants based on ratings of state anxiety and sadness. Whilst both affective states were associated with interference in decision making and information processing in comparison to a neutral control group, higher ratings of sadness were associated with high risk/high reward decisions, whilst those with higher ratings of anxiety made decisions linked to low risk/low reward (Raghunathan & Pham, 1999). This suggests that whilst low mood and anxiety have shared psychological mechanisms, exploring facets of NA such as anxiety and low mood

independently is not redundant and emotions of the same valence may effect these processes in qualitatively different ways. The majority of the existing research presented here is cross-sectional. In contrast, the present study aimed to explore the dynamic inter-relationship between the experiences of anxiety and bipolar mood symptoms. As such, NA, PA and anxiety were measured independently, whilst being mindful of the likely high association and shared processes across these experiences.

The aim of the current study was to explore the momentary interaction of anxiety and affect in daily life to establish to what extent anxiety is related to fluctuations in mood and to identify factors which trigger fluctuations in anxiety and affect. Specifically, this study tested the following hypotheses:

1. Euthymic individuals with BD will have higher average ratings of anxiety, NA and PA over a seven day period

2. Euthymic individuals with BD will experience greater variability of affect and anxiety compared to controls over a seven day period

3. Baseline anxiety will predict variability of NA and PA for all participants

4. Changes in NA, PA and anxiety will influence mood ratings at the next time point for all participants

In addition, thoughts, activities and contexts associated with changes in anxiety, NA and PA were explored and compared between individuals with BD and non-clinical controls to identify triggers to fluctuations of affect and anxiety. The EMOTE study was designed to collect data for three independent PhD theses – the current study and two others: (1) exploring sleep patterns, mood and activity and (2) mood interpretation and management. Only methods and results relevant to this thesis are presented here.

7.2 Method

7.2.1 Sample Size

Power calculations for multilevel data must address the issue of sample size at all levels; that is number of participants per group and number of observations per participant. As such, a standard power calculation is not appropriate. Few multi-level studies have carried out any power analysis prior to completion (see Dedrick et al., 2009 for a review) and previous research has used samples ranging from 10 to 49 participants with no clear rationale for these sample sizes (Havermans, Nicolson, Berkhof, & deVries, 2010; Husky et al., 2010; Myin-Germeys et al., 2003). The existing research outlining power analysis for multi-level data is still relatively new, and whilst potential methods have been proposed there is currently no consensus regarding whether proposed methods are statistically meaningful or accurate at this stage (Scherbaum & Ferreter, 2009; Snijders, 2005). As a result, a formal power analysis was not completed for this study. Instead, based on previous studies in which significant findings have been shown for small to moderate effect sizes exploring the relationships between similar variables such as NA and PA with samples $\leq$ 49 participants (Depp et al., 2010; Husky et al., 2010; Myin-Germeys et al., 2003; Knowles et al., 2007), a conservative recruitment target of 50 participants per group was set. This allowed for expected potential attrition rates based on previous ESM bipolar research of between 0% and 10% (Depp et al., 2010; Havermans, Nicolson, Berkhof, & deVries, 2011; Havermans et al., 2007; Husky et al., 2010), to leave a minimum sample of 45 per group.

7.2.2 Recruitment

This study was approved by the NHS Research Ethics Committee on 29th October 2010 (Lancaster committee, study reference: 10/H1015/76). Recruitment took place over a 12 month period starting in February 2011. Control participants were recruited primarily

from an online study exploring sleep, mood, personality style and activity in individuals with

BD, fibromyalgia and healthy controls ("Is a good mood linked to a good night's sleep?";

www.sleepandmood.co.uk; NHS ethics reference: 10/H1015/75). The online questionnaire

study recorded information about experience of past and current mental health disorders

and identified potentially eligible participants for the present study. Participants meeting

criteria for the control group in the online study and who left their contact details to be

contacted about future research were invited to take part in the EMOTE study (Everyday

Momentary Observations of Thoughts and Emotions), an ESM study exploring thoughts,

emotions, activity and sleep. Bipolar and additional control participants were also recruited

through primary and secondary care NHS services and voluntary mental health services in

the North West of England, West Yorkshire, Merseyside and Lincoln. Self-referrals were

encouraged through advertisements in the local press, on social networking sites and via

service user forums. In addition, EMOTE study information was also sent to individuals who

had registered their interest in research on a University participant database and who had

given consent to be contacted regarding new research. All participants who registered their

interest were contacted via the telephone to complete a pre-screen to confirm likelihood of

eligibility for the ESM study (see Appendix 7). The pre-screen collected information

pertaining to the primary inclusion criteria for each group as follows.

7.2.2.1 Inclusion and exclusion criteria

All participants had to be able to give informed consent, to communicate in English

to a sufficient level to allow completion of the interview and self-report measures

independently and to be aged 18 years or older. Other group-specific criteria also applied:

Inclusion Criteria - Bipolar Group: diagnosis of primary bipolar I or II disorder; no current

manic, hypomanic, mixed affective or major depressive episode, or within the past four

weeks; no current suicide plans or intent; not working night shifts.

Inclusion Criteria – Control Group: no lifetime experience of any severe or enduring

mental health problem (bipolar I or II disorder, psychosis, personality disorder,

schizophrenia, schizo-affective disorder, organic brain disorder such as dementia or brain

injury); no other mental health problem within the past two years (depression, eating

disorder, hypomanic episode, substance or alcohol abuse or dependence); no current

suicidal intent or ideation; not working night shifts; no severe sleep disturbance or diagnosis

of any sleep disorder within the past month; no current diagnosis of fibromyalgia or any

other severe pain disorder, as this is likely to have symptoms similar to BD including sleep

disturbance and low mood (Hudson, Arnold, Keck, Auchenbach, & Pope, 2004; Wolfe et al.,

2010).

To avoid including participants in the control sample who may have had experience of

sub-threshold hypomanic experiences or who had hypomanic personality styles, an

additional inclusion criteria required control participants to have a score of $\leq$ 15 on the

Hypomanic Personality Scale (HPS) (Eckblad & Chapman, 1986). The HPS is a validated, self-

report questionnaire used to identify members of the general population who may be

predisposed to hypomanic experiences and potentially at risk of BD. Example statements

include 'a hundred years after I'm dead my achievements will probably have been forgotten'

(HPS positive answer 'false') and 'I often get into excited moods where it is impossible for me

to stop talking' (HPS positive answer 'true'). In line with previous research, the threshold was

defined as a HPS score no higher than 0.5 of a standard deviation (SD) above the sample

mean (Kwapil et al., 2000). The sample mean was determined by asking a large number of

potential control participants (n = 623) to complete the HPS as part of the online

questionnaires prior to recruitment for EMOTE. The mean of this sample was 11.50, SD =

7.91, which gave a threshold score of 15 on the HPS. The online survey was left open

throughout recruitment to increase referrals. At the end of the study the total number of

participants completing the HPS online was 881. The final online sample had an overall mean

HPS score of 11.4 and SD = 7.78. As a result, the HPS threshold remained unchanged at 15.

7.2.3 Measures

Below is a description of the primary standardised interview and questionnaire measures

used in the present study, together with a description of the development of a novel coding

scheme for ESM items recorded as open questions. Where applicable, the inter-rater

reliability for these measures is also reported at the end of each relevant section. This was

done to ensure only results relevant to the primary research question are reported in the

final results section.

7.2.3.1 Observer-rated interviews and standardised questionnaires

SCID-IV - Research Version (First et al., 1997)

All participants were interviewed using the SCID-DSM-IV to confirm either absence

of any mental health diagnosis (control) or presence of a primary diagnosis of BD and any

other current axis I psychiatric disorders (bipolar). To reduce interview time and burden to

participants, individuals with a diagnosis of BD were not asked about any other lifetime

disorders except ADs.

Longitudinal Interval Follow-Up Examination (LIFE) (Roy-Byrne, Post, Uhde, Porcu, &

Davis, 1985)

Used at baseline to confirm absence of any depressed, manic or hypomanic episode

meeting SCID-DSM-IV criteria over the previous four weeks. This interview has been shown

to be reliable for up to three months recall of mood experiences in clinical samples (Simon &

Rutter, 2008). Based on answers to questions for the SCID-DSM-IV interview for depression

and mania, participants are assigned a 'LIFE' score from 1 - 6 for depression and 1 – 6 for

(hypo)mania for each of the four weeks prior to baseline. A score of 1 refers to absence of any symptoms and reflects an individual being their 'usual self'. Scores ranging from two to four represent increasing severity of sub-threshold symptoms, with scores of 5 and 6 signalling that SCID-DSM-IV criteria is met for either a manic (1 week with a LIFE score $\geq$ 5) or depressed episode (2 consecutive weeks with a LIFE score $\geq$ 5). To meet study eligibility participants were required to have LIFE scores $\leq$ 4 every week prior to baseline to confirm absence of any mood episode.

Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960)

A widely used 17-item observer rated interview which assesses presence and severity of depressed symptoms over the previous seven days. Issues have been highlighted with the HAM-D in terms of potentially limited inter-rater and retest reliability for some items and due to its multi-dimensional method of including symptoms such as anxiety to assess depression (Bagby et al., 2004). However, the HAM-D is still currently considered the gold standard for the assessment of depression in clinical research (Cusin et al., 2009) and was chosen to allow comparison to the existing literature. To address issues of reliability, the assessment was delivered using a semi-structured interview format which has been found to increase inter-rater reliability when using the HAM-D (Morriss et al., 2008).

Bech-Rafaelsen Mania Rating Scale (MAS) (Bech et al., 1978)

The MAS is a well validated, observer-rated interview which is used regularly in research with individuals with a diagnosis of BD (Bech, 2002). The MAS assesses the presence and severity of (hypo)manic symptoms based on 11 items assessing mood and behaviour over the previous week.

Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959)

A well validated and reliable 14-item observer-rated interview to assess psychic and somatic symptoms of anxiety. The interview was delivered in a standardised format using the Structured Clinical Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) which has been shown to increase accuracy and inter-rater agreement (Shear et al., 2001).The HAM-D, MAS and HAM-A assessments were incorporated into the LIFE interview to avoid repetition with other questions about mood and anxiety.

7.2.3.2 Inter-rater reliability for observer rated interviews

SCID and LIFE assessments (including HAM-D, HAM-A and MAS) were completed by one of three researchers (all part of the EMOTE team): KH (1st author), FB (doctoral student) and HR (doctoral student and research assistant). There was a relatively even split of participants in the final samples seen by each interviewer: KH (n = 31), HR (n = 31), FB (n = 33). All researchers received full training on all measures and on-going clinical supervision throughout from the wider PARADES research team which included two clinical psychologists (SJ and FL) and a psychiatrist (RM). To assess inter-rater reliability each interviewer independently coded a sample of interviews for each group. In-line with the study inclusion criteria and primary research questions, all SCID modules were subject to inter-rater assessment for 10% of control participants, and the mood and anxiety modules were assessed for inter-rater agreement for 20% of participants with BD. Inter-rater consistency on 10% of the HAM-D, HAM-A and MAS data was analysed using an intra-class correlation co-efficient, two-way mixed model. Data selected for this purpose were not random and, where possible, were selected to include participants who had a range of scores on each measure to avoid false high agreement levels produced by rating those with zero symptom scores.

There was 100% agreement between raters regarding absence of any mental health diagnosis for controls (n =6) and presence of bipolar diagnosis for bipolar participants (n = 6). The SCID anxiety modules were assessed for inter-rater agreement for bipolar participant's data (see Table 7.1). Twelve data sets were included at this stage to compare ratings for participants with a range of anxiety diagnoses, from no anxiety to multiple disorders. Rate of agreement for the presence of ADs as diagnosed by the original interviewer were assessed (see Table 7.1). At least two raters (the original interviewer and one other) agreed in 94% of cases, and rate of total agreement between all three raters was 76%.

Table 7.1 *Inter-rater agreement on the SCID anxiety modules*

SCID Anxiety Module	Number of participants rated by original interviewer as meeting threshold (n = 12)	3/3 agreement	2/2 agreement
Panic disorder	2	1/2	0/2
Panic disorder with agoraphobia	1	1/1	Na
Agoraphobia	1	1/1	Na
Social phobia	3	Na	3/3
Specific phobia	2	2/2	Na
OCD	1	Na	1/1
PTSD	3	3/3	Na
GAD	4	3/4	¼

Inter-rater agreement for LIFE and symptom ratings

Agreement on LIFE scores and symptom scores were assessed for bipolar (n = 6) and control (n = 6) participants. There was 100% agreement regarding absence of any mood episode meeting SCID-DSM-IV criteria in the four weeks prior to baseline, evidenced by LIFE scores of ≤ 4 by all raters. Looking at continuous measures of symptoms, agreement was highest for the HAM-A (ICC = 0.92, CI 95% = 0.82, 0.98) and HAM-D scores (ICC = 0.94, CI 95% = 0.85, 0.98), and only slightly lower, but still acceptable, for the MAS (ICC = 0.74, CI 95% =

0.47, 0.91). The lower ICC for the MAS may have been due to this scale having a skewed distribution, with few participants scoring positive for manic symptoms. As such, any discrepancy between raters is likely to have impacted more strongly on the ICC.

7.2.3.4 ESM assessment measures

A set of 10 diary entries (one per alert) were collated in a small, A5 booklet, with one diary provided for each day of the study. ESM assessments were designed to take two to three minutes to complete and every assessment form consisted of the same 14 individual sections. However, only seven of these sections are relevant to the present study (see Table 7.2). The complete assessment form is also provided (see Appendix 8).

Table 7.2 *ESM diary items*

Factor	Diary Item	Type of rating
Thought	What was I thinking (just before the alert)?	Open question
Affect:	Right now I feel….	
PA:	Cheerful / energetic / confident	Scale (1-7)
Anxiety:	Anxious / relaxed / worried	Scale (1-7)
NA:	Bad about myself / down / guilty	Scale (1-7)
Context	Where am I? (When I received the alert)	Open question
	Who am I with? (state relationship to you)	Open question
Activity	What am I doing?	Open question
Significant event	Since the last alert the most important / significant event that happened to me was……..	Open question
Response time	The time is now exactly…	Open question
Effect of study (completed at last response each day)	Filling in the booklet influenced my mood today	Scale (1-7)
	Without the watch / phone I would have done other things today	Scale (1-7)

Thought content, activities, context and significant event items

These were recorded as open questions and coded using a manual developed in the present study (see Appendix 9) Thoughts, activities and context data were recorded to contextualise affect and anxiety ratings. Significant events were recorded to control for any major life events which may occur during the study and which may have impacted on affect and anxiety experiences.

ESM affect and anxiety items

NA, PA and anxiety were each assessed through three items rated on a 7-point Likert scale (1 = not at all to 7 = a great deal). Items were prefixed by the phrase 'right now I feel' followed by the affect items for each scale. PA items were 'cheerful', 'energetic' and 'confident' and NA items were 'bad about myself', 'down' and 'guilty'. These items were derived by collating primary facets of PA and NA from the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), and the activation and depression index items on the Internal State Scale (ISS) (Bauer et al., 1991). PA and NA items were reduced to the three characteristics which occurred most often between measures, suggesting internal validity. Whilst PA items linked to mania and NA items to depression and low mood, items were also chosen to reflect ordinary rather than extreme emotions so as to be relevant to a euthymic bipolar sample and a healthy control sample, as is consistent with ESM practice in general. Anxiety was rated using the three items 'anxious', 'worried' and 'relaxed'. Anxiety symptoms were generated using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983), the HAM-A (Hamilton, 1959) and the generalised AD section of the SCID-DSM-IV. Again, the three items which occurred most often between measures were selected, and these were checked against NA and PA items to ensure no overlap.

Influence of study

Two additional items were included at the end of each day to assess to what extent the study had influenced mood and disrupted normal daily routines during the study. Both items were rated on a 1-7 scale, with '1' indicating no influence or disruption and '7' a large effect.

Development of a coding schedule for open questions

Reponses to open questions regarding thoughts, activities, significant events and context were coded according to content. Previous research categorising thoughts by content has used forced responses to predetermined categories (Blackburn & Eunson, 1989), assigned researcher-determined values of 'positive' or 'negative' valence to thought data (Peters et al., 2012; Roach, Salt, & Segerstrom, 2010), has limited the recording of thoughts to only those linked to a specific emotions, such as worry or anxiety (Roemer, Molina, & Borkovec, 1997) or has used a narrow coding scheme with only a small number of categories (Craske, Rapee, Jackel, & Barlow, 1989). As such, these coding methods are driven by researcher expectations or theoretical assumptions and run the risk of missing or excluding large amounts of data and may not be a realistic reflection of thought content in daily life. In addition, existing coding schemes used in ESM research to categorise thoughts and activities with clinical samples have not reported on the validity or inter-rater reliability of these (Maser & Cloninger, 1990) or have reported inter-rater reliability of those schemes from previous research without re-assessing agreement (Havermans et al., 2007; Myin-Germeys et al., 2001). Using previous coding strategies as a foundation, a novel coding guide was developed for the present study. To increase validity of categorisation, three members of the research team, KH (1st author), SJ (clinical psychologist) and DK (research assistant working in BD research), met several times to discuss, develop and finalise the coding scheme.

Thought categories

Based on earlier research by Craske et al (1989) five thought categories were identified initially: (1) interpersonal relationships; (2) finances; (3) work and study; (4) illness, injury, and health; and (5) miscellaneous. A preliminary review of the data found these categories to be too narrow, with many thoughts coded as 'miscellaneous'. The guide used by Myin-Germey et al. (2001) was used to generate an additional seven categories that best described the 'miscellaneous' data: (6) instrumental daily living (cooking, cleaning, chores) and (7) basic daily living (eating, drinking, personal hygiene); (8) independent leisure (reading, watching television) and (9) social leisure (bowling, going to the cinema; (10) abstract thoughts (about politics or religion); and (11) neutral thoughts (thoughts about the study, thoughts about objects or places where there was no clear context). In addition, the 'illness, injury and health' category was separated into two categories to distinguish between thoughts about physical and psychological health.

Activities

Activity codes were generated using a similar process. Categories outlined in a previous ESM study exploring time use in BD were used as initial codes and included (1) work; (2) household tasks; (3) social interaction; (4) active leisure; and (5) passive leisure (Havermans et al., 2007). Again, a review of a sample of data from the present study found this scheme too narrow. Remaining activities not categorised linked closely to thought categories and so the category 'household' was separated into two distinct codes: (5) basic daily living tasks, such as eating, drinking and personal hygiene and instrumental (6) daily living tasks, such as household chores and travelling. Additional categories were also created for (7) sex, (8) drug and alcohol use, (9) neutral for activities related to the study, and (10) miscellaneous for any remaining activities which could not be classified.

Significant events

At each assessment participants were asked to record the most significant event which had occurred since the last response. Significant events were coded using the Social Readjustment Rating Scale (Holmes & Rahe, 1967), which provides a list of 43 stressful life events. In addition, 'major change in medication' and 'being a victim of trauma or abuse' were added for the present study. Any events reported which were not significant life events were coded '0'.

Context

Participants recorded their location and who they were with at every alert. Categories were defined by the data at the end of the study to account for all locations and relationships. Final categories for location were: home, network (homes of friends and family), work / study, health care settings, public places, transport and other. 'Who with' categories included: alone, family, friends and neighbours, colleagues, health professionals and strangers.

7.2.3.5 Inter-rater assessment of the coding scheme

Initial assessment of frequency of responses for activity categories found that 'sex' and 'substance use' were reported very infrequently (sex n = 5, alcohol use n = 6). As such, these were removed as independent categories. Sexual activities were reclassified as 'social interaction' and 'alcohol and drug use' were reclassified as 'daily living' (eating and drinking) as the activities reported included only alcohol use at a minimal level, such as 'having dinner and a glass of wine' or 'having a beer with the football', with no drug use reported for either group. Inter-rater agreement was assessed for codings of the ESM thought and activity responses only, as significant events and context ratings were not open to rater interpretation. Checks were performed at two separate stages, once during development of

the coding scheme and once following finalisation of the schedule, with 30% of the data

being rated over-all for reliability using Cohens kappa coefficient (Cohen, 1968). Kappa

values of 0.61 to 0.80 were accepted as showing substantial inter-rater agreement (Viera &

Garrett, 2005). Initial inter-rater checks were performed on codings for the first 15 data sets

(bipolar n = 8, control n = 7). All data were coded by KH and DK, with DK remaining blind to

group status, although information regarding occupation, gender, marital status and living

arrangements was provided in order to help contextualise the data. High levels of agreement

were achieved, with 73% agreement for thoughts (Kappa = 0.66, SE 0.02, p <0.001) and 82%

agreement for activities (Kappa = 0.78, SE = 0.02, p < 0.001). Disagreement between raters

was explored at this stage and found that incongruities occurred most often due to internal

duplication of codings (Greenwood & Hoffmann, 1998). This was most prominent in the

thought categories of 'social interaction' and 'social leisure', and 'psychological' and

'physical' health, and within the 'basic' and 'instrumental' daily living categories for both

thoughts and activities. It was agreed that these categories were hard to define as they were

not inherently distinct, and so each pair of codes were merged to produce the final coding

schedule (see Table 7.3). The full coding guide is provided in the appendix (see Appendix 9).

The remaining data were coded by KH, with DK rating a random sample of 30% of the data.

Final observer agreement was 81% for thoughts (Kappa = 0.78, SE 0.02, p < 0.001) and 95%

for activities (Kappa = 0.93, SE 0.01, p < 0.001).

Table 7.3 *Final coding system for thoughts and activities*

Thoughts	Thoughts about:	Activities	Activity examples
Relationships & social interaction	Past, present or future social interactions; other people (known); non-verbal interaction e.g. email, Facebook	Social interaction	Social exchanges (verbal & non-verbal); leisure activities with others; sex & physical intimacy
Occupation	Work, study	Occupation	Tasks linked to work & studies
Finances	Current or past financial situation; bills; debt; wages; financial decisions	NA	NA
Psychological & physical health & well being	Mood; self-evaluations; physical health	NA	NA
Daily living	Household chores; self-maintenance; commuting; smoking; eating & drinking	Daily living	Household chores; self-maintenance; commuting; smoking; eating & drinking
Entertainment, recreation & leisure	Television; radio; books; computer games	Passive / independent leisure	Television; radio; reading; using the computer; library; museum; gambling; arts & crafts; relaxation; meditation
NA	NA	Active leisure	Sports; cycling; walking
Politics, religion, abstract thoughts	Government; news; religion; philosophical thoughts about life in general	NA	NA
Miscellaneous	Things that are unclear or cannot be contextualised e.g. 'Hmm' or 'wow'	Miscellaneous	Activities that are unclear or cannot be contextualised e.g. 'sorting this'
Neutral	The study; weather; places without any context	Neutral	Tasks related to the study

7.2.4 Procedure

Prior to recruitment and data collection, two pilot studies were completed with small samples of control (n = 4) and bipolar participants (n = 5) to check whether NA, PA and anxiety items were sensitive to change in both groups and that participants provided sufficient data in response to watches and phones as signalling devices (see Appendix 10). Participants were allocated one of three researchers (KH, HR or FB, all doctoral students) at the beginning of the study who completed all assessments and appointments with allocated participants where ever possible to maintain consistency and promote retention. Following a pre-screen over the telephone, all potentially eligible participants were assessed using the SCID-DSM-IV research version interview to confirm diagnosis of BDI or II in the bipolar group, or absence of any diagnosis in the control group. Interviews were completed via the telephone or in person if preferred. Following confirmation of eligibility, a baseline appointment was scheduled either at home, or another place in which they felt comfortable, and written informed consent to participate was obtained. All participants completed the standardised LIFE interview comprising the HAM-D, MAS and HAM-A to assess current mood. A short training session was then delivered to brief participants fully about the ESM procedure. Participants were provided with seven A5 diaries, one for each day of the study. All participants were given the opportunity to use either a Timex Iron Man Datalink watch or a mobile phone to receive signal alerts to complete the diary. Alerts were sent to participants 10 times each day between the hours of 8:00 and 22:00. For participants using mobile phones, this was done by syncing each phone with a googlemail email account and event calendar, which sent pre-programmed text alerts throughout the study. For participants using watches, a predetermined schedule was downloaded onto their watch device. Participants were assigned at random to one of three pre-determined timing schedules used in previous ESM research (Myin-Germeys et al., 2001; Myin-Germeys et al., 2003). Alerts were never sent less than 24 minutes or more than 2 hours 39 minutes apart.

Participants were advised to complete the diary as soon as they were able to after the alert. To ensure ecological validity, participants were required to record responses within 15 minutes for data to be considered valid. Previous research has generally used cut offs between 10 and 20 minutes to identify valid momentary responses to alerts (Barge-Schaapveld, Nicolson, van der Hoop, & DeVries, 1995; Havermans et al., 2007; Myin-Germeys et al., 2001), although the reliability of momentary subjective reports has been found to decrease beyond 15 minutes (Delespaul, 1995). Responses recorded outside of 15 minutes were excluded from analysis.

In line with previous ESM research (Kwapil, Brown, Silvia, Myin-Germeys, & Barrantes-Vidal, 2012; Myin-Germeys et al., 2001; Myin-Germeys et al., 2003; Peters et al., 2012), participants were also required to complete a minimum of 30% (21/70) ESM diary entries within this time threshold to ensure sufficient data for analysis. If unable to respond to an alert within the allocated threshold, participants were asked to record the reason this was missed and then respond as normal at the next alert, without completing any entries retrospectively. Participants were asked to record the exact time at which they completed the diary. Participants recording < 21 eligible responses on completion were offered the option to repeat the study, although no participants chose to do this. All participants were contacted by their nominated researcher at least once in the first two days of the study to offer support and resolve any issues. Additional support was offered if required. All participants were debriefed on completion and given time to talk about their experience of taking part in the study and any issues or thoughts this may have raised. Help to access additional support was offered where necessary. All participants were paid £10 for their participation, irrespective of completion or amount of data recorded.

