Investigating susceptibility to bipolar disorder, migraine and epilepsy

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This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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Thesis summary

Epidemiological and clinical studies demonstrate a high degree of comorbidity between bipolar disorder (BD) and migraine. A relationship between BD and epilepsy is also suggested, with both disorders displaying phenotypically similar symptom profiles. The overall aim of this thesis was to further explore the relationship between BD and the neurological conditions of migraine, and epilepsy, within a large, well-characterised sample of individuals with BD.

Data were utilised from the Bipolar Disorder Research Network (BDRN); a large (n>6000) UK sample of individuals with a diagnosis of BD. Lifetime history of migraine and epilepsy were assessed within BDRN using questionnaire and telephone interview methods.

Migraine was highly prevalent within the bipolar sample and was found to disproportionately affect those with bipolar II disorder. Bipolar subjects with comorbid migraine experienced a relatively distinct illness profile, with a multivariate model revealing migraine comorbidity to be characterised by an increased risk of suicide attempt and anxiety disorder. Further analysis of the migraine phenotype revealed that observed differences in the clinical presentation of BD associated with migraine were largely associated with the migraine with aura subtype. A high rate of self-reported epilepsy was identified within the bipolar sample and group differences were revealed in the clinical course of the bipolar illness according to the presence of self-reported epilepsy. Multivariate analysis revealed an independent association of a history of suicide attempt with self-reported epilepsy within BD.

Findings from this thesis highlight the importance of identifying migraine and epilepsy within BD, and that their recognition and treatment may have a beneficial impact on the course of illness and outcome in BD. This thesis also suggests that these comorbidities may represent a clinically useful subgroup characterised by specific clinical features, and may provide an opportunity for subcategorising for future aetiological studies, potentially facilitating the identification of shared pathophysiological mechanisms.

Papers resulting from work within the current thesis:

Knott, S. Forty, L. Craddock, N. Thomas, R.H. 2015. Epilepsy and bipolar disorder. *Epilepsy and Behavior* 52, 267–274.

Related papers to which I have contributed:

Gordon-Smith, K. Forty, L. Chan, C. Knott, S. Jones, I. Craddock, N. Jones, L. A. 2015. Rapid cycling as a feature of bipolar disorder and comorbid migraine. *Journal of Affective Disorders* 175C, 320–324.

Formal Statement of Contribution

The work presented in this thesis was conducted as part of the Bipolar Disorder Research Network (BDRN), which is a large, ongoing programme of molecular genetic and clinical studies of affective disorders. BDRN is a collaboration between Cardiff University and the University of Worcester, and is led by Principal Investigators Professor Ian Jones, Professor Lisa Jones and Professor Nick Craddock. I have been a member of the BDRN research team since 2012. In this section, I detail my specific contribution to the research activities outlined in this thesis.

The clinical data utilized within this thesis were collected as part of BDRN's structured clinical assessment and have been collected by the BDRN research team over a number of years. I was not involved in the collection of this data, however all activities involving the use of this data within the thesis were conducted by myself. These include the selection of clinical variables, data cleaning, statistical analysis and interpretation of results.

A questionnaire assessing the lifetime history of migraine, used within chapters 3 and 4 of this thesis, was designed and disseminated to BDRN participants by the research team in 2011, prior to my joining of the group and commencement of my postgraduate studies. The coding of questionnaire responses and derivation of migraine diagnoses were all conducted by myself. Telephone interviews were used as a means of assessing the validity of the self-report migraine questionnaire in screening for lifetime presence of migraine within a bipolar population. I selected an existing standardised telephone interview to be used within this thesis, and revised and piloted the instrument as required. Both the random selection of participants for interview and all telephone interviews themselves were conducted by myself. As stated above, all data cleaning, statistical analysis and interpretation of results for the work presented in chapters 3 and 4 were conducted by myself.

The genetic data used within the genome-wide association study (GWAS) reported in chapter 5 of this thesis were provided by Professor Elaine Green. I generated the phenotype data file for the samples included in the study. Initial quality control (QC) of genetic data was performed at the Broad Institute. However, all QC parameters were checked by myself as part of a single nucleotide polymorphism (SNP)-level and sample-level filtering process. Principal component analysis was conducted by Dr Sophie Legge to identify potential outliers and explore potential effects of population stratification. Principal components identified within this analysis were then entered as covariates in the association analysis. I performed the association analysis using PLINK and created plots (quantile-quantile, Manhattan) to visualise the findings of the GWA analysis using R. Resulting top SNPs were functionally annotated by myself using online genome browsers.