7.2.5 Statistical analysis

7.2.5.1 Analysis of baseline data

Between group comparisons of depression, mania and anxiety symptoms were performed using independent samples t-tests, with the mean difference (MD) reported to indicate effect size. To explore whether mood symptoms were associated with anxiety at baseline, correlations were calculated for groups independently. To compare groups on sociodemographic characteristics, Pearson chi square tests were applied to categorical variables (gender, marital status, employment, education, ethnicity), whilst two-sided independent samples t-tests were applied to continuous variables (age, days since last episode). Completion rates were also assessed in the same way by comparing number of valid data points between groups.

7.2.5.2 Analysis of ESM data

This study involves multiple observations of every participant, creating three levels of analysis: 1) individual response level - relates to momentary assessments of anxiety, NA, PA, time of day, thought, activity, location, who with; 2) day level - day of the week; 3) within participant level – age and gender. Repeated responses from the same participant are more likely to be related, and likewise responses from participants within days are also more likely to be similar. This results in a loss of independence within the data, which in turn results in a loss of precision with the potential for effect sizes to be inflated and misinterpreted (Killip, Mahfoud, & Pearce, 2004; Teerenstra, Moerbeek, van Achterberg, Pelzer, & Borm, 2008). In order to account for all levels of data in the analysis and to avoid inflation of effects, multi-level modelling techniques were applied, a variation of standard regression analysis which is accepted as the appropriate method of analysing multi-level data (Bryk & Raudenbush, 1992). Data were analysed using the multi-level 'nlme' function in R (R Core Team, 2012)

where *B* is the fixed regression coefficient of each predictor variable within the model and is interpreted as a single level regression coefficient would be. The independent effects of level 2 predictors (day of week, time of day) and level 3 predictors (group) on level 1 dependent variables (anxiety, NA and PA) were explored. Mood and anxiety variables were determined by calculating the mean of the three items for each mood state at each response. Level 2 and 3 predictors were entered simultaneously, so the effects of each are assessed controlling for the other variables within the equation. The association between the level 1 dependent variables anxiety, NA and PA and these same variables as predictors were also modelled to explore the interaction between affect and anxiety. The effect of other level 1 factors including thought content, activity and context (where and who with) were also estimated within-participants for bipolar and control groups independently to contextualise observed mood and anxiety experiences. As the primary analyses explored the effects of predictor variables on mean ratings of anxiety and affect, group level variance was held constant across these models. Where between-group variability was the focus of analysis, models were adapted to allow the group-level residual standard deviation to vary as a function of group and compared to the original model where this is held constant using an analysis of variance (ANOVA), thereby comparing variability at group level specifically. An exponential correlation analysis was used to control for the auto-correlation of within-participant responses; that is finding effects due to responses appearing to be related only because they are recorded close together in time. The inter-correlation coefficient (ICC) was calculated for each model to assess the level of autocorrelation between responses within participants overall, and responses within participants within days.

This study involved the testing of multiple hypotheses with multiple outcomes, which increases the risk of making Type I errors. When the significance level (alpha) is set at 0.05 for an independent statistical test, there is a 1 in 20 chance of finding a significant false positive result each time (Feise, 2002). Adjusting the p-value downwards for each test is a

potential method of correcting for multiple testing. However, this in turn increases the risk

of making Type II errors: falsely accepting the null hypothesis and missing significant effects

which are present in the data. As the present study is exploratory, Type II errors are more

problematic as missed effects may be unlikely to be studied systematically in future

research. As such, alpha remained set at 0.05 for each test, which was in keeping with

significance levels used in other ESM research and so allows for a clear comparison of

results. Any effects found here were not definitive and require further testing.

7.3 Results

7.3.1 Sample Characteristics

Of the 881 potential control participants completing the HPS online, 645 participants scored

$\leq$ 15 on the HPS and were invited to take part in EMOTE. In total, 75 bipolar and 60 control

participants agreed to complete a pre-screen for the EMOTE study, with 50 participants from

each group ultimately taking part. Details regarding exclusion are included in Figure 7.1. The

primary reasons for exclusion of participants in the bipolar group were not meeting criteria

for BDI or II at pre-screen or experiencing a mood episode at SCID assessment which did not

remit before the end of the study. Exclusion in the control group was mainly due to

participants meeting criteria for a mental health problem within the past two years or sleep

problems in the past month. The mean HPS score for the final control group was 6.88 with

scores ranging from 0 to 15. The final control sample did not differ significantly from the

online sample from which they were drawn in terms of age (t(865) = 0.54, p = 0.587), gender

(X^2(1) = .06, p = 0.812), marital status (X^2(2) = 2.75, p = 0.253) or employment status (x^2(5) =

4.07, p = 0.539) and suggests no selection bias for those who decided to take part. All control

participants completed > 30% valid entries and were included in the analysis. Three

participants with BD discontinued the study after day one, and two completed < 30% valid

assessments and were excluded from the analysis.
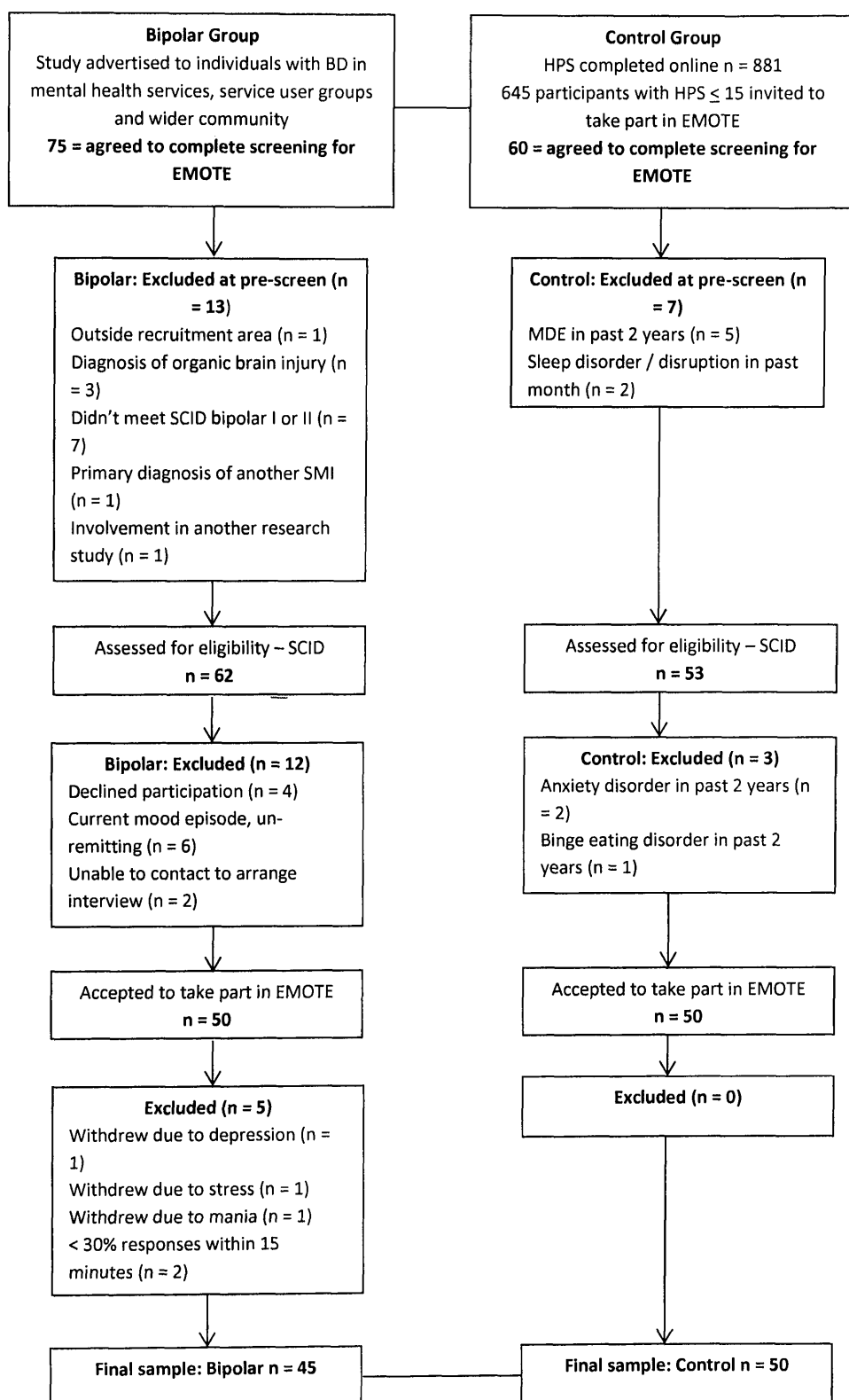
Figure 7.1 Recruitment process for the EMOTE study

Eligible control and BD group

Control participants completed an average of 48.44 out of 70 (69%) observations (SD = 11.00, range = 24–67, total data points = 2416). Bipolar participants completed an average of 45.31 out of 70 (65%) assessments (SD = 11.62, range = 26–68, total data points = 2045). The mean time taken to respond was brief, with four minutes for control participants and five minutes for bipolar participants. There was no significant difference in number of responses recorded between groups (t(93) = 1.35, MD 3.13, p 0.181, CI -1.48, 7.74). A large percentage of missed responses were accounted for in both the control (69%) and the bipolar sample (63%). The most common reason for not completing assessments for the bipolar group was due to being asleep or resting, whilst the control group failed to respond most often when at work. The four most common reasons for missed responses for both groups were sleeping, socialising, work/study and equipment problems. Equipment problems included misplacing the diary or signalling device for a short period of time or being in an area with no reception so that texts were not received. Equipment problems accounted for only a small proportion of missed responses and so are unlikely to have affected the data significantly (control 14% missed responses, bipolar 8% missed responses). Average daily ratings scored on a scale of 1-7 showed that both groups perceived the study as having little or no effect on their mood (control: mean = 2.00, SD = 0.89; bipolar: mean = 2.56, SD 1.47) or daily routine (control: mean = 1.11, SD = 0.48; bipolar: mean = 1.36, SD = 0.65), although this data was missing for three control participants.

Eligible bipolar participants were significantly more anxious and depressed than control participants at baseline, indicating mild to severe sub-syndromal symptoms for 35% of participants in this sample (see Table 7.4 and Table 7.5). One participant in the BD group met criteria for severe depressed symptoms, however still met inclusion criteria for the study as symptoms had only persisted within the past week, and so did not meet criteria for a depressed episode. The eligible bipolar group had significantly higher baseline manic

symptoms than controls, although the mean scores suggest this difference is unlikely to be clinically significant, with all participants scoring in the doubtful or absent range for mania (Bech et al., 1978). Anxiety correlated significantly and equally with depression and manic symptoms at baseline for the control group (r = 0.64, p <.001). Depression was highly correlated with anxiety at baseline for the BD group (r=0.86, p<.001), whilst mania was positively, but modestly, correlated with anxiety at inception for this group (r = 0.39; p<.01). This is likely due to the higher rates of symptoms across all baseline measures in the BD group.

Eligible bipolar and control participants differed significantly on all sociodemographic variables with the exception of ethnicity. Compared to controls the eligible bipolar group were slightly older, less likely to in a relationship and were more frequently unemployed. There was a higher percentage of female than male participants in both groups, and significantly more in the control group (80%). Over a third of eligible bipolar participants had a diagnosis of one or more current and lifetime ADs, with social phobia and GAD being the most prevalent (see Table 7.6). The majority of the BD group (73%, n = 30) who were asked about history of trauma had experienced a lifetime traumatic event, although this data was missing for a third of the sample. Missing PTSD and trauma data was primarily due to this section of the SCID being omitted by the research team in error at the beginning of the study and so was not asked in the first 14 interviews. One participant also declined to talk about their experiences related to trauma. Previous history of trauma was reported by one participant in the control group only. Female participants were significantly more likely to meet criteria for any current AD (87% female, 13% male, $X^2(1) = 7.82$, p = 0.005). Lifetime ADs were also elevated in female participants with BD in the eligible group (female 75%, male 25%) although this did not reach significance ($X^2(1) = 2.33$, p = 0.127), potentially due to the limited sample size. No one met criteria for any other current psychiatric disorders, although this data was missing for one participant. Control participants were not taking any

regular, prescribed medication for psychiatric or medical problems, other than occasional

pain relief (paracetamol and aspirin) and contraceptive medication. Only two participants

with BD were not taking any current medication. Thirteen participants were prescribed

monotherapy and the remaining 35 participants were prescribed between two and six

medications in different combinations (see Table 7.7).

Eligible and ineligible BD participants

Statistical tests were not applied to comparisons between eligible and ineligible

bipolar participants, where the small sample size of the ineligible group (n = 5) meant formal

analysis was not appropriate. Ineligible participants all had a diagnosis of BDI but did not

appear to differ from the bipolar group on sociodemographic variables or time since last

episode. Ineligible bipolar participants did not appear to be more anxious or depressed at

baseline than included bipolar participants, but did report slightly higher levels of manic

symptoms. Two participants accounted for the majority of this difference, with MAS scores

of 7 and 10 respectively. Whilst one of these participants who withdrew did cite a manic

episode as the reason, the second participant dropped out after reporting increased low

mood and stress.

Table 7.4 *Baseline mood and anxiety symptoms by category*

Symptom Score	Category	Control (N = 50)	Eligible Bipolar (N=45)	Ineligible Bipolar (N=5)
HAM-A:				
≤ 7	no / minimal anxiety	50	29	4
8 – 14	mild anxiety	0	9	1
15 – 23	moderate anxiety	0	5	0
≥ 24	severe anxiety	0	2	0
HAM-D:				
≤ 7	No / minimal depression	48	30	3
8 – 13	mild depression	2	11	1
14 – 18	moderate depression	0	3	0
19 – 22	severe depression	0	1	1
MAS:				
0 – 9	no mania	50	45	4
10 - 14	doubtful mania	0	0	1

Table 7.5 *Participant characteristics and baseline measures*

		Control n = 50, N (%)	Bipolar n = 45, N (%)	Ineligible n = 5 N (%)	Test statistic (df)[a]	MD[a]
Age	Mean	37.64	44.09	36.00	t(93) = -2.77***	-6.45
	Range	21 – 59	20 – 70	23 – 51		
Gender ratio	M/F	10/40	18/27	3/2	$X^2(1)$ = 4.56*	-
Education	Secondary	2 (4)	13 (29)	0 (0)	$X^2(2)$ = 16.51***	-
	Further	8 (16)	13 (29)	3 (60)		
	Higher	40 (80)	19 (42)	2 (20)		
Marital Status	Married/ cohabiting	34 (68)	19 (42)	1 (20)	$X^2(1)$ = 6.38*	-
	Single	16 (32)	26 (58)	4 (80)		
Occupation	Working / studying	50 (100)	25 (56)	3 (60)	$X^2(5)$ = 28.15***	-
	Not working	0 (0)	20 (44)	2 (40)		
Ethnicity	White British	48 (96)	42 (93)	4 (80)	$X^2(1)$ = 0.34	-
	Other	2 (4)	3 (7)	1 (20)		
Ham-D	Mean	1.16	6.14	7.40	t(93) = -5.72**	-4.88
	S.D.	1.93	6.04			
Ham-A	Mean	0.86	7.11	5.20	t(93) = -6.13**	-6.25
	S.D.	1.29	7.09			
MAS	Mean	0.28	1.13	4.00	t(93) = -3.98*	-0.85
	S.D	0.83	1.24			
Days since last episode	Median	-	90	150	-	-
	Range	-	1 – 3285	35 - 240		

[a] *Refers to comparisons between control participants and eligible bipolar participants only;*
*p ≤ 0.05; ** p ≤ 0.01; p ≤ 0.001

Table 7.6 *Prevalence of ADs in the bipolar participant group*

	Anxiety Disorder	Bipolar n = 45 (%)
Current anxiety	Any AD	16 (36)
	Panic disorder	4 (9)
	Panic with Agoraphobia	1 (2)
	Agoraphobia	5 (11)
	Social Phobia	9 (20)
	Specific phobia	5 (11)
	OCD	6 (13)
	GAD	9 (20)
	PTSD	4 (13)*
Number of current Ads		
	0	29 (66)
	1	4 (8)
	2	2 (4)
	3+	10 (22)
Past Anxiety	Any AD	16 (36)
	Panic disorder	1 (2)
	Panic with Agoraphobia	3 (7)
	Agoraphobia	3 (7)
	Social Phobia	6 (13)
	Specific phobia	1 (2)
	OCD	3 (7)
	GAD	3 (7)
	PTSD	4 (13)*
	History of trauma	22 (73)*

* PTSD and trauma data n = 30 due to missing data from 15 (33%) participants where 14 participants were not asked about PTSD symptoms and 1 participant declined to answer

Table 7.7 *Current medication for bipolar participant group(n = 45)*

Monotherapy	N	Combination therapy	N
Lithium	2	Lithium	9
Sodium valproate	1	Sodium valproate	12
Carbamazapine	2	Carbamazapine	1
Lamotrigine	1	Lamotrigine	6
Antipsychotics	7	Antipsychotics	37
Antidepressants	0	Antidepressants	19
Benzodiazepines	0	Benzodiazepines	8
Physical problems	0	Physical problems	21

7.3.2 ESM Results

7.3.2.1 Reporting of significant events

The number of significant life events reported was relatively low, with seven participants experiencing one life event (control: n = 4; bipolar n = 3) and one bipolar participant experiencing two life events during the study week. These were: death of a pet (n = 2); a family member becoming seriously ill (n = 4); significant improvement in the health of a family member (n = 1), attending a funeral (n = 1), buying a new house (n = 1). Mean scores were calculated for NA, PA and anxiety ratings for these participants individually and compared to the group mean to assess whether there were significant outliers on any scale (see Table 7.8). One bipolar participant (participant 1, Table 7.8) had a lower mean score for PA and was approximately one SD lower than the group mean. Similarly, one control participant (participant 5, Table 7.8) had comparably higher scores for anxiety (3.5 SDs above the group mean) and NA (4.8 SDs above the group mean), and one participant had elevated scores for anxiety only (participant 7, 1.6 SDs from the group mean) compared to rest of the control group. As this study involved a relatively small sample of participants and the statistical analysis was well controlled to prevent scores from a small number of participants biasing results, these participants were kept in the analysis to prevent further loss of power. The remaining participants did not appear significantly different compared to the respective group means on any of the scales assessed and so are unlikely to have biased outcomes. As the impact of life events was hard to estimate in this study due to events being potentially negative and / or positive (e.g. moving house), life events were not included further in the analyses.

Table 7.8 *Mean (SD) NA, PA and anxiety ratings for participants experiencing significant life events during the study (bipolar n = 4, control n = 4)*

Bipolar: mean (SD)	Participant / Group	Anxiety	NA	PA
	1	2.01 (1.04)	2.07 (1.04)	2.55 (1.09)
	2*	2.04 (0.77)	1.25 (0.41)	4.83 (0.65)
	3	2.37 (1.29)	2.31 (1.18)	3.51 (1.18)
	4	3.94 (1.55)	2.38 (1.09)	3.78 (1.29)
	Bipolar Group	2.51 (1.69)	1.96 (1.42)	4.05 (1.43)
Control: mean (SD)				
	5	4.34 (1.79)	3.51 (1.60	4.64 (1.31)
	6	1.16 (0.36)	1.04 (0.14)	3.65 (0.41)
	7	2.77 (1.46)	1.85 (0.74)	3.89 (1.27)
	8	1.35 (0.92)	1.14 (0.43)	5.23 (0.61)
	Control Group	1.47 (0.83)	1.19 (0.48)	4.53 (1.10)

Mean (SD) affect scores for participants experiencing significant life events within the study week; * Participant experienced two life events

7.3.2.2 Between-group differences in the experience and interaction of mood and anxiety at the same point in time

To provide an overview of anxiety, NA and PA, overall mean scores across all time points were calculated per group (see Table 7.9) and ratings were aggregated per hour across days to show average daily patterns of anxiety and affect (See Figure 7.2). For example, the mean NA, PA and anxiety ratings were calculated for all responses recorded between 8am-9am each day, and then averaged across days for each group. This was then repeated for each of the 14 hours where responses were observed. Observation of mean scores alone suggests that individuals with BD have elevated ratings of anxiety and NA compared to controls, and lower PA ratings, and that trajectories of NA and anxiety were similar within groups. The SD of the aggregated hourly scores across days (shown by error bars in Figure 7.2) also suggested increased fluctuations of anxiety and affect for bipolar participants.

Table 7.9 *Overall mean ratings of anxiety and affect per group (including SD and range)*

	Anxiety mean (SD, range)	NA mean (SD, range)	PA mean (SD, range)
Bipolar (n = 45)	2.52 (1.67, 1 - 7)	1.96 (1.39, 1 - 7)	4.02 (1.43, 1 - 7)
Control (n = 50)	1.51 (0.93, 1 - 7)	1.22 (0.57, 1 - 7)	4.52 (1.10, 1 - 7)

Control Mean Anxiety

Bipolar Mean Anxiety

Control Mean Negative Affect

Bipolar Mean Negative Affect

Control Mean Positive Affect

Bipolar Mean Positive Affect
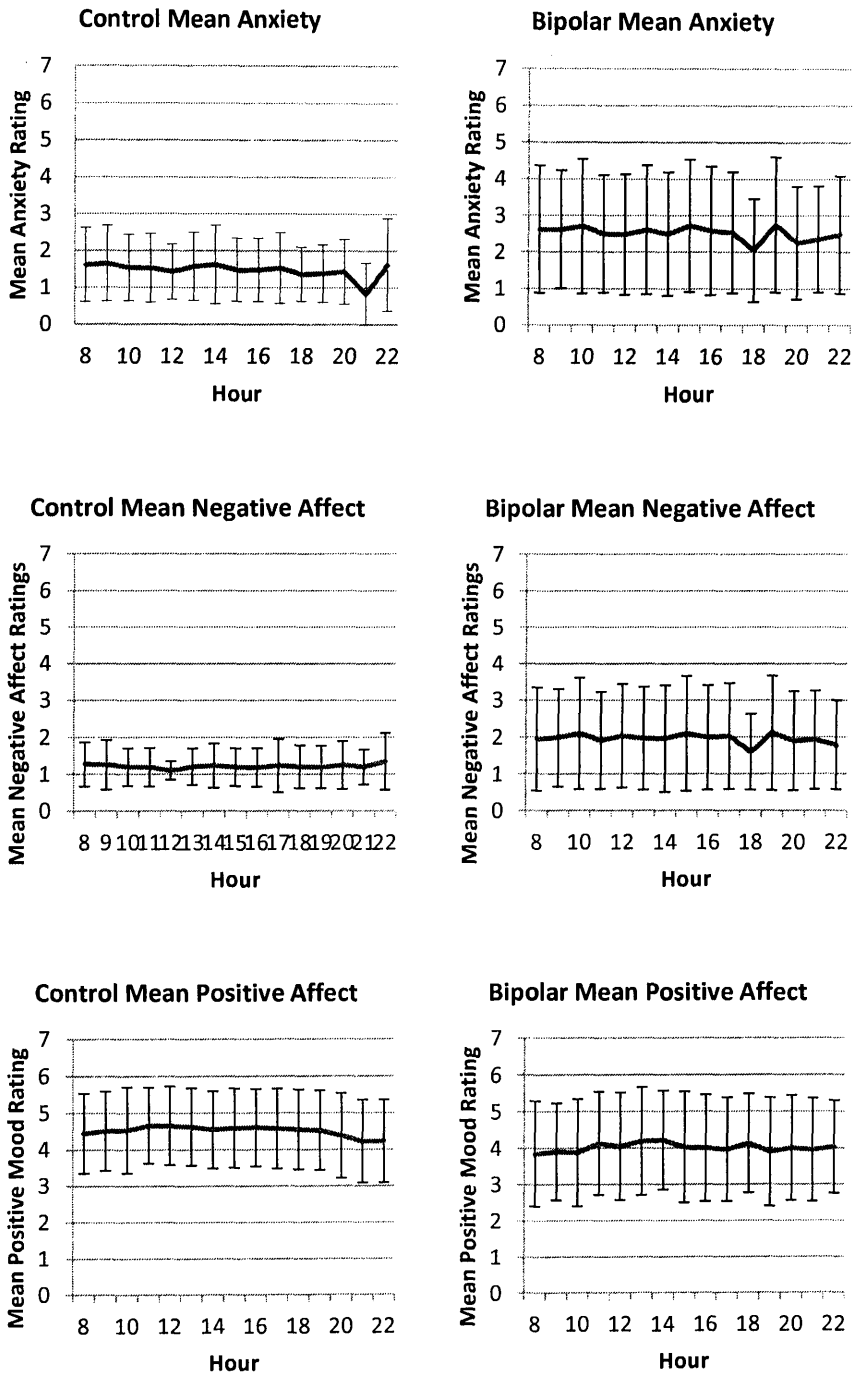
Figure 7.2 *Mean ratings of anxiety, NA and PA aggregated per hour across days (bipolar n = 5, control n = 50)*

Participants in both groups reported the full range of scores (1 to 7) for the anxiety, NA and PA scales. When assessed using data from all participants, items within the PA scale

correlated highly and this pattern was repeated for items within the NA scale ($r \geq 0.69$, p <.001 in both cases). There was a lower level of correlation between the anxiety item 'relaxed' and other items on this scale (anxious and relaxed: $r = -0.46$, p<.001; worried and relaxed $r = -0.43$, p<.01), potentially due to this being a reversed item. As a result, 'relaxed' was removed from the analysis and mean scores for anxiety were calculated using 'worried' and 'anxious' values only. Anxiety and NA ratings correlated highly for bipolar participants ($r = 0.75$, p<.001) and moderately for controls ($r = 0.47$, p<.001), suggesting these were more closely associated for bipolar participants. PA and anxiety, and PA and NA ratings were equally and negatively correlated for controls ($r = -0.44$, p<.01 respectively). NA and PA ratings were also negatively correlated for bipolar participants, but this association was smaller ($r = -0.29$, p<0.01), and PA and anxiety were negatively but moderately correlated for bipolar participants responses ($r = -0.55$, p<.01). To explore these differences when taking into account the hierarchical structure of the data, between group differences in mean ratings of affect and anxiety were compared using multi-level regression analysis. Preliminary analyses found no significant effect of age, gender, education or employment on affect or anxiety outcomes (see Appendix 11) and so these were not included in the final model.

Anxiety

Overall individuals with a diagnosis of BD reported significantly higher ratings of anxiety than controls. For all participants, increased NA ratings were associated with concurrent increases in anxiety, whilst increased PA ratings were associated with decreased anxiety at the same time point. All participants reported reduced anxiety in the evening. No group*mood interactions were observed.

NA

An initial significant effect of group was found on NA, however this disappeared once group*anxiety interactions were included. A significant interaction effect of group*anxiety suggested that bipolar participants had increased NA reactivity in response to anxiety compared to controls, and that NA increased more for bipolar participants when anxiety was elevated. There was a negative effect of PA on NA, with increases in PA being associated with decreased NA, and this was the case for both groups. There was no time of day effect on NA.

PA

NA and anxiety were both found to have a negative effect on PA concurrently and both were associated with decreased PA at the same time point. As with NA, although a significant effect of group was initially found, this became non-significant once group*NA interaction effects were estimated. There was a significant group*NA interaction, with control participants having increased PA reactivity in response to concurrent NA, with ratings of PA declining at a greater rate than did bipolar participants ratings. There was a sustained time of day effect on PA for all participants, with PA ratings significantly higher between the hours of 10:00 to 19:00, and significantly lower at 22:00. No day of week effects were observed on affect or anxiety ratings.

ICC

For anxiety and NA the ICC values suggest a moderate correlation between ratings by the same participant overall, but a strong correlation for ratings by the same participant on the same day. Correlations for responses within participant and day-within-participant were identical for PA suggesting no difference in variability between levels.

Table 7.10 *Between group comparisons of anxiety, NA and PA for all participants (bipolar n = 45, control n = 50)*

IV		B	SE	P	95% CI lower	95% CI Upper
Anxiety:						
Group		0.43	0.20	0.0361	0.03	0.83
NA		0.59	0.04	<0.0001	0.52	0.66
PA		-0.19	0.02	<0.0001	-0.23	-0.15
Group*NA		0.01	0.04	0.7497	-0.07	0.10
Group*PA		-0.003	0.03	0.9218	-0.06	0.05
DOW				>0.05		
Time of day:						
	20:00	-0.17	0.06	0.0094	-0.29	-0.04
	22:00	-0.17	0.06	0.0071	-0.30	-0.05
ICC: Participant level		0.40	-	-	-	-
ICC: day within participant		0.54	-	-	-	-
Negative Affect:						
Group		0.17	0.15	0.2474	-0.12	0.47
Anxiety		0.20	0.02	<.0001	0.17	0.23
PA		-0.17	0.01	<.0001	-0.2	-0.14
Group*Anxiety		0.16	0.02	<.0001	0.12	0.2
Group*PA		-0.03	0.02	0.1662	-0.07	0.01
DOW				>.05		
Time of day				>.05		
ICC: Participant level		0.41	-	-	-	-
ICC: day within participant		0.62	-	-	-	-
Positive Affect:						
Group		-0.29	0.19	0.1394	-0.67	0.1
Anxiety		-0.22	0.02	<.0001	-0.27	-0.18
NA		-0.51	0.04	<.0001	-0.59	-0.43
Group*Anxiety		0.01	0.03	0.6601	-0.05	0.07
Group*NA		0.17	0.05	<.0001	0.08	0.26
DOW				>.05		
Time of day:						
	10:00	0.13	0.06	0.0321	0.01	0.25
	11:00	0.31	0.07	<.0001	0.18	0.44
	12:00	0.3	0.07	0.0001	0.13	0.39
	13:00	0.25	0.06	0.0001	0.13	0.38
	14:00	0.29	0.07	<.0001	0.15	0.42
	15:00	0.21	0.08	0.0016	0.08	0.35
	16:00	0.18	0.07	0.0073	0.05	0.31
	17:00	0.16	0.07	0.0183	0.03	0.29
	18:00	0.2	0.07	0.0038	0.07	0.34
	19:00	0.18	0.07	0.0084	0.05	0.31
	22:00	-0.17	0.07	0.0134	-0.3	-0.03
ICC: Participant level		0.53	-	-	-	-
ICC: day within participant		0.53	-	-	-	-

These findings validate the necessity of controlling for auto-correlations within the data. ICC values remained consistent throughout analysis and as such are not discussed further, but were controlled for throughout. There were no day of week effects on mood or anxiety and time of day effects remained consistent in all models, therefore are not discussed beyond this point but were retained as factors in the model to account for the overall structure of the data.

7.3.2.3 Comparing variability in NA, PA and anxiety between groups

Bipolar participants had significantly higher variability in all three mood states compared to controls, as shown by the comparable difference in standard deviations of affect and anxiety ratings between groups (see Table 7.11). The largest difference was in variability of NA, which was lower for control participants. Although anxiety and PA variability differences were also significant, the scale of these differences was smaller. To explore whether anxiety is associated with more variable affect, level of baseline anxiety as a predictor of variability was assessed. Baseline HAM-A scores were categorised according to the original scale as non-anxious / minimal anxiety (0 – 7), mild anxiety (8 – 14), or moderate to severe anxiety (15 – 24), with moderate and severe being merged into one category due to the low number of participants falling into the 'severe' group (n = 2). HAM-A scores were categorised, as opposed to using continuous scores, as this allowed comparison of between group variability using the same method as when comparing variability between the control and bipolar groups previously. As all control participants had HAM-A scores in the non-anxious category at baseline, anxiety as a predictor of affect variability was explored by comparing variability within the bipolar group only in the first instance (see Table 7.12), and then by comparing variability for control and non-anxious bipolar participants separately (see Table 7.13). Bipolar participants with scores in the mild to moderate/severe HAM-A categories had greater variability in NA and anxiety, but not PA, ratings compared to bipolar participants in

the mild anxiety group. There was little or no difference in anxiety and NA variability between individuals in the mild and moderate/severe anxiety groups, indicating no incremental effect of increased anxiety. With relation to anxiety as a predictor of between group variability, non-anxious bipolar participants were still significantly more variable in ratings of all three mood states than controls (see Table 7.13), suggesting that differences in between group variability were not driven primarily by anxiety, but by diagnosis of BD.

Table 7.11 *Comparison (ANOVA) of MLM for each mood state when the SD is allowed to vary by group*

	Bipolar (n = 45)	Control (n = 50)	P
Anxiety SD	0.97	0.70	<.0001
NA SD	0.83	0.47	<.0001
PA SD	0.95	0.76	<.0001

Table 7.12. *Baseline anxiety as a predictor of affect variability in the bipolar participant group*

	Minimal (n = 29, mean = 2.59, S.D = 2.65)	Mild (n = 9, mean = 11.89, S.D = 2.32)	Moderate/Severe (n = 7, mean = 19.71, S.D = 3.15)	P
NA SD	0.72	1.04	0.99	<.0001
PA SD	0.90	0.97	0.97	0.0977
Anxiety SD	0.95	1.16	1.15	<.0001

Table 7.13 *Comparing affect and anxiety variability between control and non-anxious bipolar participants*

	Control (n = 50, HAM-A mean = 0.86, S.D = 1.29)	Non anxious bipolar (n = 29, HAM-A mean = 2.59, S.D = 2.65)	P
NA SD	0.46	0.71	<.001
PA SD	0.78	0.95	<.001
Anxiety SD	0.72	0.92	<.001

7.3.2.4 The impact of changes in affect and anxiety on subsequent ratings

The impact of changes in affect and anxiety ratings from the previous response (time 1) on subsequent ratings (time 2) were explored. Affect and anxiety change variables were created by calculating the difference between mean anxiety, NA and PA ratings at each response. Whilst the analysis relates to associations between changes from one response time to the next, time between responses was not standardised in this study. Time between alerts differed due to participants being allocated to one of three random timing schedules and varied depending on the number of eligible responses recorded per participant. Mean time between responses was 1 hour 55 minutes for both groups, (control SD: 1 hour 52 minutes and bipolar SD: 1 hour 39 minutes). These average times exclude the 10 hour overnight gap from 22:00 to 8:00 where alerts were not sent. Therefore any effects of mood and anxiety changes between responses apply to this approximate time frame.

The results followed the same pattern as concurrent affect and anxiety interactions, although all effect sizes were smaller than those for interactions at the same point in time (see Table 7.14). For anxiety, increase in NA at time 1 was associated with increased anxiety at the next response, whilst increased PA was associated with decreased anxiety. Increased anxiety was associated with subsequent increased NA and decreased PA ratings. NA and PA had a sustained negative relationship, with an increase in one state being associated with decreases in the other. There was a significant group*anxiety change interaction on NA ratings only (B = 0.07, SE = 0.02, p <0.0001, CI = 0.04, 0.10), with bipolar participants having increased NA reactivity in response to changes in anxiety from the previous response, suggesting increased sensitivity to anxiety fluctuations.

Table 7.14 *Impact of changes in affect and anxiety on subsequent response (bipolar n = 45, control n = 50)*

	IV	B	SE	P	95% CI lower	95% CI Upper
Anxiety:						
	NA change	0.26	0.02	<0.0001	0.23	0.29
	PA change	-0.10	0.01	<0.0001	-.012	-0.08
NA:						
	Anxiety change	0.13	0.01	<0.0001	0.12	0.15
	PA change	-0.08	0.01	<0.0001	-0.09	-0.06
PA:						
	Anxiety change	-0.09	0.01	<0.0001	-0.11	-0.07
	NA change	-0.18	0.02	<0.0001	-0.21	-0.15

7.3.2.5 Activity and thought content in daily life

As an overview of thoughts and time use, frequencies of thought content, activity and context responses were calculated per category as a percentage of the total valid responses for each group (see Figure 7.3). Statistical analyses of between group differences in the number of responses reported per category were not performed at this stage, but frequencies were used to determine which factors were included in the multi-level regression models based on categories where responses were recorded most often.

With the exception of work-related thoughts, bipolar participants reported thoughts in all other categories more often compared to controls, most noticeably health (psychological and physical) and leisure (thoughts about television, books, computer games). Individuals with BD were almost twice as likely to report thoughts relating to health (9.1% bipolar and 5.4% control respectively). Both groups reported thoughts about daily living activities most frequently overall. Activity responses followed a similar pattern, with bipolar participants spending less time at work and more time on all other activities compared to controls, in particular passive leisure activities. Bipolar participants reported slightly less time socialising, more time at home, and slightly more time on active leisure activities than controls.

Thought Content

Activities

Where

Who with
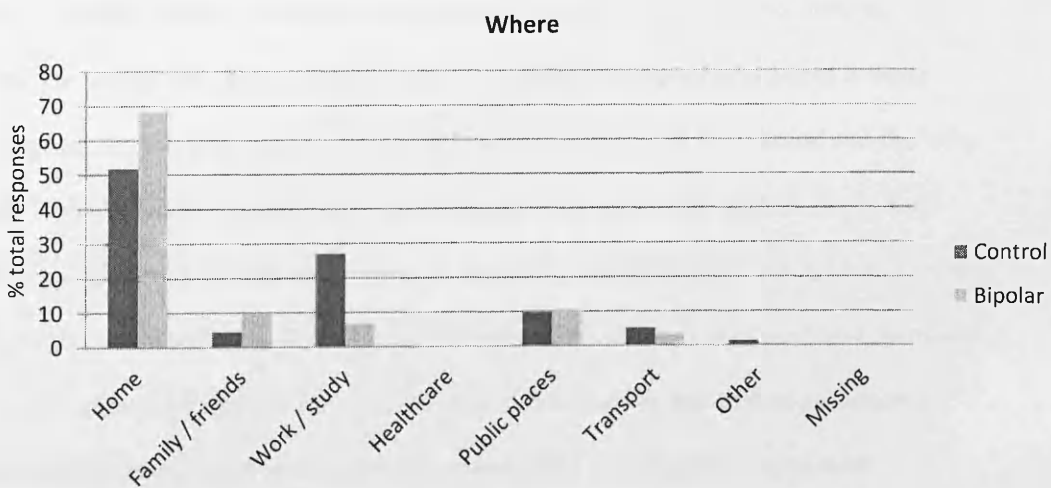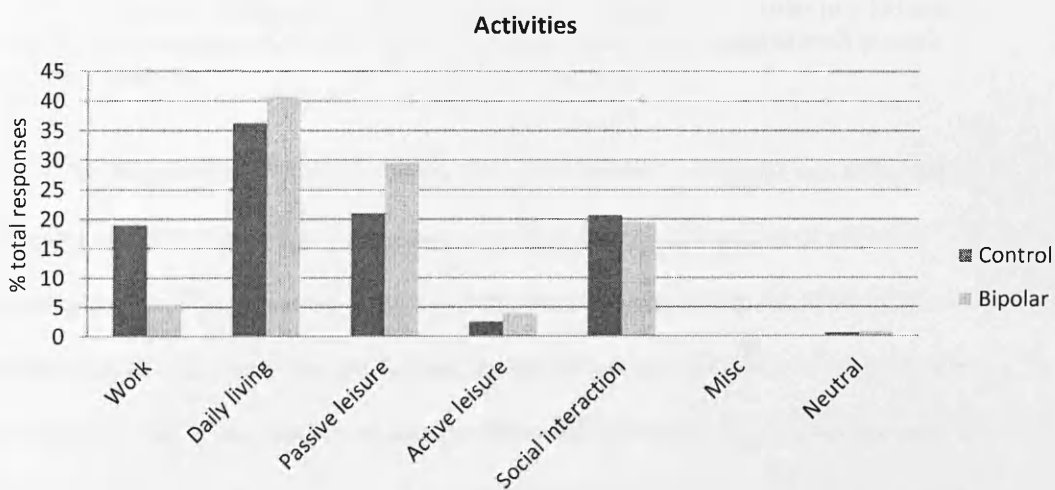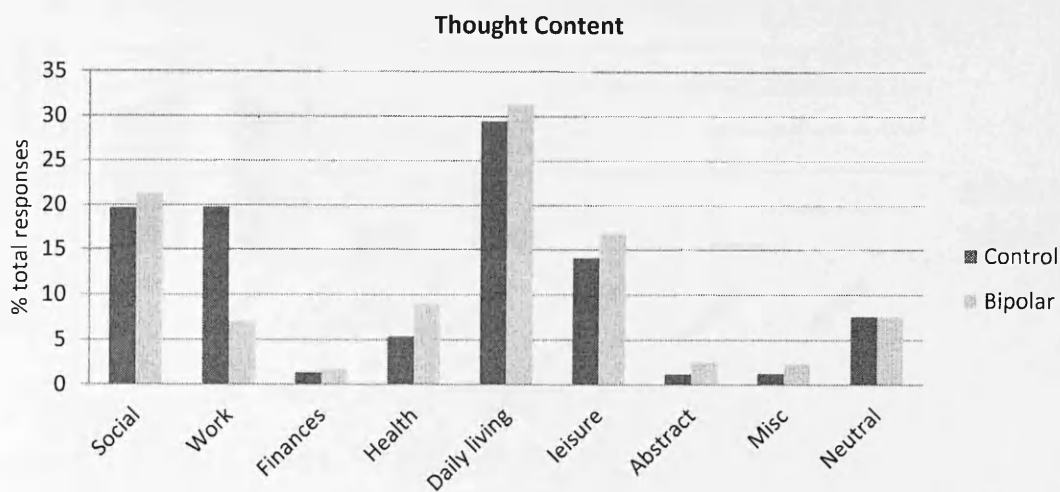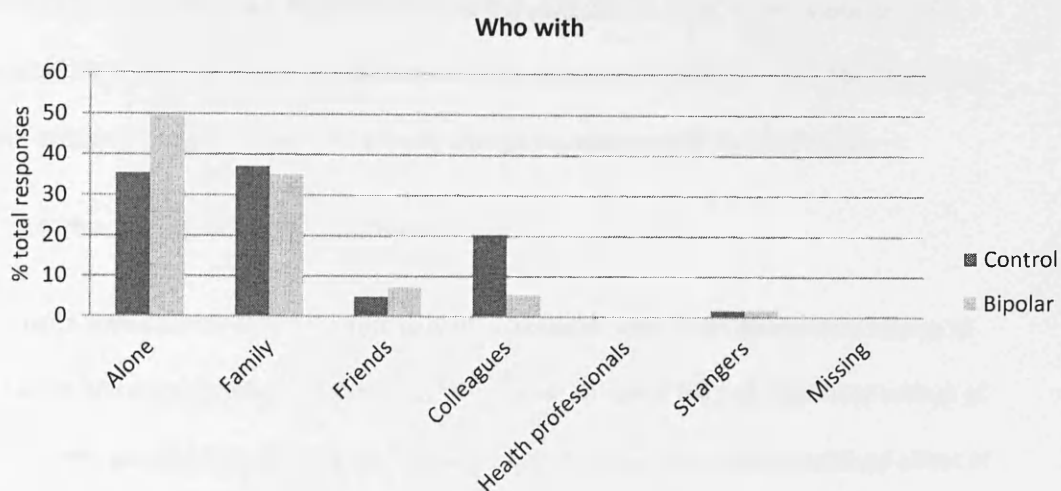
Figure 7.3 *Frequency of thoughts, activities and context responses for bipolar (n = 45) and control (n = 50) participants. Frequencies were calculated as percentages of each group's total valid responses*

The frequency of thoughts and activities in the 'neutral' categories was comparable between groups. As this category was made up almost entirely of thoughts or activities related to the study (e.g. thinking about when the next response will come, filling in the booklet), this was excluded from any further analysis as this was a product of the study and not reflective of daily life. 'Miscellaneous' and 'other' categories for all variables and the 'abstract' and 'finance' thought categories each accounted for < 3% of responses recorded for both groups. As such, these were also removed from the analysis at this point as statistical testing was not appropriate due to the limited number of data points in those categories. For the same reason, the 'where' variables 'other' and 'healthcare' and the 'who with' variable 'health professionals' were excluded from any further analysis due to each category accounting for <1% of the data. As between group differences in NA, PA and anxiety had been established in the first stage of this analysis, associations between these items and thought content, activity and context were explored for bipolar and control participants separately to assess how these factors influenced affect in each group. Concurrent

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associations were explored, together with thought, activity and context as predictors of anxiety, NA and PA ratings at the subsequent time point (see Tables 7.15 & 7.16). The latter were assessed using the affect and anxiety change variables calculated previously.

7.3.2.6 Thought content, affect and anxiety

Thoughts about health were the most strongly associated with affect and anxiety ratings at the same and subsequent time points, with increased ratings of NA and decreased ratings of PA for both groups when thinking about health concurrently. There was a sustained effect of health-related thoughts on NA and PA for bipolar participants, with increased NA and decreased PA at the next response also. Thoughts about health had an effect on anxiety for bipolar participants only, with concurrent ratings of anxiety increasing when thinking about physical or psychological health. Thinking about daily living activities was associated with increased PA for bipolar participants at the same and subsequent response. Thoughts about daily living activities were linked to decreased concurrent anxiety for controls, with thoughts about independent leisure (books, TV, computer games) also associated with reduced anxiety for control participants at co-occurring responses. Thoughts about work were associated with decreased PA ratings at the next response for control participants. Thoughts about other people or relationships did not have any significant impact on NA, PA or anxiety responses.

7.3.2.7 Activity, affect and anxiety

Only active leisure activities such as playing football, walking or going to the gym had any significant impact on affect for bipolar participants at concurrent time points and were associated with decreased NA. Socialising and active leisure activities were associated with increased PA ratings for control participants at the same time point. Whilst the effect size for active leisure activities on PA at the same time point for bipolar participants was similar to

that recorded for controls, this did not achieve significance. Socialising predicted increased PA at the subsequent responses for both control and bipolar participants. Work and daily living tasks were associated with decreased PA at the next response only for control participants, whilst spending time on passive leisure activities predicted decreased anxiety for controls at the next time point.

7.3.2.8 Associations between context, affect and anxiety

Being in the company of friends was associated with decreased NA for control participants. No other locations or social contexts had any significant effects at concurrent time points. However, spending time alone was linked to increased anxiety at the next response for control participants, and spending time with friends was associated with significantly increased ratings of PA at the subsequent rating. Public places were associated with increased PA at the next response for bipolar and control participants. There were no interaction effects of spending time with friends and spending time in public places for either group, suggesting these occurred independently. Being in a car or using public transport was associated with increased anxiety at subsequent responses for control participants only. There were no effects of location on concurrent ratings of anxiety or affect.

Table 7.15 *The cross-sectional association of thought content, activity and context with anxiety and affect*

Thoughts	Bipolar Group (n = 45)			Control Group (n = 50)		
	Anxiety	NA	PA	Anxiety	NA	PA
Social B^a	0.09	0.05	0.1	0.003	0.02	0.04
Work B^a	0.04	0.004	0.16	0.06	0.03	-0.03
Health B^a	0.19*	0.28***	-0.29***	0.09	0.15***	-0.20**
Daily living B^a	-0.0008	0.02	0.18**	-0.1*	-0.004	0.005
Leisure B^a	-0.05	-0.03	0.11	-0.1*	0.02	0.06
Activity						
Social B^a	-0.11	-0.15	0.05	0.06	-0.06	0.18**
Work B^a	-0.12	-0.12	-0.06	0.12	-0.005	-0.03
Daily living B^a	-0.14	-0.13	-0.08	0.04	-0.05	0.03
Passive leisure B^a	-0.17	-0.15	-0.13	-0.08	-0.04	0.02
Active leisure B^a	-0.14	-0.25*	0.21	0.1	0.02	0.23*
Who with						
Alone B^a	-0.05	0.04	-0.19	0.22	-0.22	-0.18
Family B^a	-0.05	0.11	-0.23	0.08	-0.22	-0.04
Friends B^a	-0.003	0.08	0.09	0.14	-0.29*	0.25
Colleagues B^a	-0.09	0.15	-0.07	0.18	-0.24	-0.18
Strangers B^a	-0.02	-0.07	0.06	0.18	-0.24	-0.08
Where						
Home B^a	0.06	-0.09	-0.15	0.09	0.04	-0.17
Family / friends B^a	0.05	-0.09	-0.13	0.10	0.03	0.09
Work / study B^a	0.11	0.04	-0.06	0.13	0.06	-0.16
Public place B^a	0.24	-0.12	0.19	0.10	0.002	0.10
Transport B^a	0.02	-0.12	-0.06	0.18	0.05	-0.14

^{a} B is the fixed regression coefficient of each predictor in the multi-level model, with all predictors entered into the model simultaneously

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 7.16 *The association of thought content, activity and context with changes in anxiety and affect between responses*

Thoughts	Bipolar Group (n = 45)			Control Group (n = 50)		
	Anxiety change	NA change	PA change	Anxiety change	NA change	PA change
Social B^a	0.07	0.09	0.03	0.04	-0.003	0.02
Work B^a	-0.02	-0.06	0.11	0.08	0.03	-0.09*
Health B^a	0.14	0.29***	-0.43***	-0.09	0.04	-0.15
Daily living B^a	-0.01	-0.02	0.13*	-0.07*	-0.01	0.02
Leisure B^a	-0.02	-0.06	0.04	-0.06	-0.003	0.08
Activity						
Social B^a	0.02	0.002	0.12*	-0.009	-0.03	0.17***
Work B^a	-0.13	0.07	0.12	0.05	0.02	-0.10*
Daily living B^a	0.01	0.02	-0.09	0.03	-0.02	-0.09*
Passive leisure B^a	-0.04	-0.02	-0.08	-0.08*	0.007	0.04
Active leisure B^a	0.01	-0.08	0.22	0.002	0.003	0.18
Who with						
Alone B^a	0.07	-0.006	-0.07	0.07*	-0.02	-0.06
Family B^a	-0.02	0.02	-0.04	-0.07	0.03	0.07
Friends B^a	-0.03	-0.03	0.28**	-0.05	-0.004	0.17*
Colleagues B^a	-0.12	-0.001	0.02	-0.0001	-0.02	-0.08
Strangers B^a	-0.22	0.04	0.19	-0.01	-0.02	0.11
Where						
Home B^a	-0.004	0.01	-0.07	-0.02	0.01	-0.02
Family / friends B^a	-0.02	0.04	-0.04	0.06	-0.006	0.07
Work / study B^a	-0.08	-0.004	0.03	-0.04	-0.004	-0.08
Public place B^a	0.12	-0.05	0.25**	-0.01	-0.005	0.15*
Transport B^a	-0.09	0.001	-0.26	0.15*	-0.01	-0.02

^{a} *B* is the fixed regression coefficient of each predictor in the multi-level model, with all predictors entered into the model independently; * *p <0.05*, ** *p< 0.01*, ***p< 0.001*

7.3.2.9 Impact of study on mood

To assess the extent to which the study may have influenced affect, 41 bipolar participants and 48 controls who completed the study provided information at debrief about this. Twelve bipolar participants and 18 control participants said that taking part in the study had made them think more about their thoughts and mood than they would usually, however this

related to being more aware of their experiences rather than changing the content of thoughts or the intensity of emotions per se.

7.4 Discussion

7.4.1 Interpretation of Key Findings

This was an exploratory study which aimed to explore the interaction of NA, PA and anxiety in real time for individuals with and without a diagnosis of BD, and to contextualise these experiences as they occur. Recruitment and retention rates were high for both bipolar and control samples, with both groups providing acceptable levels of eligible ESM entries overall (bipolar 65%, control 69%), suggesting that ESM is a feasible methodology with these participant groups. Despite participants with BD not experiencing any mood episodes at or in the four weeks prior to the study, these participants still had significantly higher scores on interviewer-rated measures of depression, anxiety and manic symptoms at baseline compared to controls. Whilst this difference was not clinically significant for mania, 35% of bipolar participants had mild to severe sub-threshold symptom scores for depression. A third of participants with BD also met criteria for one or more current AD, and depression was found to be correlated with anxiety symptoms at baseline. This is comparable to previous research which has found equally high levels of sub-syndromal symptoms and ADs in euthymic bipolar samples (Henry et al., 2003; MacQueen et al., 2003; Otto et al., 2006; Zutshi et al., 2006). In line with existing research (Altshuler et al., 2010; Fagiolini et al., 2007; Gaudiano & Miller, 2005), female participants with BD had increased current and past anxiety compared to males. However, gender had no effect on the real time experience of NA, PA or anxiety, and so this association between female gender and anxiety may not be meaningful in terms of actual subjective experiences.