The assessment of epilepsy within the thesis was conducted through the use of self-report questionnaire and telephone interview methods (chapter 6). Both selection and revision of the questionnaire tool were undertaken by myself. I, together with the BDRN team, disseminated this questionnaire as part of a larger questionnaire pack to the research cohort in the summer of 2013. All completed, returned questionnaire packs were electronically scanned and validated by myself. The telephone interview employed was an adaptation of a standardised, structured diagnostic inventory developed by the Epilepsy Phenome Genome Project and was revised by myself together with consultant epileptologist, Professor Michael Kerr. All telephone interviews were completed by myself, and interpreted together with Professor Kerr. As stated above, all data cleaning, statistical analysis and interpretation of results for the work presented in the final results chapter of this thesis were conducted by myself.

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Firstly, I would like to give my heartfelt thanks to my supervisors Dr Liz Forty, Professor Nick Craddock and Professor Ian Jones for their continuous support, encouragement and advice. Your knowledge and passion are beyond inspiring and I feel incredibly lucky to have gone through this process under your guidance. I cannot thank you enough.

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I would also like to thank Professor Mike Kerr and Dr Rhys Thomas for your advice, expertise, and for introducing me to the fascinating and complex world of epilepsy research. In particular, I am very grateful to Mike for spending numerous hours going through every detail of my epilepsy interviews and for always having time for me.

I would like to give my thanks to Professor Elaine Green for preparing the genetic data used within this thesis, and to Dr Sophie Legge and Dr Elliott Rees for your help and guidance in the analysis (and mostly for your patience with my countless questions and emails!).

Thank to you my friends and family who experienced all the ups and downs of my research - I promise to soon start extending our conversations to topics outside of my PhD. To Mum, Dad and Paul, thank you for your unwavering love and encouragement. To my husband, Rob, thank you for everything. Your endless love and support were in the end what made this thesis possible. I dedicate this thesis to you.

Thank you to the funders of this PhD; the Brain and Behaviour Research Foundation (formally NARSAD) and Cardiff University's School of Medicine. A special thank you to Mrs Miller, whose incredibly kind donation helped to fund my PhD studentship. Finally, I would like to express my thanks and gratitude to all of the participants who have taken part and provided their ongoing support to the Bipolar Disorder Research Network, without whom this work would not have been possible.

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Chapter 1

Introduction

Reported in part by Knott, Forty, Craddock & Thomas, 2015

Within this introductory chapter I will begin by providing an overview of bipolar disorder (BD) in terms of its classification, epidemiology and course of illness, and treatment and management of the disorder. I will also summarise what is known about the pathophysiology of the disorder before discussing the role and importance of co-occurring conditions within BD. The second section of this chapter will introduce the neurological condition of migraine and outline the evidence for overlap between migraine and BD. Next, the chapter will provide an overview of epilepsy; the second neurological disorder of interest within this thesis, before summarising the evidence suggesting a potential overlap between epilepsy and BD. The final section of this chapter will describe the aims and outline of the current thesis.

1.1 Introduction to bipolar disorder

Bipolar disorder (BD) is a common, enduring, and severe mental illness characterised by pathological disturbances in mood, ranging from extreme elation, known as mania, to severe depression. Such mood episodes are associated with a number of cognitive, physical and behavioural symptoms and the breadth of symptoms experienced within BD may also extend to include psychotic features, such as delusions or hallucinations.

Bipolar disorder (BD) is associated with high levels of functional impairment, morbidity and mortality. It is generally understood that BD is a chronic disorder, typified by periods of remission and relapse. As such, mood episodes are said to be separated by periods of recovery. However, the high rate of recurrence places

significant burden on both the individual sufferer and wider society. In addition, there is evidence to suggest that many patients with BD experience a continuation of residual, sub-syndromal symptoms after resolution of a major affective episode, acting to further perpetuate this burden (Judd et al., 2016).

The chronic nature of BD, together with its relatively young age of onset, contribute to BD being ranked one of the top ten leading causes of disability worldwide among adults by the World Health Organization (Ayuso-Mateos, 2006; Murray and Lopez, 1996). In 1991, a US study revealed the total annual costs associated with BD to be $US45 billion (Wyatt and Henter, 1995). Whilst this figure included significant direct costs attributable to the treatment and management of BD, these comprised of less than 20% of the total cost. Rather, the real burden lay within indirect costs associated with the disorder, such as loss of productivity due to impairments in functioning and premature mortality. Das Gupta and Guest (2002) estimated the annual UK costs of BD to be £2 billion at 1999/2000 prices, based on 297 000 people with the disorder. Similar to Wyatt and Henter (1995), much of this cost (86%) was attributed to indirect costs. Unfortunately, despite improvements in BD treatment and psychosocial interventions, it is thought that these costs are likely to be even larger today.