Partial support was found for hypothesis 1, which predicted that individuals with BD would have higher average ratings of all affect domains compared to controls across the

study period. Despite significant differences at baseline, but consistent with previous research (Havermans et al., 2010; Havermans et al., 2007; Knowles et al., 2007), between group differences in momentary responses of NA and PA were not significant once group interactions were estimated, although there was a trend for bipolar participants to experience higher levels of NA and lower levels of PA. Bipolar participants were consistently more anxious than controls based on momentary responses. This pattern was consistent over multiple data points, which strengthens the validity of this finding. There was an apparent discrepancy between the observed higher baseline anxiety and depression scores for bipolar participants and the comparatively low momentary self-assessments of anxiety and NA. This may be due to a selective recall bias for participants with experience of depression and anxiety who may be more likely to attend to negative aspects of their daily lives, and these symptoms in particular, when asked about these at interview (aan het Rot et al., 2012). An earlier ESM study with depressed participants found that although participants were rated as clinically depressed at the beginning and at the end of a 7-day study, this did not match their real-time reported symptoms of depression (Mokros, 1993). Mokros et al. (1993) found that ratings for participants were much lower than their baseline diagnosis would suggest, and for some depressed participants there was no difference in ESM ratings of depression compared to controls. The observed difference in interviewer and self-rated affect scores may be due to calibration, as observed elsewhere (Lorenz et al., 2012). This refers to the fact that interviewers are trained to make assessments based on visible symptoms rated on a scale with clear anchor points. In contrast, self-assessments using Likert scales as in the current study are likely to be calibrated differently by each person, using our own individual anchor points. As such, interviewer assessments are made out of context to the everyday world in which those experiences occur, and so are likely to be different to self-reported assessments.

In support of hypothesis 2, individuals with BD had significantly more variable ratings of anxiety, NA and PA compared to controls in the present study, indicating an inherent instability of affect for individuals with BD, even when not experiencing an acute mood episode. Hypothesis 3 stated that variability in affect would be predicted by baseline anxiety for all participants. However, although there is evidence to suggest that the link between anxiety and BD may be mediated by current mood state (Simon et al., 2003), between group differences in variability of anxiety and NA were not driven primarily by symptoms of depression or anxiety in the present study. This is indicated by evidence that non-anxious bipolar participants (who also had low levels of depression) still had increased variability in anxiety, NA and PA ratings compared to controls. In addition, bipolar participants with mild and moderate-severe anxiety symptoms at baseline had similarly increased anxiety and NA variability compared to non-anxious bipolar participants, suggesting that low levels of anxiety have an impact on mood stability with no incremental effect of increased anxiety symptoms. However, this is clinically important when considering treatment of anxiety in BD given evidence of the strong associations between mood instability and later relapse (Perlis et al., 2006; Altman et al., 2006). However, it cannot be discounted that the observed difference in variability of affect between individuals with BD and controls may be due to a tendency for the bipolar group to use more extreme ends of the ESM diary rating scale. Future research which compares groups on ratings of neutral and non-personal experiences with the same scales would be useful to gauge to what extent this may be the case.

As predicted (hypothesis 4), there was an interactive relationship between anxiety and affect, and anxiety ratings were associated with increased NA and decreased PA at the same and subsequent time points for both groups. This is clinically significant and is consistent with the other findings in this thesis which suggest a pattern whereby anxiety increases mood symptoms which further increases anxiety (see qualitative meta-synthesis in Chapter 4, Study 1 in Chapter 5 and Study 2 in Chapter 6). NA and PA had a consistent

negative relationship throughout, with increases in NA being associated with decreases in PA at the same and subsequent responses for both control and bipolar participants. There were significant between group differences in reactivity of NA and PA to changes in other affect domains. Bipolar participants had heightened NA reactivity to anxious mood compared to controls, with significantly increased ratings of NA at concurrent and subsequent time points in response to anxiety. Conversely, control participants had elevated PA reactivity in response to NA, with larger decreases in PA in response to concomitant increases in NA ratings. This is in contrast to previous research exploring the impact of stress on mood which found bipolar participants to have greater PA reactivity in response to stress than controls, but no difference in NA stress reactivity (Myin-Germeys et al., 2003). This discrepancy may be due to the use of stress as opposed to anxiety as an outcome measure. Other research exploring affect reactivity in response to daily life events has found no difference between control and bipolar participants, but did find that NA reactivity was elevated in a sub-group of bipolar participants with sub-syndromal depressive symptoms compared to bipolar participants without (Havermans et al., 2010). However, the present study found that NA reactivity was increased in response to anxiety for individuals with BD even when controlling for concurrent levels of affect. It has been suggested that increased susceptibility to anxiety and stress may occur for individuals with BD as a result of the experience of traumatic events and associated cognitive impairments and stress responses (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Simon et al., 2005). This hypothesis currently has mixed support, and whilst bipolar participants with early life stress have been found to relapse in response to lower levels of stress than those without experience of trauma (Dienes et al., 2006), additional research is required to explore this in the context of anxiety as a potential mediator between stressful life events and subsequent mood episodes. History of trauma was not explored as a predictor of mood or anxiety in the present investigation due to missing data, however 73%

of participants with BD who were asked did report previous traumatic life events, in contrast to only 2% of control participants reporting any history of trauma.

The finding that control participants had increased PA reactivity in response to concurrent NA in the present study is interesting. It is possible that this may be due to bipolar participants having lower PA levels in general, and whilst not significantly lower than controls, this may have meant there was less room for decline in PA ratings for the bipolar group, although this is speculative. More likely increased PA reactivity in controls may be explained to some extent by the observation that NA and PA were more highly negatively correlated for controls than for the bipolar group, suggesting NA and PA states are more independent for individuals with BD. Again, this may be linked to emotion dysregulation in BD and the experience of clinically relevant mixed states (Agosti & Stewart, 2008) where symptoms of depression and mania are experienced simultaneously. Mixed states have been found to be elevated in bipolar samples with anxiety (Goldstein & Levitt, 2008) and have been highlighted as a risk factor to increased anxiety symptoms even after remission from an acute mood episode (Shah, Averill, & Shack, 2004).

Past research has explored differences in time use between control and bipolar samples (Havermans et al., 2007), but has not explored associations with affect. As previously found, there was no difference in the content or type of thoughts and activities reported, with the same coding schedule adequately describing responses provided by individuals with BD and control participants in the present study (Brown, O'Leary, & Barlow, 2001; Craske et al., 1989; Havermans et al., 2007). However, the frequency of responses in those categories did vary between groups, mainly in line with differences in sociodemographic variables such as employment and marital status. Individuals with BD reported more thought and activity responses of daily living and independent leisure than controls, and concentrating on daily living tasks was found to increase PA for bipolar participants and decrease anxiety for controls. In contrast to previous research, which has

found individuals with BD to have increased reactivity in response to environmental stressors compared to healthy controls, where reactivity is defined as more rapid and intense changes in affect (Henry et al., 2008), the present study found control participants to have increased reactivity to events compared to individuals with BD. This was particularly true for activity, where work and daily living tasks were linked to decreased PA for controls and passive leisure activities were associated with decreased anxiety. Socialising and spending time with friends was linked to increased PA for both groups at concurrent and subsequent responses, despite bipolar participants reporting more time spent alone. Being out of the house and spending time in public places was also associated with increased PA for both groups at subsequent time points. This suggests a positive effect of social networks and friendships, and is in line with previous research which shows social support is associated with reduced relapse and recovery time (Cohen, Hammen, Henry, & Daley, 2004; Johnson, Winett, Meyer, Greenhouse, & Miller, 1999).

Despite spending more time than controls thinking about and completing activities such as watching television, reading or playing a computer game, thoughts related to independent leisure were only associated with decreased anxiety for controls. Active leisure activities decreased NA for bipolar participants and increased PA for controls. This suggests that whilst passive leisure activities account for a large amount of time use for individuals with BD, these activities may be less effective as a method of managing mood and anxiety than being physically active. Research evaluating exercise-based therapeutic interventions in BD is limited, and there are currently no large scale RCTs in this area. Current research is mixed in terms of the benefits of exercise in BD. Regular exercise has been found to reduce risk of physical health problems in BD (Carney & Jones, 2006; Lin, Tsai, & Lee, 2007) and lack of exercise is linked to increased symptoms of depression in UD and BD (Sylvia et al., 2013; Blumenthal & Ong, 2009). However, regular exercise has also been associated with increased symptoms and episodes of mania retrospectively (Sylvia et al., 2013).

Thoughts about health were reported twice as often by bipolar participants, but were associated with increased NA and decreased PA for both groups. However, anxiety ratings were increased in response to health-related thoughts for the bipolar group only, and had a sustained effect on anxiety and affect at the next response for this group also. This suggests that individuals with BD may worry more about their health than control participants. This is in agreement with existing qualitative research in BD within this thesis (Chapter 5) and the wider literature (Chapter 4), where anxieties and concerns have been expressed in relation to living with a mood disorder, including fear of relapse, the side effects of taking long term medication and the impact of illness on social and occupational functioning (Jönsson et al., 2008; Mansell et al., 2010; Michalak et al., 2007; Tse & Yeats, 2002). As such, it is not surprising that individuals with BD would think more often about their health and that these thoughts would impact on affect.

7.4.2 Strengths, limitations and future research

The present study intended to recruit bipolar and control participants matched on age, gender and occupation. However, due to the challenging nature of recruiting control participants to an ESM study, and the short timescale available for recruitment overall, participants were recruited for both groups in tandem, leaving little room for strategic recruitment and matching. As a result, groups differed on age, gender, marital status and employment status. The literature shows a negative impact of unemployment on those recently out of work, and this has been associated with subsequent depression and anxiety (Howe, Hornberger, Weihs, Moreno, & Neiderhiser, 2012; Montgomery, Cook, Bartley, & Wadsworth, 1999). This may account for differences observed between groups in thought content, activity and context. In addition, differences in symptoms of anxiety, depression and NA observed between groups at baseline and throughout may have been confounded or explained by lower rates of employment in the BD sample. Also of note, of control

participants who were in employment, 12 participants (24%) held clinical roles in healthcare or mental health services, 12 participants (24%) were working in research posts and 11 (22%) were working in university settings in teaching, technical or administrative roles. As a result, these participants may have differed in their knowledge and insight on the process of thoughts and emotions from other members of the general population.

The majority of bipolar participants were taking regular, prescribed psychiatric medication. Whilst this is a potential confound, as psychiatric medications are designed to affect and control mood, this reflects the clinical reality that pharmacotherapy is the frontline treatment in BD and so is a normal part of daily life and experiences. However, the possibility that any differences observed between groups were due to the presence or absence of medication use cannot be disregarded completely as adherence was not assessed. However, controlling for this statistically would have been essentially controlling out the variance that this study was aiming to explain, as medication is often closely linked to the experience of BD. Future research which compares rates and variability of affect in individuals with BD who are not taking psychiatric medication would help to determine the impact of medication on mood. Alternatively, research using parallel high risk designs to compare those at risk of BD and those who are low risk or 'normal' controls would allow exploration of vulnerabilities to mood swings without the confounding effects of illness such as medication. One potential way of identifying a high-risk sample is by including those who score highly on the HPS, as done in previous research (Kwapil et al., 2000; Pyle & Mansell, 2010). The current study may be biased by the exclusion of individuals scoring more than 0.5 SD above the mean on the HPS. Future research which includes a high-risk sample or individuals with a full-range of scores on the HPS is required to fully differentiate between processes which are specific to the clinical aspects of BD, such as medication, and those which sit on a continuum within the general population, such as mood fluctuations. In

addition, this would allow for the identification of protective factors which defend against the development of problematic mood swings.

As ESM research is still relatively new, there are methodological issues which require clarification. There is currently no empirical rationale for the requirement of participants to complete > 30% valid ESM entries to be included for analysis. This approach was adopted in the present study to compare results to previous research. However, this needs to be explored to provide a statistically supported threshold of completeness, as it may be that inclusion of all eligible data points would be more logical in future studies. This study recruited a relatively large sample with high completion rates in comparison to previous studies where sample size has ranged from 10 to 49 participants, with varying levels of compliance. Information regarding missing data was also collected in this study via participant self-reported reasons for missed responses to confirm that data was not missing due to any relevant, systematic reason, such as changes in affect. The most common reason for missingness in the BD group was being asleep, whilst controls were most likely to miss alerts due to being at work. As a formal power analysis to determine sample size was not carried out (see Section 7.2.1), the possibility that this analysis is under-powered due to an inadequate sample size or number of responses cannot be ruled out. Future research to develop a reliable method for estimating power and sample size in multilevel designs is required.

The present study involves the assessment of interactions between affect, anxiety and context through repeated assessments across time. As multiple testing increases the risk of Type I errors, (see discussion in Section 7.2.1), all results in this study are provisional and may be due to chance. Key findings require replication in future research which controls for multiple testing more rigorously. In addition, assessments of the association between variables at the same point in time are essentially cross-sectional, as outcomes relate to responses which are aggregated across time points. However, this is more robust than a

standard cross-sectional analysis, as results are based on multiple responses from every participant, increasing the validity of the observed effects. Longitudinal analyses were also carried out, assessing the interaction between responses at time 1 with change in ratings at the next response. This prospective analysis is limited to exploring relationships over a relatively short period of time. However, as time between responses varied both between and within participants due to missing data points, selecting any set time period to estimate effects would have been problematic as time between any two responses would not be analogous for all participants. In addition, this study was concerned with exploring mild changes in affect and anxiety, and so extending time thresholds beyond adjacent responses may have missed immediate but potentially brief interactions which did not last beyond the subsequent response.

Whilst ESM was found to be an appropriate method to use with individuals with BD with sub-threshold symptoms of depression in the current study, BD participants who failed to complete the study were found to have higher levels of manic symptoms at baseline. This may indicate that ESM studies are not an appropriate method of recording mood when participants are experiencing even mild symptoms of elevated mood. As such, the results may be biased towards capturing experiences of normal or low mood, but excludes experiences at the other end of the bipolar continuum. Making the method more accessible to those who are experiencing manic symptoms is important to avoid losing valuable data relevant to positive mood, for example using electronic devices which allow instant ESM entry recordings to avoid participants becoming distracted or forgetting to respond to an alert.

It is an unavoidable confound that asking questions about mood undoubtedly leads participants to think more about mood and mood symptoms than they may do in normal daily life. Attempts to limit this effect were made by interspersing diary items about mood with questions about context and current activities (Palmier-Claus et al., 2011). However, the

nature of the study would have been apparent to all participants from the outset, and this was unavoidable. However, participants reported subjectively that the study raised their awareness of emotions and associated processes, without influencing these directly.

Due to limitations of coding schedules used to categorise responses to open questions in previous similar research, a coding scheme was developed for the present study. This scheme was driven by the data and categories were kept deliberately broad to capture overall thought and activity experiences. Whilst previous research suggests that having a vast number of categories leads to internal duplication of items, with the same response being coded as multiple categories and resulting in inconsistency between raters, there is the potential that the coding scheme used in the present study may have been too simplistic. As a result, inter-rater agreement may be high, with minimum cross ratings, but detail of specific thoughts and activities that trigger changes in mood and anxiety may be lost. For example, significant findings relating to thoughts about health could not distinguish here those thoughts related to psychological or physical well-being. Future research to further explore and expand any potentially important categories would be useful.

Finally, as previously discussed (see Section 7.1), there was a conceptual issue in this study regarding the measurement of NA and anxiety as independent constructs. This study does not suggest that anxiety and NA are entirely separate experiences. On the contrary, based on the current literature and the previous investigations in this thesis (see Chapters 4 and Study 1 and 2), it appears that anxiety may in fact be an inherent part of BD. Results in the present study also support this argument, with NA and anxiety highly correlated for BD participants based on momentary ratings ($r = 0.75$), although less so for controls ($r = 0.47$), potentially due to less variability in scores for control participants. In addition, increases in anxiety were associated with significant increases in NA across groups, and a smaller but significant increase in anxiety when NA increased concurrently, which was more pronounced for the BD group. These findings support anxiety and NA as intrinsically related constructs in

BD. However, they are not perfectly correlated for either group and regression coefficients do not show a comparable increase in anxiety or NA in response to a change in the other, also indicating that measuring these experiences independently was not redundant. In addition, there were also differential patterns observed for anxiety and NA. For example, increased anxiety for individuals with BD compared to controls, but not elevated NA or PA. Results also indicated variations in thoughts and activities which increased and decreased NA and anxiety differentially. As such, NA and anxiety in this study were closely related experiences with some subtle, but potentially important, qualitative differences. However, care must be taken not to over-estimate these differences based on limitations of sample size and multiple testing.

7.4.3 Clinical Implications

The finding that individuals with a diagnosis of BD were consistently more anxious than control participants in this study, and that anxiety was significantly associated with mild, short-term fluctuations in PA and NA in daily life, is clinically relevant. This supports existing research that anxiety is a core experience in BD and should be addressed as a key part of treatment and future research. Whilst there is nothing that can be done retrospectively to alter some other markers of a more severe illness course in BD, such as previous number of affective episodes or early age of onset of BD, anxiety can be addressed at any stage. Heightened NA reactivity to anxiety for individuals with BD in the present study suggests interventions which address the interpretation and management of anxiety may be key to reducing symptoms of both anxiety and NA. In addition, the interactive relationship observed for anxiety with NA and PA in the present study also suggests that interventions which address the interpretation and management of 'traditional' bipolar mood symptoms would potentially have a similar effect. Graded exposure to anxious experiences together with skills training to re-structure cognitions and manage anxiety has been recommended

(Otto et al., 2004). The finding that cognitions related to physical and psychological health in particular are associated with anxiety in BD in the present study highlight this as a potential target for treatment. The present study found that being occupied with daily and leisure activities, being physically active, and increasing social networks helped to decrease NA, increase PA and reduce anxiety for bipolar and control participants in different ways. Future research and therapies which explore the effectiveness of these strategies to stabilise mood and reduce anxiety are required to see if these are effective strategies long term.

Several effective psychological and pharmacological treatments for anxiety exist, but need to be adapted and tested for their effectiveness in treating anxiety in bipolar populations. Research has begun to develop and evaluate specific interventions targeting anxiety in BD, and transdiagnostic interventions which treat a range of emotional disorders, based on evidence for shared psychological processes (see Chapter 1, Section 1.7). As a feasible methodology with individuals with mood swings, ESM could be employed to explore the real time effects of interventions aimed at addressing mood fluctuations, as has been done previously to compare psychoeducation and cognitive behavioural therapy for depression (Husky et al., 2010). ESM could also be utilised as a clinical tool to support individuals to identify and understand the link between thoughts, feelings and behaviours. However, the practicalities of doing this long term may need to be considered due to the demands of ESM methodology, and may require a reduction in number of daily assessments or the length of time over which data are collected. As the input and analysis of ESM data can be time-consuming and impractical in clinical practice, the use of electronic devices which enable data to be collected, downloaded and analysed quickly would be important to ensure this is practical for clinicians working in current healthcare services where evaluation of treatment is important but often restricted by demanding clinical roles.

7.4.4 Conclusions

This study found anxiety, NA and PA to have an interactive, bidirectional relationship, with changes in one mood state impacting on others. Increased anxiety reactivity, elevated overall anxiety and increased mood variability linked to even mild anxiety symptoms for individuals with BD highlights the importance of recognising and exploring anxiety as a key aspect of future research and treatment.

Chapter 8: General Discussion

8.1 Overview

The aim of this chapter is to consider the results from both the qualitative and quantitative elements of this thesis and to provide a coherent understanding of the experience of anxiety in BD. Results from the differing methodologies employed will be discussed together, to identify consistencies and discrepancies in findings across studies, whilst also acknowledging the inherent differences arising from the methodologies used. The implications of the findings for theoretical development and for clinical practice will be discussed, along with potential future directions for this area of research. Importantly, some of the key methodological issues will be discussed to ensure these are taken into account when drawing final conclusions. Results from both methodologies are given equal weight and are discussed below.

8.2 Main findings

8.2.1 Anxiety as an important experience in BD

A review of the current literature highlighted the absence of existing research exploring the lived experience of anxiety in BD. Chapter 4 reported a meta-synthesis which explored themes from relevant qualitative research regarding the experience of anxiety in BD. Study 1 (qualitative interviews, Chapter 5) then explored the experience of anxiety in BD directly through the use of semi-structured interviews with individuals with BD with a range of anxiety experiences. There was a high degree of convergence between themes identified in the meta-synthesis and Study 1. Anxiety was consistently reported as an important subjective experience which impacted significantly on important life domains. Individuals reported being concerned about relapse, which in turn heightened worry related to everyday stressors. Perhaps most significantly anxiety was reported as a barrier to goal achievement in many areas of life including work, leisure and self-management. In addition,

inter-personal difficulties related to forming and maintaining close relationships were identified as an important negative consequence of anxiety. Despite a general perception that anxiety was inevitable and difficult to change in Study 1, when asked, individuals said that anxiety was something they would like more help with, and felt that the scale and impact of anxiety could be addressed with help and support. Anxiety was also found to be an important experience clinically, and was consistently associated with increased NA and depression across studies. This suggests that the impact of anxiety may be most clinically relevant in the context of negative mood. However, anxiety was also subjectively reported as a trigger to and consequence of manic episodes in Study 1. In contrast, the results of Study 2 (analysis of data from the PARADES Psychoeducation study) and Study 3 (ESM) indicated that anxiety was either unrelated to manic symptoms (Study 2) or associated with decreases in PA (Study 3). However, this difference may be due to the low level of current manic symptoms and PA observed in the quantitative studies, whereas in the qualitative interviews participants described past experiences relating to very high levels of manic symptoms and episodes. This highlights a strength of the mixed methods approach in this thesis, where Study 1 allows the exploration of important experiences of anxiety linked to manic episodes which could not be captured in Study 3 or 4 due to lack of variability in manic symptoms. Similarly, Study 3 and 4 are able to capture more subtle interactions and experiences which occur out of mood episodes and which may be less likely to be reported subjectively, potentially because these experiences are more familiar and have less impact on bipolar mood experiences and daily life. Anxiety as a trigger to both depressed and manic episodes is considered in more detail below (see Section 8.2.2).

8.2.2 Anxiety as a trigger to mood fluctuations

Subjectively, anxiety was identified in the meta-synthesis and Study 1 as a trigger to both manic and depressed episodes, and there appeared a vicious circle linking anxiety and mood

symptoms. Worry about relapse often led to increased anxiety about other aspects of daily life, which in turn led to worsening of mood symptoms, maintaining anxiety about relapse as a consequence. This was consistent with findings in the quantitative studies presented in this thesis to some extent. Study 2 found that anxiety symptoms were a significant and consistent predictor of later symptoms of depression across all follow-up points where data were collected every 16 weeks up to 96 weeks. Anxiety was also associated with increased NA and decreased PA for all participants in Study 3, irrespective of BD status. However, BD participants differed from controls in terms of reactivity. The BD group were more sensitive to changes in anxiety, with greater increases in NA compared to controls when anxiety increased. Anxiety also increased in response to increases in NA, however this effect was smaller. Control participants were more reactive to changes in NA, and ratings of PA decreased much quicker in comparison to the BD group when NA increased. However, this was only at concurrent time points for controls, whilst increases in NA in response to increases in anxiety for the BD group were sustained at the following response. This suggests that individuals with BD are less able to regulate their mood when change occurs, potentially due to the associated anxieties identified in the meta-synthesis and Study 1 regarding perceived changes in internal state. Thoughts about having to control mood and avoid relapse co-existed with beliefs that monitoring mood and behaviour was restrictive (meta-synthesis and Study 1). This is consistent with current psychological models of BD, in particular the ICM (Mansell et al., 2007), which proposes that extreme and conflicting beliefs about mood swings lead to attempts to control mood symptoms. Worry about mood generally won out in this thesis, as individuals reported attempting to control mood using a number of different strategies, which are outlined below.

8.2.3 Cognitive responses to the experience of anxiety and mood fluctuations

Cognitive responses to anxiety included thought suppression: individuals reported avoiding thinking about the future in general and trying not to think about BD when well (Study 1 and meta-synthesis). Worry and rumination about relapse were also reported, and although not explicitly described as a coping strategy this would be categorised as such clinically. This was also evident in the belief that participants could never really be sure their mood was "under control" which was linked to hypervigilance and worry about mood. Thoughts about psychological and physical health were linked to increases in NA for individuals with BD and controls in Study 3, however the BD group thought about health almost twice as often as the control group. In contrast, thinking about daily living tasks was found to increase PA for BD participants, suggesting that distraction from negative thoughts may be helpful. However, this was not associated with decreases in NA or anxiety as might have been expected. The finding that cognitions and cognitive strategies are involved in the experience of anxiety in BD suggests that anxiety may to some extent drive attempts to manage mood due to past negative experiences of mood episodes and current negative thoughts about relapse. However this ultimately increases the risk that a mood episode will occur due to the nature of the strategies used. The avoidance of thinking about mood or planning ahead when well may also feed into the perceived unpredictability of BD and the sense that relapse could "sneak up" on you (Study 1).

8.2.4 Activity linked to changes in mood and anxiety

Behavioural responses were linked with both anxiety and mood fluctuations. Individuals subjectively reported the use of short term strategies to manage anxiety, including drugs and alcohol, avoidance of social situations and relationships, and the restriction of stimulating or pleasurable experiences (Study 1 and meta-synthesis). Socialising with friends and spending time out of the house was linked to increases in PA for individuals with BD and controls (Study 3). Social Phobia (SoP) was also found to be significantly associated with decreased

manic symptoms prospectively (Study 2). This suggests a positive effect of social networks and friendships, but also links to beliefs that social situations could be activating and trigger changes in mood, which may explain SoP as a protective factor to mania. This is consistent with previous research which has also found negative associations between mania and SoP (Perugi et al., 2001). Changes in social rhythms have been associated with manic episodes (see Chapter 2, Section 2.5), which is consistent with the finding in this study that socialising increases PA, and it may be that significant increases in social activities exacerbate manic symptoms in BD, leading to avoidance of those situations when people are concerned about becoming unwell. This is also consistent with avoidance of activity and lack of pleasurable experiences as a trigger to depression, as reported in the meta-synthesis and Study 1. Active leisure activities such as exercise or sport were associated with decreased NA for individuals with BD in Study 3, which has implications for intervention, particularly in the avoidance of depression. No other activities were associated with changes in anxiety, PA or NA for individuals with BD in Study 3. This may be significant as BD participants spent the majority of their time on daily living and passive leisure activities, which were not found to have any impact, positive or negative, on anxiety or affect. Anxiety as a barrier to activity such as socialising (relationships) and meaningful occupation or employment was more often highlighted (meta-synthesis and Study 1). Anxiety was described as a trigger to depression due to the potential for failure and, more often, a general lack of positive experiences and reinforcement due to anxiety being a preventative factor to engagement in activities.

8.2.5 Associations between anxiety, mood and sleep

Sleep disturbance was identified subjectively as a potential link between anxiety and subsequent mood swings. Anxiety was reported as a precursor to sleep disruptions, and resulted in increased worry about relapse if sleep patterns did not return to normal. Disruptions in circadian rhythms, and the appraisal of these changes in internal states, have

been linked to the onset of bipolar mood episodes (see Chapter 2, section 2.5). It may be that anxiety leads to disruptions in sleep, and these disruptions are appraised as catastrophic (e.g. if I don't get more sleep, I will have a relapse), which leads to rumination about sleep loss. This may result in attempts to manage sleep, such as napping, avoiding stimulation or staying at home, which disrupts sleep further and perpetuates increases in mood symptoms. Again this suggests a vicious cycle, where anxiety leads to sleep disruption, which leads to mood symptoms and more anxiety. However, the association between sleep and anxiety was not measured directly in the current thesis and future research should assess the link between sleep and anxiety in BD.

8.2.6 Anxiety as a barrier to goal achievement and positive experiences

In all three empirical studies in this thesis, individuals with BD have had low rates of employment and were significantly less likely to be employed or in relationships than controls in Study 3. Subjectively anxiety was identified as a barrier to achieving important life goals such as finding a partner or getting a job. A large body of research has found there may be increased sensitivity to goal attainment and failure for individuals with BD (Chapter 2, Section 2.3.6). Mania has been found to occur as a result of striving for achievement and excessive goal-orientated behaviour, whilst there is evidence that depression may occur in the event of perceived failure, potentially due to the negative way in which these events are appraised (See Chapter 1 Section 2.3.6). In this thesis, anxiety was cited as disrupting engagement in meaningful employment, education and important relationships. This may result in frustrative non-reward or appraisals that goals may be achieved if an individual tried harder, possibly resulting in manic experiences. Alternatively, this could also lead to failure and negative appraisals that trying is hopeless as anxiety is impossible to overcome (Study 1), leading to a reduction in activity and depression. In addition, difficulty in achieving goals and forming relationships may result in a lack of protective factors such as positive

experiences and supportive social interactions, which are likely to be a source of self-esteem and self-efficacy. As such, this may maintain anxiety experiences and mood swings.

8.2.7 Anxiety as an inherent part of BD

All aspects of this thesis provided important information regarding the nature of the relationship between anxiety and BD and there was agreement across studies that for these participants, anxiety was an inherent part of bipolar experiences. Study 1 found that individuals with BD perceived anxiety as being related to all aspects of mood experiences. Many participants reported having always been anxious and "up and down" in mood from a young age, alluding to an inherent dysregulation of emotion which included anxiety, depression and elation. This is contrast to previous research which has argued for anxiety as a separate, comorbid experience in BD (see Chapter 1, Section 1.6.3). Study 3 found that individuals with BD were consistently more anxious than controls, and had increased variability across all mood states, including anxiety, when compared to controls. This is not to say that anxiety is a core part of BD for everyone, and there are likely many people with BD who do not experience anxiety as a problematic experience. However, participants in Study 3 were not selected on the basis of current anxiety experiences and associations were still found between anxiety and affect. Still, what this thesis may not capture as clearly is the experiences of those who are not anxious and the protective factors which may build resilience to anxiety. This is a potential area for future research.

8.2.8 Heightened sensitivity to anxiety and emotion in BD

Participants in Study 1 reported a perceived increased sensitivity to anxiety and amplification of emotions as a result of BD. Previous research exploring the positive aspects of BD has suggested heightened emotional experiences can be seen as beneficial by some people (Lobban et al., 2012). However, in the context of anxiety this sensitivity was seen as negative,

with the experience of anxiety also being heightened, and life stressors and situations perceived as more difficult to cope with. The notion of heightened sensitivity to emotions and stressors is consistent with other conceptualisations of BD. For example, BAS theory suggests that a trait vulnerability to dysregulated affect interacts with and increases sensitivity to life stressors, resulting in symptoms of depression or mania due to excessive up or down regulation of approach behaviour (Alloy & Abramson, 2010; Depue & Iacono, 1989; Johnson, 2005; Urošević et al., 2008). The BAS theory also suggests that individuals with BD will have increased reactivity in all aspects of affect compared to those without BD. Findings in the quantitative elements of this thesis regarding mood reactivity in BD were mixed. Overall, individuals with BD had significantly more variable affect in all domains compared to controls in Study 3. However, when assessing reactivity to changes in affect and anxiety, real time repeated assessments in Study 3 found evidence for increased sensitivity to changes in anxiety in BD compared to controls, but not to changes in NA or PA. In addition, controls were found to have increased PA reactivity to changes in NA compared to individuals with BD, which was unexpected and also in contrast to previous ESM research (Myin-Germeys et al., 2003). It may be that although controls experienced a greater decline in PA when NA increased, overall fluctuations in affect occurred less, changes were smaller and changes were not sustained beyond that response, and so these fluctuations may not be problematic and are essentially self-correcting, even when they do significantly impact on the experience of positive emotions. However, this requires further exploration. In addition, the reactivity of the BD group may have been in response to signals of reward or punishment, which were not explored explicitly in this thesis.

8.3 Theoretical Implications

8.3.1 Integrating experiences of anxiety into existing psychological models

The model presented in Figure 8.1 is based on the ICM by Mansell et al. (2007) but has been adapted to include the experience of anxiety in BD. This model was chosen to interpret the theoretical implications of the findings in this thesis as the ICM is an integrative model that takes elements from the predominant cognitive and behavioural psychological models in the literature (BAS, disruption of circadian rhythms, cognitive therapy model, extreme appraisals) and was felt to best account for the experiences of anxiety described and observed in the current PhD. This is not a definitive model of anxiety in BD, as this thesis did not set out to test the ICM directly: rather it was decided that this represents a coherent way of bringing together the findings across studies in this thesis, applying them to the current literature and identifying potential areas for intervention and future research.

It is proposed that worry and anxiety may act as a trigger to changes in internal states (see Figure 8.1, Box 2), for example anxiety leading to physiological and cognitive changes as reported in Study 1, such as restless energy, loss of sleep or the speeding up of thought processes ("the Christmas tree light effect" ; Figure 8.1, Box 3). These internal changes were interpreted by individuals with BD as having extreme personal significance (Figure 8.1, Box 4), specifically that these were early warning signs of an impending mood episode. The ICM states that extreme appraisals of internal states are based on past experiences and beliefs about others. This thesis found evidence for specific beliefs about mood and anxiety (Figure 8.1, Box 5). Specifically, participants believed that being anxious was perceived as less serious than bipolar mood experiences by others, and so individuals felt less able to seek support for anxiety. This was also accompanied by a relatively helpless perception of anxiety, which was often seen as inevitable (Study 1). However, whilst participants felt there was nothing they alone could do to change their experience of anxiety,

there was a general desire for more formal help and support for anxiety, which indicates that beliefs about anxiety weren't entirely hopeless. Individuals also held beliefs that mood should be controlled, which appeared fuelled by their anxiety about becoming unwell. Anxiety about illness was directly linked to past negative experiences of relapse (Figure 8.1, Box 6). This resulted in attempts to control mood, in particular through descent behaviours such as rumination and worry about relapse, being constantly vigilant to changes in mood, and the avoidance of anything that might be stimulating to minimise risk of manic symptoms, but which ultimately increased symptoms of depression (Figure 8.1, Box 7). Ascent behaviours were less well defined in this thesis, however physical activity and socialising with others have been added to the model as potential ascent behaviours (Figure 8.1, Box 8). Physical activity was found to increase PA (Study 3) and so may be used as a strategy to avoid depression and lift mood. Socialising with others has also been added as an ascent behaviour in the context of anxiety experiences as these situations were associated with striving to hide anxiety and put a 'brave face on it', which may have been activating in terms of working to achieve this goal, or due to individuals socialising more to prove they were OK. Attempts to control mood through behaviour were ultimately contributed to past and on-going life experiences (Figure 8.1, Box 6). Negative life experiences were linked consistently to anxiety and relapse. Anxiety was identified as a barrier to goal achievement such as engaging in meaningful occupation and relationships, and this in itself became a source of failure, worry and further anxiety as this conflicted with personal goals such as the desire to be close to others, to have a meaningful career and to engage in enjoyable activities. This resulted in a lack of protective factors which maintained anxiety, and this persistent anxiety appeared to have become a direct route to changes in internal state. Underlying beliefs and anxieties about mood were also a direct route to behaviours and attempts to control mood, with this happening even when not experiencing mood episodes.
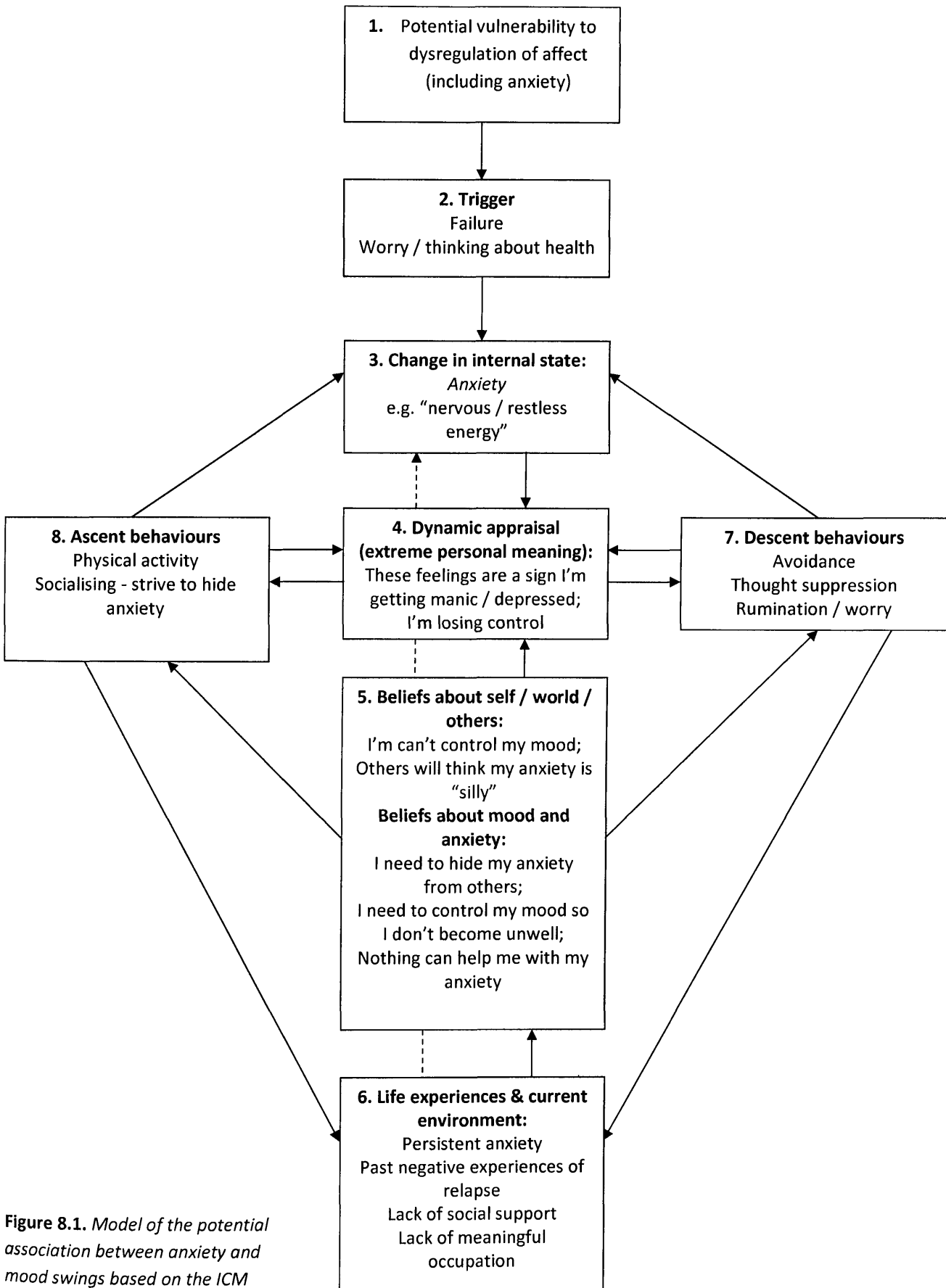
Figure 8.1. *Model of the potential association between anxiety and mood swings based on the ICM*

The content of the figure boxes:

1. Potential vulnerability to dysregulation of affect (including anxiety)

2. Trigger
Failure
Worry / thinking about health

3. Change in internal state:
Anxiety
e.g. "nervous / restless energy"

4. Dynamic appraisal (extreme personal meaning):
These feelings are a sign I'm getting manic / depressed; I'm losing control

5. Beliefs about self / world / others:
I'm can't control my mood; Others will think my anxiety is "silly"
Beliefs about mood and anxiety:
I need to hide my anxiety from others;
I need to control my mood so I don't become unwell;
Nothing can help me with my anxiety

6. Life experiences & current environment:
Persistent anxiety
Past negative experiences of relapse
Lack of social support
Lack of meaningful occupation

7. Descent behaviours
Avoidance
Thought suppression
Rumination / worry

8. Ascent behaviours
Physical activity
Socialising - strive to hide anxiety

For example the tendency to avoid thinking about illness and failure to plan ahead even when well due to the anxiety associated with doing so. However, the tendency for individuals with BD to think about health more than controls in Study 3 suggests that, like many thought suppression strategies, this was unsuccessful and may have actually increased thoughts and worries about health. As such, a vicious cycle of anxiety exacerbating mood symptoms which also increased anxiety was maintained.

Although the model in Figure 8.1 has been drawn to show the potential role of anxiety in the escalation of both depression and mania, this thesis found greater evidence for the link between anxiety and depression overall. Anxiety as a trigger to mania was subjectively reported, although less consistently so than for depression. Anxiety was found to have a negative association with PA in repeated daily assessments (Study 3), indicating that there was a possible negative relationship between anxiety and sub-threshold manic experiences. However, there was no significant link between anxiety and increases in manic symptoms observed prospectively in Study 2 or 3, which is in contrast to what is suggested based on subjective reports in Study 1. This aspect of the anxiety-mania relationship may have been missed in this thesis, potentially due to low levels of manic symptoms and PA in Studies 2 and 3 generally. As such, this is another possible area for future research.

The ICM (Mansell et al., 2007) incorporates principles from other models of BD, and there was also evidence to support aspects of other theoretical concepts in this thesis. There was a reported inherent dysregulation of emotion from childhood (Study 1), which is consistent with biological and BAS models of BD which postulates a genetic or trait component to the experience of extreme mood swings in BD. In-line with the cognitive therapy model and other research exploring dysfunctional assumptions and extreme appraisals of changes in internal states, there was evidence for this in the current study as discussed above. This linked most clearly to extreme negative appraisals in relation to mood

experiences, whilst any link between anxiety and extreme positive appraisals was less evident.

8.4 Clinical Implications

The evidence in this thesis for anxiety as an inherent part of BD contrasts with the current ways in which psychological treatment is currently provided by the NHS. In trying to access help for anxiety, individuals with BD are likely to be excluded from many services, for example the Improving Access to Psychological Therapy (IAPT) service, due to their bipolar experiences, or may be offered treatment for anxiety without regards for their BD. However, in accessing services for BD, anxiety is likely to be ignored or overlooked, reinforcing beliefs held by participants in this thesis that anxiety was seen by others as a less serious problem. This created a barrier to help-seeking and support. Overall, participants seemed to be asking for a therapist who can use formulation skills to develop idiosyncratic models which can integrate their anxiety and mood experiences, rather than relying on existing psychological models which tend to focus on one or the other.

Comprehensive guidelines regarding the treatment of anxiety in BD are noticeably absent in both the UK and around the world. Current NICE guidelines for BD state that additional, separate intervention for anxiety should be offered when anxiety is persistent and problematic (NICE, 2006). In terms of psychological help, this is currently offered as individual, structured psychological interventions which are based primarily on the monitoring of early warning signs and relapse prevention (see Chapter 2, Section 2.4.7). As has been highlighted in this thesis and elsewhere (Mansell et al., 2007), for some people psychological interventions may maintain excessive hypervigilance to mood symptoms if delivered poorly, for instance by therapists who are not appropriately trained or supervised, and could exacerbate anxiety due to maintaining fear of an impending mood episode. More recently, attempts have been made to explore combined interventions for anxiety and BD,

where therapy addresses both anxiety and bipolar mood experiences together. This research is currently in its infancy and results from RCTs evaluating effectiveness are not yet available (see Chapter 1, Section 1.7.2). In terms of directions for clinical intervention, the use of alternative cognitive approaches, for example mindfulness, may be helpful in allowing people to tolerate changes in internal state and to not get caught in the ruminative vicious cycle of worry about relapse. Mindfulness is being increasingly used in clinical practice and mindfulness-based cognitive therapy (MBCT) has been added to the NICE guidelines as recommended treatment for UD where individuals are at high risk of relapse (NICE 2009). Mindfulness has also been explored within BD and has been found to prevent the increase of anxiety (Williams et al., 2008), decrease symptoms of depression (Weber, Jermann, Gex-Fabry, Nallet, Bondolfi & Aubry, 2010) and to increase positive emotions and ability to regulate mood (Deckersbach et al., 2012; Gilbert & Gruber, 2014). However, the majority of this research is based on pilot studies of mindfulness-based therapies with small samples, and future research with large-scale RCTs to evaluate effectiveness is required.

Thoughts about health were found to be a trigger to anxiety and NA in this thesis (Study 1 and 3). In particular, time of diagnosis was an anxiety provoking time (Study 1), which highlights an opportunity for early intervention. The provision of information and support at this time may be helpful in enabling individuals to feel less anxious about the implications of having a diagnosis of BD and more confident that they are able to manage their mood and still achieve important goals and ambitions. The way in which a diagnosis of BD is given is likely to be extremely important, as it will determine the framework or model that the individual then uses to frame all subsequent information and experiences. If the model presented is one of a serious, chronic mental health problem which will always be present, which requires lifetime medication to manage, and which requires the avoidance of anything stressful or stimulating, this is likely to result in feelings of hopelessness, and lead to behaviour changes which reduce the opportunity for positive reward. For example, people

may leave or not look for work, avoid relationships, not plan for the future and so on. In essence, the diagnosis itself becomes a self-fulfilling prophecy. Alternatively, if a framework is presented in which mood fluctuations exist on a continuum, with pros and cons at all stages, this can help to open a dialogue about the utility of understanding mood better, including what makes it change, and how to manage these changes where needed, whilst not restricting life to a very narrow bandwidth of mood in an attempt to avoid relapse. Given the current system of service provision within the NHS, it is unlikely most people would be able to receive this help via formal, psychological therapy, as waiting lists are long and services are increasingly restricting access to therapy based on need, severity and risk. However, psychoeducation and support could be offered in the form of brief interventions during consultations with psychiatrists, Community Psychiatric Nurses, GPs and other health professionals. For this to be effective, models held by clinicians would also need to be addressed. Those who adopt a more psychological view of anxiety and bipolar experiences would likely naturally deliver these messages to clients, and may also be more effective in delivering information formally. Individuals could also be directed to voluntary organisations such as Mind, Mood Swings or Bipolar UK. Online information and interventions could also be accessed for psychological support and information, such as MoodSwings (Lauder et al., 2013) or the Recovery Road program (Barnes, Harvey, Mitchell, Smith & Wilhelm, 2007). Peer to peer support from people who have experienced extreme moods but have found ways to live full and meaningful lives with these experiences could also be very helpful in reducing anxiety about the impact of mood on life goals. However, clinicians may need to give some direction and support regarding the most helpful resources to consult, as likely some of these areas of information will highlight positive as well as negative experiences of others, and a mixture of effective and ineffective coping strategies, which may increase anxiety and concern if support to discuss this is not available.

Timing of support was also raised as an important issue in this thesis. Support for traumatic experiences was highlighted as being most helpful at the time at which the trauma occurred (Study 1). Support offered at a later time was felt to be less effective due to individuals having developed learnt coping responses which included the avoidance and suppression of difficult emotions, which made it more difficult to engage with therapy where emotions were the focus of the intervention. Therefore timely intervention appears key in the treatment of BD, although this potentially contrasts with current evidence which contraindicates psychological debriefing immediately following trauma. As discussed previously (see Chapter 5, Section 5.4.2), the way in which this support is offered is likely to be important.

The perceived need to hide anxiety was another key finding within this thesis. This was due to an underlying belief that others would think that they were "silly" and would not understand (Study 1). This impacted negatively on existing relationships and prevented individuals from forming new relationships. This indicates that working systemically with family and friends to help them understand the experience of anxiety and how best they can support their relative would be very beneficial. Again, this does not need to be through formalised family therapy, although there is evidence that this is helpful (Miklowitz et al., 2013; West et al., 2009). This could instead be done through the dissemination of relevant information and literature from health professionals and agencies which provide support to carers.

Research exploring specific and combined psychological interventions for anxiety and mood in BD is in its infancy (see Chapter 1, Section 1.7.2). However, the link between the experience of anxiety and bipolar mood symptoms highlighted in this thesis, and the potential transdiagnostic processes identified across emotional disorders in the current literature, indicates that the use of current evidence-based psychological interventions for ADs may also be beneficial for the treatment of anxiety and mood symptoms in BD. Two

potentially applicable therapeutic techniques used in the treatment of ADs include exposure-based therapy (EBT) and mental imagery. Graduated EBT is recommended in clinical guidelines for SoP (NICE, 2013), and re-living is an integral part of trauma-focussed CBT recommended for PTSD (NICE, 2005). Exposure therapy has been found to be effective in the treatment of a range of ADs including PTSD, OCD, PD, SoP and SP (see Olatunji, Cisler & Deacon, 2010 for a review). EBT works by exposing individuals to a feared stimulus and dropping safety behaviours, and decreases anxiety through habituation, extinction, re-appraisal and increased coping skills (Kaplan & Tolin, 2011). The evidence of extreme appraisals of changes in internal state, and avoidance and hypervigilance as safety behaviours which attempt to self-regulate emotions in BD (see Chapter 2, Sections 2.4 to 2.6 for a review) indicates that there may be some benefit to incorporating exposure techniques in the treatment of BD. Interventions may include exposure to feared triggers to mood change, or tolerance of symptoms of feared mood states when detected, without the use safety behaviours. Graded exposure to anxious experiences together with skills training to re-structure cognitions and manage anxiety has also been recommended specifically for the treatment of anxiety in BD (Otto et al., 2004). A key evidence-based treatment for both ADs and BD is CBT, which incorporates the challenging of catastrophic thoughts and extreme appraisals together with exposure to feared stimuli through behavioural experiments. A review of the literature found that behavioural experiments were more effective than exposure therapy alone for ADs (McMillan & Lee, 2010), and it seems that the use of behavioural exposure *and* cognitive re-structuring techniques may be the most effective treatment in emotional disorders. However, there is currently a lack of empirical research to determine the effectiveness of exposure techniques in BD in comparison to cognitive interventions alone. In addition, research suggests that therapist reservations about exposure therapy may preclude it being offered as an option or being delivered effectively, potentially due to the prolonged and intense exposure recommended in treatment manuals

(Abramowitz, Deacon & Whiteside, 2010; NICE, 2013). Therefore it may be unlikely to be used effectively amongst therapists in routine clinical practice with individuals with BD. In addition, there are ethical implications of exposing individuals to identified triggers to mood episodes as this may trigger relapse if not done in the correct way. Finally, some psychological interventions are highly structured and manualised, requiring safety behaviours to be identified and dropped early in therapy (e.g. Wells, 1997). However, safety behaviours often develop and are maintained because they have a number of protective, as well as maladaptive, qualities. For example, avoidance of stimulation for individuals with BD may prevent the experience of positive emotions and activities, but may also prevent manic relapse, which is potentially perceived as a greater benefit to some individuals. As such, it may be helpful for therapists to adopt a more collaborative approach to support clients to distinguish between helpful and unhelpful safety behaviours, with a focus on individuals making informed choices about interventions and treatment.

The role of mental imagery is also well-documented in ADs (Hirsch & Holmes, 2007) and it has been hypothesised that imagery may amplify emotion in BD by escalating extreme appraisals of changes in internal states (Holmes et al., 2008). Imagery techniques including imagery re-scripting have been well researched and evidenced in the treatment of ADs, in particular SoP (Hirsch, Clark & Mathews, 2006), Sp (King, Heyne, Gullone & Molloy, 2001), GAD (Lang, 2004) and PTSD (Ehlers & Clark, 2000). However, there is a lack of research which recognises and explores the role of imagery in the experience and treatment of BD. Despite research which has found high levels of mental imagery during recall of specific and general memories in BD (Mansell & Lam, 2004) imagery is often a neglected aspect of psychological therapy and research (Holmes et al., 2008). Clinicians should assess and incorporate the experience of mental images into psychological assessments, formulations and interventions for individuals with BD. However, imagery alone may be insufficient to create change

(Strauss, Calhoun & Marx, 2009) and interventions for emotional disorders which combine real-life exposure, cognitive re-structuring and imagery are indicated.

The majority of participants who contributed to this thesis were well educated, however employment levels were low across studies. Many participants reported wanting to engage in employment (Study 1), however there were several barriers to doing this. Very strict work routines with no flexibility had proved problematic for participants in the past. In addition, fear of becoming unwell at work and the loss of confidentiality and sense of embarrassment this would bring also maintained low confidence levels in being be to get and hold down a job. Again, working within the wider system and with employers directly to develop their understanding of both BD, and the role of anxiety in BD, would be beneficial so that they can support some of these highly educated people to enter and remain in the work place. However, education provided to employers would need to be based on a continuum approach to mood swings and anxiety, in which experiences are normalised, as opposed to a biological understanding which pathologises experiences.