1.1.1 Origins and classification

The modern concept of bipolar disorder (BD) originated in the 19th century, with the writings of Jules Baillarger (1809-1890) and Jean-Pierre Falret (1794-180). In 1854, Baillarger and Falret, both students of the French psychiatrist Jean-Étienne-Dominique Esquirol, independently described a disorder in which mania, depression and symptom-free periods occurred within regular cycles. In his description of the disorder, Baillarger coined the term *folie à double forme* ('dual-form insanity'), with Falret referring to *folie circulaire* ('circular insanity') (Healy, 2008). In addition, in 1882, German psychiatrist Karl Kahlbaum described cyclothymia; a specified mood disorder from which patients could recover (Healy, 2008).

Using Kalhbaum's concept of cyclothymia, Emil Kraepelin brought affective syndromes together and first introduced the term 'manic-depressive' to the field of

psychiatry in the early 20th century. Kraepelin distinguished this unitary concept of mood disorder from dementia praecox (what is now commonly known as schizophrenia), based on a family history of mood disorder, an episodic nature, and a relatively benign illness course (Kraepelin, 1921). Kraepelin's distinction between the two disorders produced a concept that formed the basis for the understanding of psychiatric illness for over a century and continues to shape the World Health Organisation's International Classification of Disease (ICD), and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) classifications to this day.

In 1959, Karl Leonhard proposed the sub-classification of affective disorders into unipolar depression and bipolar illness (Leonhard, 1959), following his observation that manic-depressive patients with a history of mania had a higher incidence of mania in their families, when compared to those with recurrent depression only. This distinction proved a revolutionary development and was adopted by the American Classification Diagnostic Statistical Manual of Mental Disorders-III (DSM-III) in 1980. By the mid-1990's, the term bipolar disorder had almost completely replaced manic-depressive Illness, which was largely attributed to the wide-spread use of the term bipolar disorder outside of America with the International Classification of Disease-10 (ICD-10).

Current formal diagnostic classifications continue to follow the bipolar-unipolar dichotomy established by Leonhard. Psychiatric disorders are classified by two major nosological systems; the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5; American Psychiatric Association, 2013), and the International Classification of Diseases (ICD-10; World Health Organisation, 1992). Within the framework of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5; American Psychiatric Association, 2013), bipolar disorder is defined by the presence of at least one episode of mania, which may or may not be accompanied by one or more episodes of depression. The main distinction within bipolar disorder is made between bipolar I disorder (BDI) and bipolar II disorder (BDII). A diagnosis of BDI requires at least one or more manic episodes, whereas BDII is characterized by the presence of at least one episode of major depression, and one hypomanic episode.

Mania is defined by the DSM5 (American Psychiatric Association, 2013) as a distinct period during which patients experience abnormally and persistently raised, expansive, or irritable mood, as well as notably persistent goal-directed activity. A manic episode must last for at least seven days, or less if hospitalization is required, and must have caused marked impairment to the individual's functioning. Mood disturbance experienced within a manic episode must be accompanied by at least three additional symptoms from a list that includes: inflated-self-esteem or grandiosity; flight of ideas; distractibility; pressure of speech; reduced need for sleep; increased involvement in goal-directed activity or psychomotor agitation; and excessive involvement in pleasurable activities with a high risk for damaging consequences. A hypomanic episode is defined as being less severe than mania. The minimum duration criterion for hypomanic episodes is shorter (at least four days) and although there is a clinically significant elevation of mood, the disturbance is not severe enough to cause the degree of impairment seen within mania, or to require hospitalization. The characteristic feature of a major depressive episode is a period of at least two weeks during which there is depressed mood, or a loss of interest or pleasure in almost all activities. To meet the DSM5 criteria for major depression, the patient must experience at least four additional symptoms from a list that includes: changes in appetite or weight; sleep and psychomotor activity; decreased energy; difficulty with thinking, concentrating or decision-making; feelings of worthlessness or guilt; recurrent thoughts of death or suicidal ideation, plans or attempts. Finally, a mixed episode is characterized by a period of at least one week in which the criteria are met for both manic and major depressive episodes.