Finally, Study 3 found that physical activity was linked to increases in PA, and increased PA was linked to decreases in anxiety and NA. Exercise has been found to have positive effects for individuals with UD, and has been associated with higher remission rates and increased quality of life even after controlling for confounding variables such as age, gender, medical conditions and negative life events (Harris, Cronkite & Moos, 2006; Blumenthal et al., 2007; Trivedi et al., 2011). However, as previously discussed in Chapter 7 (Section 7.4.3), there are a limited number of studies exploring the positive effects of physical activity on bipolar specific mood symptoms and other important domains, such as quality of life (Blumenthal & Ong, 2009; Carney & Jones, 2006; Lin et al., 2007; Sylvia et al., 2013). Evidence in this thesis that physical activity was effective at increasing positive affect is promising and further research in this area is required.

8.5 Strengths and limitations

The current thesis reports relevant findings and potentially important clinical implications regarding understanding and helping people with experiences of anxiety in BD. However, there a methodological limitations and strengths, which are discussed below and which should be considered when interpreting the results and designing future research.

8.5.1 The conceptualisation of mood and anxiety as independent constructs

The conceptualisation of anxiety as a separable construct from mood experiences, in particular NA and depression, has been an important issue throughout this thesis. The existing literature has, for the most part, conceptualised anxiety as a psychiatric comorbidity, despite the convergence of research to suggest that anxiety is very closely linked to, and potentially an inherent part of, bipolar mood experiences. Although the author is mindful of anxiety not being an entirely separate entity to mood experiences, this thesis has at times explored anxiety and mood as independent constructs, specifically in the quantitative elements of this thesis. This was done for several reasons. Previous research has found there is some merit to measuring anxiety, depression and mania independently, and that this can be done reliably (e.g. Sears & Kraus, 2009). Existing research has found that, whilst anxiety and depression in particular are closely linked, suggesting shared psychological mechanisms, there may be qualitative differences in how those emotions affect psychological processes (e.g. Raghunathan & Pham, 1999). The qualitative analyses within this thesis also highlighted that experiences of anxiety and mood are conceptualised and appraised in different ways by individuals, who discuss these experiences as separate, but closely intertwined. Finally, to understand how anxiety and mood may interact, it was necessary to evaluate these experiences separately to explore temporal relationships (Study 3) and the link to clinical outcomes (Study 2). Both quantitative studies were mindful of the possibility that measures of anxiety, NA and depression, may have essentially have been assessing facets of a global

experience of negative emotion and related psychological processes. However, the analyses controlled for this accordingly, adjusting for current or baseline mood as appropriate to allow the assessment of anxiety as a predictor of outcomes over and above other mood domains.

8.5.2 Exploratory nature of research

Current psychological models of BD reviewed in this thesis do not include anxiety in their explanation of mood swings, and no single model of BD was felt to be dominant in its ability to account for anxiety as an integrated experience at the start of this thesis. As such, this thesis did not set out to test a causative model and all results are exploratory at this stage. However, the results of the present thesis have been considered in the context of an adapted psychological model of BD based on the ICM (Mansell et al., 2007), which was felt best able to account for the experience of anxiety in BD. This has contributed to the current research in beginning to conceptualise how these experiences interact and how anxiety may be a trigger to and a consequence of bipolar mood experiences. This thesis has also generated hypotheses and directions for future research, which may be particularly important given evidence that research in this area has begun to decline in recent years (Provencher et al., 2011).

8.5.3 A mixed methods approach

The strengths and limitations of adopting a mixed methods approach were discussed fully in the methodology chapter within this thesis (Chapter 3). The current chapter has attempted to discuss findings from all sections of this thesis using a complementary approach, where results from the range of qualitative and quantitative methodologies used have been considered together to enhance understanding of the experience of anxiety in relation to BD (Sale et al., 2002). However, this has been done whilst being mindful that qualitative and

quantitative designs are based on very different paradigms which have different assumptions about reality, and therefore the phenomenon of anxiety in BD studied is not identical across studies. However, this is also a strength in this thesis. The meta-synthesis and Study 1 have allowed insight into aspects of anxiety experiences which cannot be accessed through quantitative research alone. Specifically, a deeper understanding of the lived experiences, social context and factors which influence anxiety and bipolar mood experiences, such as sleep, work, relationships, cognitions and behaviour. Individual beliefs and perceptions of anxiety and mood fluctuations were also elicited. The inductive nature of the qualitative approach in Study 1 allowed these issues to be explored using open ended questioning, allowing the key themes to emerge from the data, rather than testing a priori hypotheses. In addition to this, the quantitative elements of this thesis have provided information on the utility of a range of anxiety variables to predict clinically relevant outcomes in BD (Study 2), and have explored subtle interactions and contextual factors which are associated with changes in anxiety and affect (Study 3), which may not be accessed through the qualitative analysis of subjective experiences if they are outside the realm of conscious experience or memory. Results from different methodologies within this thesis have been given equal priority and have provided insight into the lived experiences of anxiety and the measurement of anxiety in relation to mood and other important experiences in BD. This has allowed the exploration of consistencies within subjective and objective reports, whilst also highlighting discrepancies within results and gaps which require further research.

8.5.4 Multiple testing

Study 2 and 3 both utilised multiple testing within a single dataset. Study 2 accounted for this by adjusting the Alpha level to 0.01, partially minimising the risk of Type I errors, although more conservative approaches could have been adopted, such as Bonferroni

corrections. However, this would have increased the risk of not detecting potential areas of interest, which was felt to be a greater risk in the context of the current thesis. Study 3 set the threshold for significance at 0.05, as the risk of Type 2 errors was considered greater in an exploratory study of that nature with a smaller sample size compared to Study 2. As such, multiple testing will have increased the chance of finding significant effects due to chance, and all significant findings in both quantitative studies require replication. In particular, findings from the ESM study relating to the interaction between anxiety, NA and PA require replication in longitudinal research which controls for multiple comparisons.

8.5.5 Power

Power calculations were not completed for Study 2 or Study 3, although Study 2 was an analysis of data from a sub-sample of participants taking part in a large scale RCT where a power calculation had been performed, and so is less likely to have been problematic. This has been discussed in detail in the relevant chapter. However, as a general limitation of this thesis, the lack of analysis to establish power in the quantitative studies, primarily Study 3, may limit the extent to which the results can be interpreted. The potential for both quantitative studies to be underpowered means there is a risk that important interactions between anxiety and affect may not have been detected. In contrast, Study 3 may have been at risk of finding false positives, as small samples can result in the observation of large, but misleading, effect sizes due to larger variability in smaller samples. However, relatively small effect sizes in Study 2 and Study 3 were found to be highly significant ($p<0.01$ or <0.001), which is the opposite of what might be expected if studies were underpowered. The quantitative aspects of this thesis were designed as an exploratory analysis of the impact and interaction of measures of anxiety with bipolar mood experiences. Specific information regarding causality of fluctuations in anxiety and mood experiences cannot be inferred. As such, tentative interpretations and hypotheses regarding anxiety in BD have been made

which require replication and further testing with more rigorous designs which are adequately powered.

8.6 Future directions

The quantitative elements of this thesis have made efforts to control for extraneous variables where possible. This was to allow the specific contribution of anxiety to outcomes in BD, over and above other mood domains, to be assessed. This has included controlling for sociodemographic factors and current and baseline mood when comparing individuals with BD to non-clinical controls (Study 3), which are meaningful differences between groups. Controlling for variables in this way runs the risk of essentially controlling for having BD, which is the current area of interest. For example, differences between control and participants with BD in Study 3 may have been due to lower levels of employment in the BD group. A suggestion was made in the discussion of this study for future research to match participants on variables such as employment to control for the impact that being out of work may have on mood. However, doing this would also by definition control for a key aspect associated with BD, as people often find it difficult to remain in work when experiencing bipolar mood episodes (see Chapter 1, Section 1.2.4 and Study 1). Studies comparing individuals with BD to non-clinical controls fundamentally show correlates of illness once that illness has developed (Gottesman & Gould, 2003). An alternative solution is the exploration of anxiety and mood experiences through parallel high risk designs. This could explore the state-independent characteristics of anxiety and mood in those at risk of BD, but who are not currently symptomatic. Measures such as the HPS or other markers of vulnerability to BD could be used to define a high risk sample. This would also allow for the exploration of causal pathways between anxiety and BD, which could not be established in the present thesis. Another potential option is the inclusion of a non-BD chronic illness control group, which would manage the non-specific effects of having an enduring health

condition. Previous research has included individuals with a diagnosis of fibromyalgia as this has been associated with symptoms similar to BD including sleep disturbance and low mood (Hudson et al., 2004; Wolfe et al., 2010).

This thesis found evidence for a consistent link between anxiety and depression across a range of empirical studies and methodological approaches. Study 1 reported subjective experiences of anxiety and manic symptoms which were not observed in the quantitative aspects of this thesis. This may have been due to the lack of variability and generally low level of manic symptoms and PA in Study 2 and 3 overall. It may also have been due to anxiety functioning primarily as a trigger to, and consequence of, manic episodes, which were not observed in this thesis due to Study 2 focusing on symptom rather than relapse data, and Study 3 which included only individuals with BD who were out of a full mood episode. Future research which explores the interaction of anxiety and positive mood experiences would be beneficial to understand this link further. In particular the link between anxiety symptoms and recurrence of (hypo)manic episodes is important to address this gap in the knowledge, as this was subjectively reported as an important part of the experience of anxiety in BD in Study 1.

The quantitative aspects of this thesis explored anxiety using a general anxiety symptom questionnaire (HADS-A; Study 2), categorical diagnostic criteria for ADs (Study 2) and two general symptoms of anxiety (anxious and worried; Study 3). Future research which explores self-reported symptoms of ADs more extensively may be beneficial to capture interactions between anxiety and mood in BD. For example, the use of continuous measures for specific ADs, such as the Generalised Anxiety Disorder assessment (GAD-7; Spitzer et al., 2007) or the Social Anxiety Scale (SAS; Liebowitz, 1987), would extend the findings of Study 2, where GAD, OCD and SoP were found to predict manic and depressed symptoms over time. In addition, cognitive style and extreme appraisals of internal states have been indicated as a risk factor to the experience of BD (see Chapter 2, Sections 2.4 to 2.6), as

assessed using measures such as the IDQ (Jones & Day, 2008), HIQ (Jones, Mansell & Waller, 2006), HAPPI (Mansell & Jones, 2006) and HPS (Eckblad & Chapman, 1986). However, there is little research which explores the role of these same factors with regards to the vulnerability to and experience of ADs, and future research in this area is required. Finally, the role of trauma and other aversive experiences in disorders such as PTSD and BD is well established (Laugharne, Lillee & Janca, 2010; Maguire et al., 2008). However, the importance of traumatic events in other ADs is less clear and is often neglected in research and treatment (Laugharne et al., 2010). Future studies which explore the association between trauma and ADs is required in order to inform psychological interventions for individuals with those experiences.

Finally, this thesis aimed to explore the experience of anxiety in BD. In particular the focus was placed on the negative implications of these experiences and interactions to understand why anxiety may lead to poorer outcomes in BD. It was beyond the scope of this thesis to explore fully the factors which may build resilience to anxiety and future research should focus on protective factors to anxious experiences.

8.7 Conclusion

This thesis explored the lived experience of anxiety in BD, and the interaction of anxiety and mood over time, with the aim of understanding how anxiety may link to worse outcomes in BD. The data shows that anxiety was an inherent part of BD for many people, often manifesting in an inherent dysregulation of emotion. Anxiety was a trigger to both depressed and manic episodes, and the quantitative aspects of this research found a consistent association between anxiety and depression in particular. Contextual factors contributed to fluctuations in mood and anxiety. Socialising and physical activity were linked to positive mood experiences, whilst ruminating about health was linked to negative emotions. The link between anxiety and mania could not be explored in detail and requires further attention.

Overall, this thesis found evidence for anxiety as an intrinsic part of BD which interacts with bipolar mood experiences in a clinically significant way to escalate symptoms. Anxiety was identified as a key barrier to achieving important life goals and was something participants wanted more help with. This highlights the importance of continuing to develop and evaluate combined interventions for anxiety and BD, whilst thinking of creative ways to ensure this help is accessible to people both in and out of therapy and services.

"But yes anxiety is, is a controlling thing. If you could take the anxiety away you would cure the problem I think..." (Study 1, Participant 14).

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Table 1a. *Topic guide used for qualitative interviews in Study 1*

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1. **Introduction:**

Things to discuss before the interview begins:

- "The aim of this interview is to understand your experience of anxiety in bipolar disorder and what anxiety means to *you*."

- "I believe that *your* experiences could be very valuable in helping me to understand *how* people experience anxiety and how you feel this affects your life".

- "Things I may ask you about might include; your experience of anxiety, difficult times you may have had connected to bipolar disorder and anxiety, how you feel anxiety impacts on important areas of your life, what you feel has helped you with these difficulties, and what you feel would be helpful in managing your anxiety. However, we don't have to talk about anything you don't feel comfortable talking about so please let me know if there is anything you don't want to answer. If there are any questions you are unsure about or you would like repeating, please just let me know."

- "Also, we can stop the interview at any time if you want to and you can take breaks at any time that you would like. If you decide whilst completing the interview that you no longer want to take part we can stop and the tape will be destroyed."

- "I am going to record what we talk about today so that I don't have to rely on my memory to remember everything you say but just to let you know, anything you tell me today is strictly confidential. The only circumstance in which I would have to break confidentiality is if you told me that you or another person was at risk of being harmed in some way."

- "Hopefully the things we talk about today will benefit people in the future who have experiences similar to your own. You will not receive an intervention as a result of taking part in this project today. The information I get from you and other people who take part in the study will help to inform the next stage of this research project, which will be a series of treatment planning sessions to develop an intervention for people who experience bipolar disorder and anxiety. You will have the opportunity to take part in this stage of the project if you would like to, and I can tell you more about this later if you would like to be involved. However, you are under no obligation to do so."

2. Completion of forms and questionnaires

All forms and questionnaires should be completed by the participant, unless they have problems with reading which require the forms to be read, in which case they can be.

a. *Consent Forms*

Before we begin, would it be OK to get a bit of information from you?

1. Complete the stage 1 consent form

2. Complete the participant panel form, if participant would like to be contacted about future research.

b. *Questionnaire Measures*

Now we will complete three questionnaires if that's OK? The first is asking general information about you. The second two will be asking questions about your mood and experiences that you might have had.

1. Complete the demographics form together

2. Complete the HADS questionnaire together

3. Complete the MDQ together

Participants can score any score on the HADS-A to be included but must meet criteria on the MDQ to be eligible for the project.

3. Qualitative Interview

Start by repeating interviewer name, participant ID number and date of interview.

OK, now we're going to talk a bit more about anxiety or similar experiences that you might have had.

1   Many people describe having felt anxious / worried / stressed / (own word) at some point in their life. Is this something that you have experienced?

          If Yes: Can you give me an example of the last time you felt like that?
                       Probe for context, triggers, thoughts, emotion, physical experience etc.

          If No: Do you ever find certain situations are more difficult to manage than others? Can you give me an example?

          Or

Do you know anyone that experiences anxiety / worry / stress / (own word)? What do you think this is like for them? Have you ever had times when you felt like this?

How does anxiety / worry / stress / (own word) affect you in your
2   life?
- Work / day to day routine
- Relationships
- Physical and emotional health

3   How, if at all, do you think your anxiety / (own word) impacts on your BD? Do you think the two are related in anyway?
     If Yes:
- How / why are they related?
- Example of this

Did you experience any anxieties surrounding your diagnosis of Bi-Polar
4   disorder?
     If Yes:
- About having 'mental illness?'
- Anxiety about future disclosure/stigma?
- What positives / negatives do you take from it?

5   What things have you found make your anxiety / (own word) worse?
- How / Why / Example

6   What things do you find helpful in managing your anxiety / (own word)? (*Probe for medical and psychosocial treatments, self-management.*)

- Is there anything you do that helps? How / why?
- Is there any treatment you have tried that has helped with this? How / why?
- Any experience of CBT? Or heard about it even? Something you have thought about at all?
- Do you find medication helpful? How / why?
- Ask for examples of each if appropriate
- FOR ALL TREATMENTS / THERAPIES / STRATEGIES:
   i.   How much do you feel those therapies / treatments / strategies addressed your anxiety? How / in what way? OR why not?
   ii.   How helpful were they in reducing / managing your anxiety? Why? In what way? OR Why not?
   iii.   How could this have been more helpful?

7   What do you think would help you to manage your anxiety / (own word)?
- Why would this be helpful?
- In what way would it help with your anxiety in particular?

8   Are there any things that make it difficult to get the help you / people need to manage anxiety / (own word)?
- *Probe for what barriers and why*
- *Solutions to overcome this*
- What would help to make therapies / treatment for your anxiety more accessible?
- What format should help / treatment / therapy be offered in? (e.g. phone, face to face, evening etc.).

9   Is there anything else you would like to talk about which you think would help me to understand about your experience of anxiety and BD?

	4. Debrief
a.	How have you found the interview today over all?
b.	Thank you for completing this interview. Increasingly, we are trying to involve service users in health research. In doing an interview such as this, what difference do you think it makes having a service user or a non-service user asking the questions?

	5. Ending
a.	Has there been anything particularly difficult or distressing that you feel you need additional support for?
b.	Thank you very much for taking part and for sharing your experiences with me today. We will let you know the outcome of the analysis if you would like to be informed. The second stage of this project will use what we have found out from doing these interviews to develop an intervention for anxiety in bipolar. This will be done by running focus groups with service users and professionals. Would you like us to let you know when this will be happening?

Appendix 2: Additional quotes which informed the qualitative analysis (Study 1)

Table 2a shows additional quotes from participants taking part in the qualitative study

(Chapter 5). This is not an exhaustive list of all qualitative data collected or all participants

who contributed to each theme, but rather aims to show a sample of the data and a range of

participants and experiences which informed each individual theme.

Table 2a. *Quotes which informed the qualitative analysis reported in Chapter 5*

Theme	Participant ID	Quotation
1. Which came first? The temporal relationship between anxiety and bipolar mood episodes	Participant 15	" I mean perhaps even before I was getting really low I used to arrive at school every day when I got dropped off and butterflies in my stomach then, so maybe I have always had this anxiety element in my life"
	Participant 8	"I don't know, bipolar disorder is a mood disorder it's not classed as a disorder of perception but it is and as well with the anxiety, it's definitely, everything as I look back has been triggered by stress or my interpretation of what was stressful."
	Participant 5	"Yes. The first time, erm, I experienced anxiety was when I was attacked as a student coming home erm from the Union in Manchester err way back when I was twenty......The result of that obviously was that erm I was quite distressed but it wasn't dealt with in an adequate manner. I was just offered aspirin to help me sleep."

1. Which came first? The temporal relationship between anxiety and bipolar mood episodes	Participant 3	"Errm the bipolar was the trigger to my anxiety."; "...because in a sense this (anxiety) is where all my problems started.......That's where it all started. So, to me, that's an extremely important ..thing..that everything else has sort of sprung from that" ; "I think generally bipolar can give you a lot of uncertainty and anxiety because errm, because when you've got a change in mood you are like a different person and you've got to err..like re-gather..." ; "...when I got it at 14 I wasn't diagnosed for the first 10 years so it was really scary. You just didn't know what was going on and nobody understood you"
	Participant 13	Well I think and there is a relationship I think. Perhaps more as a precursor in that I think you know having a good deal of anxiousness and being a bit shy in childhood and teenage years, it was kind of a warning for getting ill later on and often it's being anxious about something which adds a bit of stress, and like university generated a lot of anxiety, both with you know the stress of kept awake but also not doing very well and not doing as well as I might have expected to............. yes I would say anxiety is a precursor and now I tend to think of it as being sort of a warning sign"
	Participant 10	"The anxiety started with the breakdown. The anxiety started with the realisation once I suppose when you think about it, when you get realisation when somebody is telling you and telling you and everybody is telling you and telling you, the anxiety started coming in then because I was panicking and I knew there was something wrong."
	Participant 12	"Yes actually I have never thought of it that way, I have never thought of it like that but yes I have always been worried."

1. Which came first? The temporal relationship between anxiety and bipolar mood episodes	Participant 19	"Not really sure, I don't know how long I have had bipolar. I know I have always been up and down, even in third year secondary school I had a lot of problems, even though people said I was just an awkward teenager but even then I used to get panic attacks, going back I can even remember as a child going to sing with a choir and having a massive anxiety attack turning to panic attack, hyperventilating and passing out. I can't really say, whether that is just part of me or part of the bipolar"
	Participant 16	"I think that's probably true for quite a lot of people who do get a lot of anxiety, is that it becomes a way of life so that you, you aren't aware of what it's like not to have something to worry about almost becomes, don't know you would call it a dependency but it's a bit like that, because it's been the norm for you,..."
	Participant 14	"I mean the anxiety, the illness whatever you would call it, has directly affected me probably ever since I was in my 20s."
	Participant 9	"I think probably the bipolar...impacts on the anxiety. In that everything you feel even when you're relatively stable. I, I think is like magnified by, by bipolar"
	Participant 4	"Well before I had these episodes of the bipolar I never had any problem with anxiety..... it was only... once I'd started once we've looked back and seen that was was a er a manic episode and that was a really depressed episode and you were manic a but there and...that I've started with the anxiety and....so yeah, I think it is linked to it.....But I never was (anxious) until, until the bipolar"
2. The specific interaction of anxiety with depression and mania	Participant 15	"You have just got to rationalise things, even if someone was to make an insult about you, because I think the thing that has happened with me is people have said things and I have got overly concerned by the minor details and that is what has led me down sort of the slippery path into this depression."

2. The specific interaction of anxiety with depression and mania	Participant 11	"Actually its...you know its pervasive and all the time..." ; "If I get anxious it will trigger me into a depression or into mania and it doesn't matter what I am being anxious about, if you know, work completely screws me up, it's not the clients, it's the environment, it's the noise, and if I am anyway tense or anxious it will push me one way or the other"; "Yes and I know that something is wrong but then you know, sort of so it is a trigger. If I don't get enough sleep or I go to somebody's party or I have a late night, or have to fly overnight or something like that, I am screwed and that you know brings a whole lot of panic and you know anxiety as well"
	Participant 8	"The same kind of things cannot make me anxious it just depends when I am sort of having an anxious I don't know, I would say that in the same way as bipolar my anxiety is kind of episodic and kind of goes hand in hand with the bipolar...."; "I wouldn't say I am depressed at the moment, in a sort of tearful, sad, depressed way it's more of a kind of nothingness, loss of interest, motivation, concentration, things like that, and more recently anxiety has crept back in as well, so..."
	Participant 4	"The anxiety can have an effect on my appetite. But it's not always the same affect...... but it is a definite change in appetite because it either a lot more or a lot less. And it's not just a little bit more or a little bit less it's a lot......"

2. The specific interaction of anxiety with depression and mania	Participant 14	"…if you suddenly get anxious about something that anxiety within you promotes you to activity, most definitely." ; "…that's exactly what starts you off because then you are low but you are panicking, why are you panicking, oh panicking because of this." ; "The anxiety is the trigger, without a doubt. If you look at everything you can be depressed, you can be really, really low, but without the anxiety trigger, to fire you into a manic mood you won't go anywhere, you will just sit there…" ; "…why I would do something as dramatic as abandon my son, jump in my car and drive to France, what possibly could, what why would that be a good idea but that is driven seriously by anxiety…"
	Participant 6	"Yeah well they definitely are I mean my anxiety can trigger a mania it can trigger depression erm" ; "Oh yeah the anxiety can cause….depression and erm…in, in, in that dyna, dynamic it could be……me avoidance behaviours kicking in. Erm, so that I cancel places that I was looking forward to going because I got anxious…and then I don't go and I regret the fact that I didn't go and then you can go on a downer" ; "I think anxiety is like erm….is probably like a virus or, o, o, or a common cold on erm….on the sleep pattern. So in one sense I'm supposed to be self-managing me bipolar by…erm… maintaining a regular sleep cycle and the anxiety's….working against that it, it's erm……it's hard to, to maintain the sleep cycle with the anxiety. And I'm talking pre-you know m-mania… its, it's almost as like the anxiety co, affects the sleep cycle which then triggers a mania or an episode"
	Participant 19	"If I am high, there is, I don't get anxiety if I am high. But if I am getting depressed and I am getting really low then yes I get very tired and very anxious about everything"
	Participant 3	"I'm the sort of person that, funnily enough, when I'm on the manias I don't feel anxiety…"; "..if you're mood's down you can be anxious about everything."

2. The specific interaction of anxiety with depression and mania	Participant 10	"Hard to define anything, it's hard to put your finger on every emotion that you go through because when you are having a breakdown you go through 156 different emotions in one minute. So it's hard to put your finger on what is connected and what is normal..." ; "My side of the bipolar years ago would have been more the high side, more the couldn't care less side, and where other people think oh for weeks it would go through their mind what did I do last night, I would forget about it the next day, because I didn't think I was doing anything wrong, I was just being, because of the drink you know, as I would put it down to, so anxiety probably didn't play a major part in the bipolar then..."
	Participant 7	"I tend to...cycle through depression and anxiety, they tend to go in cycles erm..."; "it's as though you go through the depressive side, when the depression's quite strong the anxiety isn't as bad, but then as the depression starts to lighten the anxiety starts kicking in and so you'll get an overlap between the two. And then you get the sort of full blown anxiety. When that starts to diminish the depressive side starts kicking in again. That's why I've assumed that they are linked. There's a correlation between the two"
	Participant 16	"So, then I think you tend to get into you know you think about things and you make them more awful, I think the term is called awfulising isn't it, you make them worse than they are, and then that can lead to, for me hyper mania. I seem to have more problems with hyper mania than with the depressed side"
	Participant 2	"...(coughs) erm...when I'm not anxious, I'm able to erm be.. more of a normal person and if anything can sometimes take on more than what I probably should do and, and that's when I start to get a little bit high."