Within their description of bipolar disorder, DSM5 (American Psychiatric Association, 2013) also define cyclothymia, and bipolar disorder not otherwise specified (BPNOS). Cyclothymia is a chronic disorder, requiring more than two years of fluctuating mood disturbance, whereby the patient experiences numerous periods with hypomanic symptoms and periods with depressed symptoms that do not meet criteria for major depressive disorder. BPNOS is diagnosed when the patient experiences bipolar features that do not meet criteria for formal disorder.

Whilst the DSM and ICD classification systems are considered to be largely similar, there does exist some heterogeneity between the two in the criteria for BD. These differences are mainly focused around the number of episodes required for a diagnosis and the distinction between the two major subtypes, bipolar I (BDI) and II (BDII) disorders. According to the tenth revision of the International Classification of Diseases (ICD-10), a diagnosis of BD requires two discrete mood episodes, at least one of which must be manic in polarity. In contrast, within DSM5, a diagnosis of BD can be made following a single episode of mania. In addition, within ICD-10, BDII is not recognized as a separate entity, but rather describes a single category of 'bipolar affective disorder' where mania is distinguished from hypomania, on the basis of severity.

Inherent within both systems is the description of diagnostic categories based on clinical symptomatology, rather than underlying etiological factors. Advances in understanding of the underlying pathogenic mechanisms and genetic susceptibility for major psychiatric disorders, including BD (discussed later in this chapter), suggest that we should be moving away from current descriptive categories, to entities or dimensions that are based on the underlying workings of the brain (Craddock and Owen, 2010).

The clinical manifestations of bipolar disorder are diverse and over recent times, there has been an increasing recognition of a spectrum of bipolar disorders. Such a notion conceptualizes a continuum of affective pathology, ranging from severe mood disturbance observed within BDI, to 'softer' forms of mood variation, including recurrent depression accompanied by a hyperthymic temperament and a family history of bipolar disorder, and recurrent depression with antidepressant-induced mania (Akiskal et al., 2000).

A further topic of contention when considering a spectrum of affective illness concerns the classification of schizoaffective illness within that continuum. As already mentioned, within acute, severe episodes of mania, patients can exhibit classic signs

of schizophrenia, including thought disorder, delusions and hallucinations. Schizoaffective illness is considered when an individual experiences psychotic symptoms together with affective disturbance, and can be difficult to distinguish from very severe forms of BD. The diagnosis of schizoaffective disorder itself has been ever-changing in the different editions of the Diagnostic and Statistical Manual (DSM) and its diagnosis remains controversial because of poor diagnostic reliability, weak validity and its overuse within clinical practice (Malaspina et al., 2013). Diagnostic criteria for schizoaffective disorder were first introduced within the fourth edition of the DSM (DSM-IV; American Psychiatric Association, 2000) and was continued within the most recent edition of the DSM (DSM5; American Psychiatric Association, 2013). The DSM states that the diagnosis should be made when an individual experiences at least one episode where psychotic symptoms dominate the clinical picture, with fleeting mood symptoms, or when psychotic symptoms persist for more than two weeks without affective symptoms. DSM further specifies schizoaffective, bipolar type (for those experiencing a current or previous manic syndrome) and schizoaffective, depressed type (for those with no current or previous manic syndrome).

Uncertainty and disagreement continue over whether schizoaffective illness is a separate disorder, a subtype of affective disorder, or a subtype of schizophrenia. Some investigators postulate that the position schizoaffective illness plays on the schizophrenia-affective spectrum, may depend on the type (bipolar or depressed type) that is being considered. Family studies have shown increased risks for schizoaffective disorder in the relatives of probands with bipolar disorder, and for probands with schizophrenia (Laursen et al., 2005), suggesting that schizoaffective disorder may constitute a subtype for either disorder.

1.1.2 Epidemiology and course of illness

The lifetime prevalence of strictly defined bipolar I disorder (BDI) within the general population is reported to be approximately 1% (Merikangas et al., 2007; Merikangas et al., 2011; Pini et al., 2005; Waraich et al., 2004). Estimates of the lifetime prevalence of bipolar II disorder (BDII) range from 0.5% to 3% (Oliver and Simmons, 1985;

Stefánsson et al., 1991; Weissman and Myers, 1978). Moreover, when a wider range of bipolar spectrum disorders were considered, prevalence estimates have been reported to increase to approximately 6% (Pini et al., 2005). Evidence suggests that there exists an equal gender ratio in the prevalence of bipolar disorder (Lloyd et al., 2005; Smith and Weissman, 1992; Wells et al., 2006). While this does appear to be true for BDI, studies have repeatedly reported that BDII is more common in females than males (Baldasanno et al., 2005; Cassano et al., 1992; Di Florio and Jones, 2010).