2. The specific interaction of anxiety with depression and mania	Participant 5	"And you know, what anxiety does sometimes it gets me angry (laughs). It does get me angry and then I have a little shouting match and so, shouting down the phone" ; "I think that if there's anxieties, little anxieties in my life that can't be dealt with and they become greater, then definitely that brings my mood right down." ; "Well basically I think anxiety has in the past has built up to such an extent that I have become depressed. I would say the anxiety is the beginning of depressions for me."
	Participant 5	"That [anxiety] caused me to miss five weeks of my final year at University....and, I was studying pharmacy at the time and wasn't really very good at organic chemistry, so I spotted questions which didn't come up. So I failed that particular subject. So I had to repeat the whole of my final year, So it did cause quite a major problem."
3. The consequences of anxiety in BD	Participant 3	"....my feeling was that it was going to ruin the rest of my life. In a way it has, because I couldn't get on in school, get on with school. So I didn't get the qualifications I needed. Errm.... and then it's been very difficult working....I mean it's completely destroyed my life"; "I'd go to work to distract myself and... which can you imagine the effect you know it didn't do my career prospects a lot of good because you were just thinking about the anxiety rather than the work, you're just using the work to distract yourself."

3. The consequences of anxiety in BD	Participant 13	"...it just kind of jams you up from doing other things, yes and difficult to get back into hobbies and interests and things like that, and projects I might have got involved in, maybe just languish..." ; "And, you know I mean, then I suppose when it comes to actual opposite sex relationships fear of rejection, generates a bit of anxiety, so while I am sort of maintained this sort of few sort of friendships, I have tended, most of the people I am kind of friends with that I have any sort of degree of friendly relationship with tend to be older people, I have tended to avoid, avoided my immediate peer group, partly I think from the school experiences of being bullied a lot I have kind of given up on them"
	Participant 2	"it's caused a lot of rows..because..no matter how much I suppose a person is.. understanding of your problem, unless you've act- actually suffered it (anxiety) yourself, you don't actually know what, what it's like..." ; "And..as I explained when she came in about the medication, she's my carer..and..we'd sort of sat and talked about the fact that I was, feeling well enough to..cope without, without her for like three or four days, but after a fortnight..I was in bits. I was in complete bits"
	Participant 8	"Yes, it stops me being able to do things that you know, that I want to do. In the past it has stopped me working, at the moment its stopping me studying, even though I am at home at the moment I have not done any work because I can't, I can't read a page, I can't even read a newspaper article, I can't concentrate on it you know." ; "I guess its stopped me in terms of sort of like, what shall I call it, settling down, you know, I always end up back here with my mum which I don't dislike, but at 28 you know, but when things go bad and I don't cope well, I end up needing people to be there, so I am quite dependent in a lot of ways."

3. The consequences of anxiety in BD	Participant 6	"You know even in peanut factories or erm breweries where I've worked.... it's er....it's been a different kind of stress that I've experienced there but. Anxiety is...you know s-stopped me from.....performing e-even in, in jobs where...they'd be considered stress free I suppose"
	Participant 7	"There was something else there but I've forgotten. Oh yeah (chuckles)...memory! Er....erm.....as the anxiety develops the ability to speak coherently diminishes because you lose words, you forget words, erm (cough). Erm, there was one time when I was working and I had to introduce somebody into the general office. And these were people I had worked with for years (loud cough). So I walked into the office and said "this is"....and I couldn't remember a single name of anyone in that office" ; "...there is a constant underlying sense of anxiety floating around. Erm...it makes con-concentration very difficult"
	Participant 12	"It's like me brain is working overtime all the time and sometimes even, even if I try and watch telly it doesn't shut down. Errm It's like I couldn't,...... I couldn't read a book because by the time I've done two pages I'll have forgot. My concentration's crap. It doesn't store any information whatsoever. It just feels like the whole of my head is full up, absolutely full up... errm" ; "Yes, I, this is a big, big area for me. I do get really anxious over relationships. I keep everyone at a distance, I think when I was younger and had a lot of friends from school and you know kind of my well years, going out and things, I used to go out a lot, but I think I was quite high a lot of the time and I think a lot of people kind of they almost feed off it, they kind of like a lot of people like you when you are high, you know because you are the life and soul and but they find you very confusing when you kind of turn up like a few days later or, the next time they see you and you are just"

3. The consequences of anxiety in BD	Participant 9	"I think the person who suffers...well no the two people who suffer most from my anxiety are the two people who I spend most time with. Which is me Mother and me partner"
	Participant 4	"I think it stops you from being yourself, because you're having to...because I've always been known as quite a strong independent woman and....doing lots of things in the community I've always been...like a front face for things. So when you've suffering with anxiety and you can't do that....if, you feel like you're letting people down. So it's, it's quite hard to...erm....to let the anxiety win in a way"
	Participant 11	"I don't make friends because of anxiety" ; "Every little thing is too much, you know for me to deal with, telephone call or you know having to decide what to have for dinner, you know I wouldn't be able to do that. That is just too much for me, not being, not able to concentrate, I am not able to focus"
	Participant 14	"...and then the each thing that you have done obviously has a detrimental effect on how you are feeling so then you spiral down further, and then you don't actually worry about it, it's all ok, until you start worrying about it, hence the anxiety kind of thing, you were saying, and then you worry that you have done the wrong things but they are irreversible decisions because they are very final, you are slamming doors, all the way along, you just want to get out, that's what happened to me particularly. It was a very, very deliberate destruction of my own life..."
4. The perceptions of anxiety in BD	Participant 13	"So, you know having to think through different strategies of outcomes that are unlikely to have been necessary anyway but most anxiety comes from worrying about things that aren't going to happen. So you needn't really be worried about them and you tend to be anxious about being anxious, and rather than just being anxious sort of thing"

4. The perceptions of anxiety in BD	Participant 20	"Yes for sure yes. I do like keeping in my comfort zone but I also like stretching it a bit as well.....So I do try and push the boundaries by going to volunteering work and things like that. Some days I don't want to go and I really have to push myself to go"
	Participant 11	"I am not anxious now. Erm, it but you would sort of like see me in strange situations being anxious. You know having to hold my own, having to I think what makes me anxious a lot is I have gone through a lot of my life being terribly, terribly broken and something being horribly wrong and I could not let anybody know, and so I have, I am a huge pretender you know and people when they first met me, and I used to go, especially when in the other counties, mental health team I always used to get misunderstood, because I present together, I am not" ; "Because I am an anxious I don't realise my depression, other people don't realise my depression, other people don't realise the seriousness of a highly strung, yes I am jolly, actually no I am disguising"
	Participant 21	".....I believe in a gradual sort of attack on your comfort zones, and just breaking down the barriers bit by bit, by thinking what is it that scares me, right how can I approach that, not in a really challenging way but in a tiny challenging way and next week I will do it in a bit more of a challenging way"; "I think anxiety is the only thing that I have got left to tackle now, I think I have got to the stage where I can accept my problems with my illness and you know..."

4. The perceptions of anxiety in BD	Participant 8	"...then it gets put down to oh well, it's just anxiety, well it's not just anxiety, because anxiety can be one of the worst things in the world..." ; "But, on the other hand, you can only ever have your own perception of stress can't you anyway, but I can get stressed over tiny, tiny things, that nobody else would get stressed over, just like that, just because I think its stressful at that moment, and that's kind of the way it works." ; "...it's just the stress at certain times, or perceived stress and I think that is what my problem is with anything, and particularly with anxiety, what kicks it off or what triggers it is what I perceive to be stress or what I perceive to be able to not be able to deal with, or be struggling with, and then anxiety kicks in. I don't know why."
	Participant 9	"Your friends and relatives not understanding and saying, what the hell have you to worry about?..... People not understanding like, but your always smiling how can you be anxious" ; "And some people say, said, s-say to me I can never imagine anyone getting the better of you or...I can't imagine you ever getting depressed or angry and I think....well I must be putting on a good....a good s-, front despite what's going on inside"; "People not understanding like, but your always smiling how can you be anxious? Well some of the greatest comedians were big depressives weren't they"
	Participant 17	"It's a very difficult one this one because it's quite a contradiction, most people meeting me will see me as confident and outgoing and I think well if they really knew what was going on inside they would think what the heck is that about you know"
	Participant 1	"Mediating on something you can't do anything about, to me, is worry, that's the, why, you know, it's classed as a, a sin. Erm...anxious I think is more concern for me, you know we've gotta be more concerned that the average person but anxious, anxiety, yes..."

4. The perceptions of anxiety in BD	Participant 14	"...anxiety its, its disproportionate to what you are doing the amount of worry you put into it."
	Participant 7	"this is ridiculous....there is thousands upon thousands of bus journey's done every single day just in Manchester. And they're not a hundred percent accident free. But the safety record is exceptionally good. So you know that, everything you're feeling is..... it does have a rational element, the bus could crash but it's irrational in assuming that every single journey you make on that bus it will crash. So all the time you've got your mind at war with itself. One side saying you're irrational and the other saying it's rational"
	Participant 18	"I am so intolerant with myself, for being stupid, for being neglectful for being you know if I do the slight, I give myself such a hard time, and get so infuriated with myself, over things..."
	Participant 4	"But then realistically I have to think well I've been stable for so long now that...the chances are I am going to be stable a week on Tuesday. So why am I worrying? But...it's still there"
	Participant 16	"Erm, well I think a lot of the experiences that I have had, have started off with rational fears about things like losing a job, or losing a member of the family or being short of money or that kind of thing, because you are worrying about that kind of perfectly rational thing to worry about it sometimes escalates into other things which might be a bit less rational."

Appendix 3: Defining groups for analysis in Study 2

Previous research assessing the impact of anxiety on outcome has been inconsistent in regards to the analysis of data for participants who meet criteria for lifetime, but not current, ADs at study entry. Whilst some longitudinal studies have chosen to make comparisons between those with current anxiety only (Otto et al., 2006), others have analysed data for those with current and lifetime anxiety together (Gaudiano & Miller, 2005), as there is evidence to suggest that those with lifetime anxiety are more likely to endorse elevated anxiety symptoms and worse outcomes over time (Forty et al., 2009; Frank et al., 2002). To determine classification of groups for analysis in Study 2 (analysis of data from the PARADES Psychoeducation study), participants meeting criteria for lifetime ADs at study entry, but not current ADs (ANX-lifetime) were compared to those meeting criteria for any current AD (ANX+) and participants with no anxiety history (ANX-) on HADS-A scores at baseline using a one-way ANOVA and Tukey post hoc tests to assess differences between individual groups. The presence of any primary SCID anxiety symptoms at baseline were also compared between groups using a Chi Square analysis.

A one-way ANOVA showed that there was a significant difference in HADS-A scores between ANX+, ANX- and ANX-lifetime participant groups at baseline (F = 8.55, df = 2, p <0.01). Post hoc tests showed no significant difference between participants in the ANX-lifetime and ANX- groups, and that this difference was due to ANX+ participants being significantly more anxious at baseline than ANX- participants (see Table 3a). There was a trend for ANX+ participants to have higher baseline HADS-A scores than ANX-lifetime participants also, although this did not reach significance. A similar pattern was found when comparing SCID primary anxiety symptoms reported at baseline for each group (see Table 3b). ANX+ participants reported significantly more anxiety symptoms than the other two groups and accounted for the majority of the between group difference in the Chi square

analysis (X^2 = 46.21, df = 2, p <0.01). There was a trend for ANX-lifetime participants to report more SCID anxiety symptoms than ANX- participants overall and in all categories, with the exception of obsessions and compulsions. However, a sub-analysis of ANX- and ANX-lifetime participants only using Chi square tests found that none of these differences were significant (p > 0.01). As ANX-lifetime participants presented as more anxious than the ANX-group, but less anxious than the ANX+ group, it was felt that they could not reliably be assigned to either participant category and were excluded from the current analysis.

Table 3a. *Tukey post-hoc comparisons of baseline HADS-A scores between participants*

	ANX+ (n = 106*]	ANX- (n = 120*)	ANX-Lifetime (n = 37*)		
HADS-A: mean (SD)	11.04 (4.68)	8.50 (4.82)	8.86 (4.67)		
	MD	SE	P	95% CI Upper	95% CI Lower
ANX- and ANX+	-2.54	0.63	<0.01	-4.03	-1.05
ANX- and Lifetime	-0.36	0.89	0.91	-2.47	1.74
ANX+ and Lifetime	2.17	0.90	0.05	0.04	4.31

N is less than number of participants allocated to each participant group due to missing baseline HADS-A questionnaires: ANX+ n =21 missing, ANX- n =12 missing, ANX-lifetime n = 2 missing

Table 3b. *Comparison of primary SCID anxiety symptoms reported by ANX-, Anx-lifetime and ANX+ groups at baseline*

	ANX+ n = 122* (%)	ANX-lifetime n = 37*(%)	ANX- n = 111*(%)
Any anxiety symptom(s) %	94 (77.05)	17 (45.95)	37 (33.33)
Panic attacks %	43 (35.25)	4 (10.81)	7 (6.31)
Agoraphobia %	50 (40.98)	10 (27.03)	18 (16.22)
Social anxiety %	32 (26.23)	5 (13.51)	4 (3.60)
Specific phobia %	24 (19.67)	3 (8.11)	8 (7.21)
OCD: Obsessions/compulsions %	35 (28.69)	3 (8.11)	12 (10.81)
Excessive worry (GAD) %	48 (39.34)	7 (18.92)	18 (16.22)

* N is less than number of participants allocated to each participant group due to missing data for baseline anxiety symptoms: ANX+ n = 5 missing, ANX-lifetime n = 2 missing, ANX- n = 19 missing*

Appendix 4: Preliminary analyses - Study 2

Full output data for the preliminary analyses completed in Study 2 are provided below in Tables 4a to 4c.

Table 4a. *Testing the independent effects of specific covariates on prospective HAM-D scores (n = 259)*

Outcome = HAM-D	B^c	SE	P	99% CI Lower	99% CI Upper
Age at consent*	-0.02	0.03	0.5473	-0.09	0.06
Gender*	1.21	0.65	0.0636	-0.48	2.90
Current personality disorder	7.71	1.39	<0.001^	4.11	11.31
Bipolar diagnosis^d	0.35	0.81	0.6698	-1.77	2.46
Current eating disorder*	2.68	1.53	0.0821	-1.30	6.66
Current alcohol abuse / dependence*	4.03	2.17	0.6510	-1.62	9.67
Current substance abuse / dependence	-1.36	2.18	0.5325	-5.66	2.93
Number of previous episodes:					
8-19[a]	3.06	0.97	0.0018^	0.54	5.58
20+[a]	4.03	0.90	<0.001^	1.69	6.37
Time point*[b]:					
32 weeks	0.37	0.51	0.4694	-0.94	1.67
48 weeks	-0.32	0.51	0.5361	-1.64	1.01
64 weeks	-0.24	0.52	0.6510	-1.58	1.11
80 weeks	-0.65	0.53	0.2219	-2.02	0.72
96 weeks	-0.64	0.56	0.2506	-2.08	0.80

[a] *Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 week;* [c] *Refers to the regression coefficient where prospective HAM-D scores are the outcome variable;* [d] *Bipolar diagnosis coefficient refers to individuals with BDII compared to those meeting criteria to BD;* * Site removed as a random effect*

Table 4b. *Testing the independent effects of specific covariates on prospective MAS scores (n = 259)*

Outcome = MAS	B[c]	SE	P	99% CI Lower	99% CI Upper
Age at consent	-0.02	0.01	0.1389	-0.05	0.01
Gender*	0.18	0.25	0.4732	-0.47	0.82
Current personality disorder	1.17	0.56	0.0369	-0.28	2.62
Bipolar diagnosis[d]	0.09	0.31	0.7655	-0.51	0.70
Current eating disorder	-0.20	0.59	0.7374	-1.72	1.33
Current alcohol abuse / dependence	0.19	0.85	0.8253	-2.01	2.38
Current substance abuse / dependence	-0.67	0.82	0.4139	-2.29	0.95
Number of previous episodes*:					
8-19[a]	0.55	0.38	0.1494	-0.44	1.54
20+[a]	0.61	0.35	0.0850	-0.31	1.53
Time point*[b]:					
32 weeks	-0.35	0.25	0.1679	-1.00	0.30
48 weeks	-0.30	0.26	0.2399	-0.97	0.36
64 weeks	-0.13	0.26	0.6161	-0.80	0.54
80 weeks	-0.42	0.27	0.1141	-1.11	0.27
96 weeks	-0.17	0.28	0.5353	-0.89	0.55

[a] *Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 weeks;* [c] *Refers to the regression coefficient where prospective MAS scores are the outcome variable;* [d] *Bipolar diagnosis coefficient refers to individuals with BDII compared to those meeting criteria to BD;* *Site removed as a random effect*

Table 4c. *Testing the independent effects of specific covariates on prospective SOFAS scores (n = 259)*

Outcome = SOFAS	B[c]	SE	P	99% CI Lower	99% CI Upper
Age at consent*	-0.01	0.06	0.9313	-0.16	0.15
Gender*	1.60	1.36	0.2396	-1.93	5.14
Bipolar diagnosis[d]	2.48	1.67	0.1426	-0.84	5.80
Current personality disorder*	-9.55	2.98	0.0016	-17.29	-1.80
Current eating disorder*	-3.48	3.19	0.2759	-11.77	4.80
Current alcohol abuse / dependence*	-2.92	4.51	0.5177	-14.64	8.79
Current substance abuse / dependence	-6.79	4.52	0.1342	-15.70	2.11
Number of previous episodes:					
8-19[a]	-5.23	2.07	0.0120	-10.60	0.14
20+[a]	-6.80	1.92	0.0005	-11.79	-1.81
Time point*[b]:					
32 weeks	-0.61	1.00	0.5430	-3.20	1.98
48 weeks	2.55	1.02	0.0127	-0.09	5.19
64 weeks	1.54	1.04	0.1385	-1.14	4.23
80 weeks	2.59	1.05	0.0141	-0.13	5.32
96 weeks	1.33	1.11	0.2293	-1.53	4.19

[a] *Individuals within the ≤ 7 episodes category are the reference group;* [b] *Reference time point is 16 week;* [c]*Refers to the regression coefficient where prospective SOFAS scores are the outcome variable;* [d]*Bipolar diagnosis coefficient refers to individuals with BDII compared to those meeting criteria to BD;* * Site removed as a random effect*

Appendix 5: Specific ADs as predictors of longitudinal outcome - Study 2

Full output data for analyses in Study 2 which assessed associations between individual categorical ADs and prospective outcomes are provided in Tables 5a to 5c.

Table 5a. *Estimating the effect of individual ADs on HAM-D scores across follow-up (n = 259)*

IV	B^a	SE	P	99% CI lower	99% CI upper
PD with / without Ago*	0.003	1.00	0.99	-2.56	2.62
Agoraphobia*	0.57	1.37	0.67	-2.98	4.13
Social Phobia*	-0.84	1.00	0.40	-3.44	1.75
Specific Phobia*	1.11	1.02	0.28	-1.54	3.75
OCD*	2.75	1.12	0.01	-0.15	5.65
PTSD*	3.16	1.55	0.04	-0.87	7.20
GAD*	1.95	0.77	0.01	-0.06	3.96

Results are for the mixed effects model where 'number of previous episodes', 'current personality disorder' and 'time point' are included as fixed effects and 'participant' as a random effect; ^{a}All regression coefficients refer to the effect of having an individual AD compared to participants in both the ANX+ and ANX- group who do not having a diagnosis of that disorder

Table 5b. *Estimating the effect of individual ADs on MAS scores across follow-up (n=259)*

IV	B^a	SE	P	99% CI lower	99% CI upper
PD with / without Ago*	-0.71	0.40	0.08	-1.75	0.32
Agoraphobia*	-0.58	-0.55	0.29	-2.00	0.84
Social Phobia*	-1.18*	0.41	<0.01	-2.24	-0.12
Specific Phobia*	0.62	0.41	0.13	-0.45	1.68
OCD*	1.39*	0.42	<0.01	0.29	2.49
PTSD*	-0.03	0.60	0.95	-1.60	1.54
GAD*	0.54	0.30	0.07	-0.24	1.32

Results are for the mixed effects model where 'time point' is included as a fixed effect and 'participant' as a random effect; ^{a}All regression coefficients refer to the effect of having an individual AD compared to participants in both the ANX+ and ANX- group who do not having a diagnosis of that disorder

Table 5c. *Estimating the effect of individual ADs on SOFAS scores across follow-up (n = 259)*

IV	B[a]	SE	P	99% CI lower	99% CI upper
PD with / without Ago*	-3.16	2.24	0.16	-8.98	2.67
Agoraphobia*	-5.45	3.08	0.08	-13.45	2.56
Social Phobia*	0.04	2.23	0.99	-5.76	5.84
Specific Phobia*	2.72	2.33	0.24	-3.32	8.77
OCD*	-3.46	2.51	0.17	-9.99	3.07
PTSD*	-3.94	3.49	0.26	-13.01	5.13
GAD*	-2.05	1.74	0.24	-6.56	2.46

Results are for the mixed effects model where 'number of previous episodes', 'current personality disorder' and 'time point' are included as fixed effects and 'participant' as a random effect.
[a]*All regression coefficients refer to the effect of having an individual AD compared to participants in both the ANX+ and ANX- group who do not having a diagnosis of that disorder*

Appendix 6: Estimating the association between primary SCID anxiety symptoms and longitudinal outcomes - Study 2

Full output data is provided in Tables 6a to 6c for the analysis assessing primary SCID anxiety symptoms as longitudinal predictors of outcome for individuals with no current and past ADs (ANX- group; Study 2).

Table 6a. *Estimating effect of primary SCID anxiety symptoms on HAM-D scores at follow-up for participants with no current or past AD at baseline (ANX-; n = 132)*

Baseline Symptom	B	SE	P	95% CI Lower	95% CI Upper
Any anxiety symptoms*[a]	4.05	0.75	<0.01	2.10	6.01
Panic attacks*[a]	0.93	1.57	0.56	-3.20	5.06
Agoraphobia*[a]	1.72	1.07	0.11	-1.09	4.53
Social Phobia*[a]	3.11	2.20	0.16	-2.67	8.89
Specific phobia*[a]	0.40	1.51	0.79	-3.58	4.38
Obsessions / compulsions*[a]	2.56	1.34	0.06	-0.97	6.09
Worry*[a]	2.29	1.22	0.06	-0.91	5.50

*Controlling for number of previous episodes as this covariate remained a significant predictor of HAM-D scores at FUP in the ANX- group; [a]site is removed as a random effect

Table 6b. *Estimating effect of anxiety primary SCID symptoms on MAS scores at follow-up for participants with no current or past AD at baseline (ANX-; n = 132)*

Baseline Symptom	B	SE	P	95% CI Lower	95% CI Upper
Any anxiety symptoms	0.78	0.37	0.04	-0.19	1.75
Panic attacks	1.55	0.78	0.05	-0.50	3.59
Agoraphobia	0.62	0.54	0.25	-0.79	2.03
Social Phobia	0.52	1.10	0.63	-2.35	3.40
Specific phobia	0.29	0.76	0.71	-1.70	2.27
Obsessions / compulsions	0.39	0.67	0.56	-1.36	2.14
Worry	-0.08	0.61	0.89	-1.70	1.53

Table 6c. *Estimating effect of primary SCID anxiety symptoms on SOFAS scores at follow-up for participants with no current or past AD at baseline (ANX-; n = 159)*

Baseline Symptom	B	SE	P	95% CI Lower	95% CI Upper
Any anxiety symptoms*[a]	-4.25	2.01	0.04	-9.55	1.04
Panic attacks*[a]	1.02	4.01	0.80	-9.55	11.59
Agoraphobia*[a]	-2.65	2.88	0.36	-10.24	4.94
Social Phobia*[a]	-1.37	5.82	0.81	-16.71	13.97
Specific phobia*[a]	-0.77	4.19	0.85	-11.82	10.27
Obsessions / compulsions*[a]	-3.44	3.49	0.33	-12.63	5.74
Worry*[a]	-4.32	3.31	0.19	-13.04	4.39

*Baseline SOFAS is included as a covariate; [a]Site is not included as a covariate in the model

Tables 7a and 7b below provide the pre-screening assessment used in Study 3 to confirm

likelihood of eligibility for both either the control or bipolar participant groups.

Table 7a. *Pre-screen for Study 3 – confirming eligibility for the bipolar participant group*

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1   Introductory questions

- Were you expecting a call from us?
- Have you received a Participant Information sheet about this study?
- What do you already know about our study?
- Do you have any questions that I could clarify for you about this research?
- Do you think you would be interested in taking part in this study?

    If yes:
    Is it ok if I ask you a few questions to check this study is likely to be suitable for
- you?
- Would you confirm with me what your age is please?
    - *(exclude if NOT between 18 and 90 years old)*

---

2   Bipolar Disorder

- Do you have a diagnosis of a mental health problem? What is it?
(Confirm BDI/II primary diagnosis. Exclude if primary diagnosis of schizophrenia or personality disorder or any diagnosis of dementia, organic brain injury)

---

3   Depression

- Has there ever been a time when you were feeling depressed or down most of the day nearly every day?
- How long did this last? (as long as 2 weeks?)
- Have you felt this way in the last month?
    If 'yes' : has it lasted as long as 2 weeks?

4   Mania

- Has there ever been a period of time when you were feeling so good, 'high', excited or hyper that other people thought you were not your normal self?
- How long did this last? (4 days/1 week/hospitalisation?)
- *If no, ask:* has there ever been a period of time when you were so irritable that you found yourself shouting at people or starting fights or arguments?
- *If 'yes', ask:* how long did this last for?
- Have you felt this way (high/irritable) in the last month?
- *If 'yes':* has it lasted for as long as 4 days/1 week/ resulted in hospitalisation?