There is general agreement that the age of onset of BD is early, usually occurring in adolescence and young adulthood. The peak age at onset of the first symptoms of BD is estimated to be between 15 and 19 years (Weissman et al., 1996). It was reported by Mantere et al. (2004) that bipolar patients report an average delay of 8 years from first experience of mood symptoms to receiving a formal diagnosis. A delay in diagnosis subsequently means a delay in appropriate treatment, and as such can lead to a worse prognosis (Angst and Cassano, 2005). Conversely, early detection and treatment of BD can reduce the risk of serious events, such as suicide, a finding that is particularly important given that between 25-50% of patients with BD will attempt suicide at least once in their lifetime (Goodwin and Jamison, 1990; Hawton et al., 2005; Jamison, 2000; Valtonen et al., 2006).

Whilst the peak onset of BD occurs in early adulthood, a minority of patients may develop the disorder within their adolescent or even childhood years, although there is controversy surrounding the diagnosis and treatment of BD in children (Parens and Johnston, 2010). Such an early onset of BD (particularly childhood onset) has been associated with long delay to first treatment, a greater number of lifetime mood episodes, higher rate of comorbid conditions, more severe manic and depressive episodes and fewer days spent well (Leverich et al., 2007).

The rate of recurrence in BD is high, and more than 90% of individuals who experience a first manic episode will have future episodes. The frequency of mood episodes in bipolar patients is highly variable. Some patients will experience discrete episodes, occurring perhaps no more than once a year and will make a full recovery in-between.

Other patients may experience a far greater number of episodes and some may fail to fully recover in-between episodes. An individual is said to suffer from a 'rapid cycling' illness course if they experience four or more distinct episodes of mania or depression over a 12-month period. However, this criterion is deemed to be arbitrary. Data on the prevalence of rapid cycling in patients with BD is inconsistent. A meta-analysis conducted by Kupka et al. (2003) including data from 1972-2002, noted a range between 12-25%, with an overall prevalence of 16.3%. Kupka et al. (2003) also reported rapid cycling to be significantly more prevalent in women than in men. Although a wealth of previous studies have suggested a relationship between rapid cycling and female gender (Bauer et al., 1994; Coryell et al., 1992; Tondo and Baldessarini, 1998), a more recent large, prospective study reported an almost equal prevalence of a rapid cycling illness pattern in men and women (Schneck et al., 2008).

When compared to the general population, individuals with BD are found to have a significantly increased risk of premature mortality. A national cohort study of 6,587,036 Swedish adults (including 6,618 individuals with BD), found that both men and women with BD died prematurely from multiple causes, including cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disorder and suicide (Crump et al., 2013). The excess deaths associated with BD have also been associated with unnatural causes such as suicide, a leading cause of death among individuals with BD. As noted above, between 25%-50% of patients with BD will attempt suicide at least once in their lifetime (Goodwin and Jamison, 1990; Hawton et al., 2005; Jamison, 2000; Valtonen et al., 2006). Suicide has also been reported to be the leading single cause of excess mortality in BD, with suicide mortality rates reported as being 15-fold high than that in the general population (Harris and Barraclough, 1997). A recent review of the risk factors for suicidal behavior indicated that a: younger age of bipolar onset; history of past suicidal behavior; family history of suicidal behavior; predominantly depressive illness course; comorbid alcohol and substance misuse disorders; and comorbid borderline personality disorder, were all associated with increased suicidality (Latalova et al., 2014).

1.1.3 Treatment and management

Treatment of bipolar disorder (BD) is concerned with the acute management of mood episodes and symptoms, as well as the prevention of future episodes and ensuring optimal functionality. Whilst much of the treatment for BD is pharmacologic in nature, the combination of psychological and lifestyle approaches with medication is essential for the long-term management of the disorder. Within the UK, the National Institute for Health and Care Excellence (NICE) produce evidence-based treatment recommendations to act as guidelines for the National Health Service (NHS), which recommend a range of both pharmacological and non-pharmacological approaches for the management of bipolar disorder (NICE, 2014; https://www.nice.org.uk/guidance/cg185).