- *If 'Yes' to manic or depressive episode in past month: complete pre-screen to check eligibility but appointments will need to be made when participant is 4 weeks episode free.*

- *Check for eligibility: At this stage participant must meet criteria for BDI (at least 1 manic episode lasting 1 week or requiring hospitalisation with or without a depressed episode) OR BD ii (1 episode of hypomania lasting at least 4 days and at least 1 depressed episode lasting at least 2 weeks).*

  - *If participants DO meet criteria for BD I or ii: Continue*
  - *If participants DO NOT meet criteria for BD I or II: Explain that unfortunately the participant does not meet criteria for this study but that we would like to offer them the opportunity to register with the Spectrum Centre Participant Panel. If the participant would like to join get address/ email and send out application pack.*

5   Other Enduring Mental health problems

- Have you ever been diagnosed, by a health professional, with:
  a) A physical brain injury?
  b) Dementia?
  c) Personality disorder?
  d) Schizophrenia?
  e) Bipolar Disorder?
  (Exclude if primary diagnosis of schizophrenia or personality disorder or any
- *diagnosis of dementia or organic brain injury)*

6   Night Shifts

- Are you currently working night shifts?
  - *(Exclude if 'yes')*

7 General questions

- Are you currently taking part in any other research programs?
- *If yes:* what is it?

    NB participants taking part in another intervention study cannot participate. If participants are involved in several other research projects discuss with the participant and decide together if taking part in this project is manageable.

    - Is the participant eligible?
    - If 'YES' continue:
- Is it ok for us to contact a health professional that knows you well? *(e.g. GP, so we can check it's ok to visit you at home/ in case there is an emergency)*
- <u>yes</u>: Please can I take their contact details?
- The next stage of the project requires us to conduct a short interview with you, which just tells me a little more about your mood and other experiences you may or may not have had. This should take between 5 and 30 minutes, depending on your answers, as sometimes I might need to ask you a few more questions. Would you be happy for me to do this with you now?

    - If 'YES' complete the SCID overview with the participant, asking additional questions from the SCID for any questions which are answered 'yes'.
    - If 'NO': When would be a good time for me to call back to complete this interview with you?

    Time ....
    Date ....
    Pre-screen completed by
    ....

Table 7b. *Pre-screen for Study 3 – confirming eligibility for the control participant group*

Pre-screen questions

1. **Introductory questions**

- Were you expecting a call from us?
- Have you received a Participant Information sheet about this study?
- What do you already know about our study?
- Do you have any questions that I could clarify for you about this research?
- Do you think you would be interested in taking part in this study?

  If yes:
- Is it ok if I ask you a few questions to check this study is likely to be suitable for you?
- Would you confirm with me what your age is please?
  - *(exclude if NOT between 18 and 90 years old)*

2. **Depression**

- Has there ever been a time when you were feeling depressed or down most of the day nearly every day?
- How long did this last? (as long as 2 weeks?)
- When was the last time you felt this way? (Was it within the last 2 years?)
  - *(exclude if depression within the last 2 years)*

3. Mania

- Has there ever been a period of time when you were feeling so good, 'high', excited or hyper that other people thought you were not your normal self?
- How long did this last? (4 days/1 week/hospitalisation?)
- *If no, ask:* has there ever been a period of time when you were so irritable that you found yourself shouting at people or starting fights or arguments?
- *If 'yes', ask:* how long did this last for?
  - *(Exclude if: a) 1 week/hospitalisation OR b) 4 days AND depressive episode*

4. **Mental health problem**

- Have you ever been diagnosed, by a health professional, with:
  A physical brain injury / dementia / personality disorder / schizophrenia / BD?
  - *(exclude if 'yes' to any of the above)*
- Do you have a diagnosis of any other mental health problem?
- *If yes,* could you tell me what your diagnosis is?
  - *(Exclude if: any severe and enduring mental health problem including BD I or II, schizophrenia, personality disorder, dementia, organic brain injury)*

  If not enduring ask: Has this been a problem in the last 2 years?
  - *(Exclude if 'yes')*

Table 7b continued

5. Sleep Disturbance

- Have you had significant and prolonged sleep disturbance in the past month? (sought professional help/taken medication?)

  - (Control: exclude if sleep disturbance. HYP: include)
- Have you ever been diagnosed with a sleep disorder by a health professional? (e.g. narcolepsy, insomnia, sleep apnoea)

  If yes, what was the diagnosis and when was it given?

6. Fibromyalgia

- Have you experienced widespread pain for more than 3 months on both the left and right sides of your body, above and below your waist?
- Do you experience pain in at least 11 tender points i.e. places on muscles that elicit a feeling of sensitivity when they are pressed?
- Do you have a current diagnosis of FM, given by a health professional?
- Do you have a current diagnosis of any chronic pain disorder, given by a health professional?

  - (exclude if 'yes')

7. Night Shifts

- Are you currently working night shifts?

  - (Exclude if 'yes')

8. General questions

- Are you currently taking part in any other research programs?
- *If yes:* what is it?

  NB participants taking part in another intervention study - find out what the intervention is and if this would affect sleep, mood or activity in any way - if so they cannot participate. If participants are involved in several other research projects discuss with the participant and decide together if taking part in this project is manageable.

  - Is the participant eligible?
  - If 'YES' continue:
- Is it ok for us to contact a health professional that knows you well? (*e.g. GP, so we can check it's ok to visit you at home/ in case there is an emergency*)

  <u>yes</u>: Please can I take their contact details?

- **General questions continued:**

The next stage of the project requires us to conduct a short interview with you, which just tells me a little more about your mood and other experiences you may or may not have had. This should take between 5 and 30 minutes, depending on your answers, as sometimes I might need to ask you a few more questions. Would you be happy for me to do this with you now?

- *If 'YES' complete the SCID overview with the participant, asking additional questions from the SCID for any questions which are answered 'yes'.*

- if 'NO': When would be a good time for me to call back to complete this interview with you?

Time ………………………………………………………………..
Date ………………………………………………………………..
Pre-screen completed by ……………………………………………………………………………………………

Appendix 8: ESM Diary - Study 3

The complete diary used in Study 3 is provided in Table 8a and includes all items relevant for this thesis and two other PhD projects that this data was collected for.

Table 8a. *Original ESM diary used in Study 3 – all items*

	EMOTE diary questions

A What was I thinking (just before the text alert went off?)

....

B Right now I have trouble concentrating	Not		Moderate		Very		
	1	2	3	4	5	6	7

C Please describe your mood just before the text alert went off:

I feel......	Not		Moderate		Very		
• Cheerful	1	2	3	4	5	6	7
• Energetic	1	2	3	4	5	6	7
• Confident	1	2	3	4	5	6	7
• Anxious	1	2	3	4	5	6	7
• Relaxed	1	2	3	4	5	6	7
• Worried	1	2	3	4	5	6	7
• bad about myself	1	2	3	4	5	6	7
• Down	1	2	3	4	5	6	7
• Guilty	1	2	3	4	5	6	7

D Overall I'm feeling happy	Not		Moderate		Very		
	1	2	3	4	5	6	7

E My current mood...

is affecting me at the	Negatively			Not affecting		Positively			
• moment	-4	-3	-2	-1	0	1	2	3	4

My current mood...	Not									Very
• is controllable by me	1	2	3	4	5	6	7	8	9	10
• is causing me concern	1	2	3	4	5	6	7	8	9	10
• makes sense to me	1	2	3	4	5	6	7	8	9	10
• will continue for a long time	1	2	3	4	5	6	7	8	9	10
• was caused by my own behaviour	1	2	3	4	5	6	7	8	9	10

Table 8a continued

<u>F</u>

I want to make my mood (please underline)	Go up	Go down	Stay the same

I intend to make my mood go up/down/stay the same by (please state the main thing you intend to do)

....

<u>G</u>	Not at all	Some what	Quite a bit	A great deal
Right now I am...				
• In high spirits and full of energy	1	2	3	4
I feel like this because...				
• I am a talented person with lots to offer	1	2	3	4
• Things happen to be going well for me at present	1	2	3	4

<u>H</u>	Not at all	Some what	Quite a bit	A great deal
Right now I am...				
• Feeling down on myself	1	2	3	4
I feel like this because...				
• I am a bad person, even towards myself	1	2	3	4
• Current problems are leading me to be rather hard on myself	1	2	3	4

<u>I</u> Where am I? (when you received the text alert) ....

Who am I with? (state their relationship to you) ....

....

In the company of these people I feel:

	Not		Moderate		Very	
• Comfortable	1	2	3	4	5	6	7
• Threatened	1	2	3	4	5	6	7

<u>J</u> What am I doing? (Just before the text alert went off) ....

....

Table 8a continued

K	Since the last text alert, have you done anything <u>with the intention</u> of modifying your mood (make your mood go up/down/stay the same)? If so, what is the main thing you have done?	....							

L	Since the last text alert, the most important/significant event that happened to me was:	....						
		Very unpleasant					Very pleasant	
	• This was:	1	2	3	4	5	6	7

M		Not		Moderately			Very	
	This text alert irritated me:	1	2	3	4	5	6	7

N	It is now exactly	.... Hrs ....mins

Appendix 9: A novel coding scheme for the EMOTE study (Study 3)

Table 9a provides the full coding scheme which was developed in this thesis to categorise written responses to open questions in the Study 3.

Table 9a. *Coding scheme for written responses in the EMOTE study*

Category	Code	Examples
A. <u>Thoughts</u>		
Relationships / social interaction	1	• Thinking about other people known to the person - friends, family, colleagues, acquaintances etc. This Includes work related interaction where the interaction is not the person's job role e.g. 'thinking about teaching students' would be coded as 2 for work, but ' thinking about chatting with my colleague earlier about TV last night' would be coded as social interaction. • Thoughts about past, current or upcoming social situations e.g. parties, confrontations, conversations, pub quiz, family meal, concert etc. • Thoughts about non-verbal interactions e.g. 'I must check my email / texts / voicemails.' • Thoughts about pets • Social leisure activities – family meals, going bowling, going to the cinema etc. • Thoughts about doing things for other people e.g. thinking about cooking the kids tea, thinking about putting the kids to bed • Thoughts about appointments with other people (psychiatrist, doctor, dentist, CPN)

Table 9a continued

Work / study	2	• Thoughts about work or work related tasks e.g. thinking about the document I'm working on, thinking about the deal I'm doing
Finances	3	• Any thoughts about financial situation, money, debt etc. E.g. 'I need to ring virgin to sort out my bank account', 'this train ticket is really expensive' • Deciding **how much** to spend on something – so making a decision related to finances. NB: if just deciding what to buy this is coded as '6' for shopping e.g. thinking 'I could do with some new slippers', 'deciding if I should buy the blue one or the red one' etc.
Psychological / physical health and well being	4	• Thoughts about current mood e.g.' I was thinking that I feel sad / happy / bored' • NB this is not to be coded when participant describes how they feel about what they are thinking about e.g. if the thought is 'happy my husband is home' this would still be '1' as thought and feeling is about husband, not a thought about mood specifically. • Self-esteem & self-evaluations about appearance or ability: I look great in this dress; about self in general – 'I'm a slob', 'I'm really productive', 'about how stupid I am'; thoughts about body image: 'I feel fat' • Thoughts about physical health e.g. 'I feel really ill', 'I feel so tired', 'my knee hurts'

Table 9a continued

Daily living & self-maintenance	6	• Thoughts about instrumental daily tasks and routine e.g. planning what to cook for tea, thinking about how to get to work, thinking about shopping whilst doing the shopping, planning e.g. 'about things I need to do for tomorrow' (where no context specified), DIY, housework • Thinking about basic daily life tasks e.g. sleeping, eating, dressing, washing, taking medication, putting on make-up, having a cigarette
Independent entertainment / recreation / leisure	8	• Thinking about any independent recreational activity e.g. 'the book I'm reading', 'the website I'm looking at', 'the TV programme I'm watching'
Neutral	0	• About the weather - 'it's sunny' • Thoughts about unknown people (celebrities etc. – where not clearly linked to an activity such as watching TV or a social situation) • Thoughts about the ESM study • Thinking about 'nothing / not much' • When the person writes 'I was asleep' indicating no thought code here
Politics / religion / abstract thoughts	17	• E.g. 'about the selfishness of humanity' • E.g. 'about the current government' • 'About life in general' (with no clear content / context) • About religion
Miscellaneous / unable to code	999	• Thoughts that don't fit into any other categories • Thoughts that are unclear e.g. 'Hmm', 'wow'

Table 9a continued

B. <u>Activities</u>

Any social interaction / activity	18	• An activity that involves socialising or interacting with others e.g. talking, laughing, arguing, emailing, texting, telephone conversations, putting kids to bed, having evening meal with family, going to a concert, having a coffee with a friend, intimacy or intercourse
Work / study	10	• Any activity related to occupation or education: NB Direct social interaction with colleagues is coded as '18' where the interaction is general e.g. 'gossiping with colleagues', but coded as '10' where it is part of occupational activity e.g. 'attending a meeting', 'talking to a student about their project'
Basic or instrumental daily living & self-maintenance activities	11	• Washing, dressing, eating, sleeping, using the toilet, taking medication, applying make-up, other personal hygiene, walking around the house, chores, cooking, cleaning , driving, viewing a flat, commuting, shopping, smoking, DIY, masturbation

Table 9a continued

Passive / independent leisure	13	• 'Pampering myself', surfing the net, watching TV, reading, listening to the radio, looking at books in the library / going to the library, doing arts and crafts, building Lego, gambling (e.g. 'putting a bet on the horses'), relaxing ('practicing meditation')
Active leisure	14	• Sports e.g. badminton, golf, football • Cycling (even if to / from work) • Walking (including walking to / from work, walking to town, taking a stroll), walking the dog
Sex	15	• Any sexual activity
Substance use	16	• Any alcohol or drug use
Neutral	0	• Where 'nothing / not much' is written • Activities related to the study
Miscellaneous / unable to code	999	• Activities that don't fit into any other categories

C. <u>Significant life events</u>

*(NB- these are events that are out of
the ordinary and not part of everyday
life. All other events should be coded
as '0')*

21

- Bereavement (person / pet)
- Relationship breakdown/divorce
- Prison / trouble with police
- Personal injury or illness
- Marriage / reconciliation
- Hospitalisation (any reason)
- Marriage
- Dismissal / retirement from work
- Change in the health or behaviour of a family member
- Pregnancy / Sexual Difficulties
- Gaining a new family member
- Business adjustment/job change/job responsibility change
- Change in financial state
- Change in number of arguments with spouse or other family members
- Taking on a mortgage/loan
- Foreclosure on a mortgage or loan
- Son or daughter leaving home (marriage, college, military, etc.)
- Outstanding personal achievement
- Spouse beginning or ceasing work outside the home
- Beginning or ceasing formal schooling
- Change in living condition (i.e. new home, re-modelling, moving in with family)
- Revision of personal habits (i.e. quit smoking, increase in exercise etc.)
- Troubles at work
- Change in working hours or conditions
- Major change in religious activity (i.e. a lot more or less)
- Major change in social activities (i.e. a lot more or less)
- Change in sleeping / eating habits
- Vacation/holiday
- Victim of trauma/abuse
- Major change in medication

D. CONTEXT

Where am I?

Place	Code
Home	18
Network (homes of family & friends)	19
Work / study	20
Health care	21
Public places (indoors and outdoors)	22
Transport	24
Other	25
Can't code / missing	NA

Who am I with?

Who	Code
Alone / alone with pets	0
Family (partner, children, parents, siblings)	1
Friends / neighbours	2
Colleagues	3
Health care professionals	4
Strangers	5
Missing / can't code	NA

General guidance for this coding schedule

1. Up to 3 thoughts or activities can be coded to reflect that participants may be thinking about several different things or doing several different activities at once. However, each separate thought or activity should be coded only once i.e. multiple codes reflect that a participant was doing or thinking about multiple things, not that they were thinking of one thing that could potentially be coded using more than one code. Use the context to help you decide the most appropriate coding.

2. Multiple thoughts or activities that would potentially fit within the same coding group are coded only once e.g. where a participant reports thinking 'about an earlier meeting at work and the piece of work I need to complete for tomorrow' – this would generate just one code for work.

3. If it is helpful the context of a situation (where, who with etc.) can be used to help determine which thought / activity code is most appropriate. However, care must be taken to code the thought and activity directly without making inferences based on the context alone.

4. If you have any thoughts, comments, queries or feedback about this coding guide whilst using it, please enter these on the 'notes' tab on the database.

Appendix 10: Two pilot studies (Study 3)

To ensure the watch and paper diary method was appropriate for a study exploring changes

in affect and anxiety in bipolar and control samples, two separate pilot studies were carried

out prior to the start of data collection. The first pilot tested the sensitivity of ESM and its

ability to capture variability in affect. As the Iron Man Timex Datalink watches used for alerts

in pilot 1 went out of production unexpectedly at the beginning of the study, the second

pilot assessed the acceptability and practicality of the use of mobile phones as alternative

signalling devices. In addition, data from both pilots were assessed to determine likely

response rate for each group. For both pilot studies, participants were recruited through a

university research database and included current staff and individuals with BD who had

taken part in previous research and who had consented to being approached for future

studies.

Pilot 1: A test of sensitivity to change in affect and anxiety

Three bipolar participants and two controls took part in this pilot. As the primary

goal was to assess the sensitivity of the diary items to measure change in anxiety and affect,

only those items were of interest at this stage. As such, no threshold for response time from

alert to completion was set. Watches were used as signalling devices and were set to beep at

randomly selected but pre-determined times each day. Due to the small size of the sample,

multilevel analysis was not appropriate to test variability. Instead, the overall frequency of

ratings of anxiety, negative affect (NA) and positive affect (PA) for each group was plotted to

provide an overview of changes in ratings (see Figure 10a). It was found that all scales were

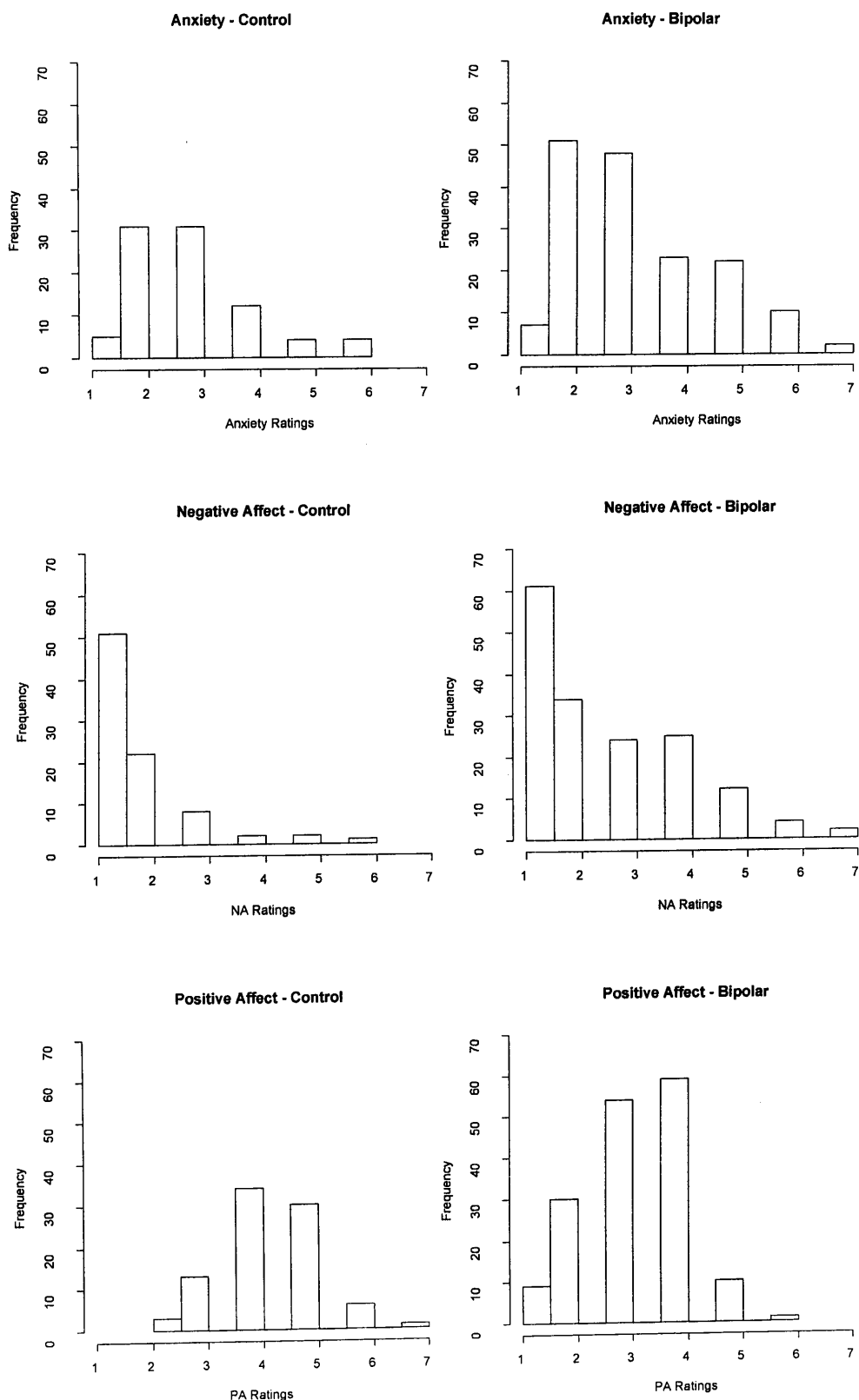sensitive to change, evidenced by fluctuations in scores for all participants.

Figure 10a. *Frequency of affect and anxiety ratings for bipolar and control participant*

Pilot 2: A test of equipment

A second pilot was conducted to compare the use of watches with the use of mobile phones as signalling devices. This was with the intention of allowing participants to choose their preferred signalling device if both methods yielded sufficient eligible responses. As the variable of interest in this pilot was the ability of signalling devices to prompt immediate, 'in the moment' diary entries, a response time threshold was set. Previous research has generally used cut offs between 10 and 20 minutes to identify valid momentary responses to alerts (Barge-Schaapveld et al., 1995; Havermans et al., 2007; Myin-Germeys et al., 2001) and so a conservative limit of 10 minutes was applied at this stage. Two additional bipolar participants and two more control participants were recruited for the second pilot study. Again, all participants completed the ESM study, this time using their own mobile phone as a signalling device, or a phone provided by the research team. Alerts were sent to the phones by syncing the device with a googlemail email account and event calendar, which sent pre-programmed text alerts throughout the study.

The mean number of responses recorded within 10 minutes in this study was compared with participant data from pilot 1, where watches had been used to signal diary entries (see Figure 10b). Valid responses from bipolar participants reduced from 82% with watches to 55% with mobile phones. However, control participants showed a slight increase in valid 10 minute responses from 58% with watches to 64% with the use of mobile phones. Bipolar participants reported forgetting to charge mobile phones, having phones on silent and leaving phones at home as the main problems linked to reduced responses. However, all participants completed > 50% valid responses using both devices. Whilst there is no statistically accurate number of responses required per person to be included in a multi-level analysis, the current ESM research generally employs a response rate of > 21 data points per person to be included for analysis (Havermans et al., 2007; Myin-Germeys et al., 2003), although there is no firm evidence to explain this threshold. As both mobile phones and

watches generated a sufficient level of data from both participant groups to meet the > 21

data points threshold, the decision was made to allow participants the choice of using either

device, and choice was noted as part of the research. It was decided that 10 alerts would be

sent each day to maximise the chances of participants providing sufficient eligible data at the

end of the study. To control for the potential additional problems using phones, a study

handbook was created which detailed the study method fully, including reminders to charge

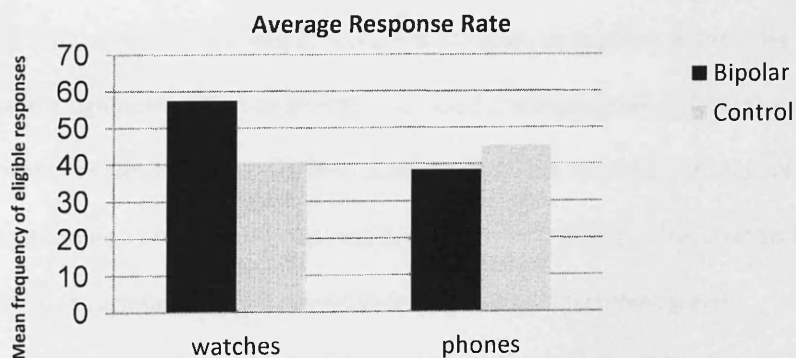phones and keep them nearby and turned on at all times. This was reiterated at briefing.

Figure 10b. *Comparing the use of wrist watches and mobile phones as signalling devices*

Appendix 11: EMOTE Preliminary Analyses (Study 3)

Preliminary analyses were carried out to determine which factors were significant independent predictors of anxiety and affect and should therefore be controlled for in the final models. The analysis for the sociodemographic factors considered is provided here. Due to the small number of participants in the 'secondary' highest education category (n = 15), the secondary (GCSE) and higher (A-level) education groups were combined and compared to individuals with further (post-graduate) qualifications. Employment was assessed by comparing those in full or part-time work and study with individuals who were not working or studying. Although the BD and control groups differed significantly when compared by age, gender, employment status and education at baseline, none of these variables were found to have a significant effect on anxiety and mood outcomes (see Table 11a) and therefore were not adjusted for in the final analysis. However, the categorisation of variables such as education into broad categories may have limited the ability of the analysis to identify effects of sociodemographic variables on outcomes. Sociodemographic characteristics should be assessed in future research with a larger participant group which can support a wider range of categories for each variable.

Table 11a *Preliminary analysis of sociodemographic variables*

IV	B	SE	P	95% CI lower	95% CI Upper
Anxiety:					
Education	0.02	0.34	0.96	-0.66	1.5
Employment	0.35	0.30	0.24	-0.24	0.94
Gender	0.33	0.27	0.22	-0.20	0.86
Age	0.001	0.01	0.75	-0.02	0.02
NA:					
Education	0.01	0.27	0.98	-0.52	0.54
Employment	0.15	0.24	0.52	-0.32	0.63
Gender	0.23	0.21	0.28	-0.19	0.65
Age	-0.002	0.008	0.78	-0.02	0.01
PA:					
Education	-0.07	0.28	0.79	-0.63	0.48
Employment	-0.15	0.25	0.55	-0.64	0.34
Gender	-0.01	0.22	0.95	-0.45	0.42
Age	0.003	0.009	0.71	-0.01	0.02