The goal of treatment for BD is to regulate both depressive and manic states, which is often achieved through the use of a mood stabilizer. Mood stabilisers can also be used in the long-term treatment of BD, acting as a preventative measure to reduce risk of future mood episodes. Lithium was introduced by John Cade in 1949 and was the first mood stabilizer to alleviate acute manic and depressive episodes and remains the best established maintenance drug for the prevention of subsequent episodes, as highlighted by a recent meta-analysis (Miura et al., 2014). Moreover, lithium is the only known pharmacological agent to be effective in reducing the rate of suicide in the long-term treatment of patients with BD. Evidence from a recent systematic review of 48 randomized controlled trials (6674 participants) confirmed the anti-suicidal effect of lithium in people with mood disorders (Cipriani et al., 2013).

Several anticonvulsive medications (drugs used in the treatment of epileptic seizures), such as valproic acid, carbamazepine and lamotrigine, are also known to be effective mood stabilisers. They can be used in the primary treatment of BD however evidence suggests a greater efficacy for their anti-manic and prophylactic ability over their anti-depressive properties. Among the anticonvulsants, maintenance of BD is particularly well-established for valproic acid, which has been used in the prophylactic treatment of BD in Europe since 1966 (Lambert et al., 1966). Valproate is still frequently used in clinical practice (Geddes and Miklowitz, 2013), however evidence suggests that

combination with lithium is more effective than treatment with valproate monotherapy (Geddes et al., 2010).

Atypical antipsychotics such as olanzapine, aripiprazole, quetiapine and risperidone, are also known to play an increasing role in the treatment of BD. They are particularly helpful in instances where lithium or anticonvulsants alone may be ineffective, such as the treatment of agitation and psychotic symptoms that occur within severe mood episodes. Where monotherapy fails to sufficiently reduce symptoms, a combination of mood stabilisers and/or antipsychotics is the next recommended line of treatment. If symptoms of depression cannot be managed by mood stabilisers and antipsychotic medication alone, then an antidepressant can be added, however the role of antidepressants in the treatment of bipolar depression remains controversial, given the risk of a rapid switch to mania, or the triggering of a rapid cycling illness course. It has been noted, however, that selective serotonin reuptake inhibitors (SSRIs) may pose less of a risk for inducing mood switches than tricyclic antidepressants (Salvadore et al., 2010).

Although pharmacotherapy is the mainstay of treatment for BD, many people do not respond fully to medication and continue to experience sub-syndromal, inter-episode symptoms (Keck et al., 1998). For example, it has been noted that up to a third of patients with BD do not respond to treatments in naturalistic studies (Geddes and Miklowitz, 2013). Electro-convulsive therapy (ECT) is among the non-pharmacological treatments for BD that has a documented positive effect on severe episodes of both depressive and manic polarities in patients (Dierckx et al., 2012; Medda et al., 2009) and is particularly useful for treatment resistant BD (Gitlin, 2006).

Non-adherence to drug treatment among bipolar patients is also a problem, with non-adherence rates of up to 60% following acute episodes (Strakowski et al., 1998). A lack of awareness or insight into their disorder is considered a major source of non-adherence among bipolar patients (Colom et al., 2005). Adverse side effects of medication, particularly weight gain and sedation (Velligan et al., 2009); comorbid alcohol dependence, youth, greater number of affective symptoms and a recent manic or hypomanic episode (Baldessarini et al., 2008) and have also been cited as important factors associated with non-adherence. Treatment non-adherence can have serious

clinical and economic consequences; therefore, non-pharmacological approaches adjunctive to medication are essential in ensuring optimal outcomes for patients with BD.

A number of psychosocial interventions have been established for the treatment of BD which broadly fall into five categories: psychoeducation, integrated treatments, family-based therapy, cognitive behavioural therapy, and interpersonal and social rhythm therapy (Castle et al., 2009). Psychosocial therapies look to improve the self-management of the disorder and common objectives include: increasing acceptance of the illness, improving drug adherence, identifying triggers and early warning signs, enhancing communication and relationships, and stabilizing sleep cycles and daily routines (Geddes and Miklowitz, 2013). The role of self-management is an important theme in psychosocial therapy, encouraging patients to take increased responsibility for their health through learning about the illness itself and developing the skills to recognise and control symptoms.

1.1.4 Overview of pathophysiological mechanisms

Early biological theories concerning the pathophysiology of bipolar disorder (BD), focused on the dysfunction of several neurotransmitter systems. Such studies have implicated abnormalities in monaminergic systems such as, dopaminergic, noradrenergic and serotonergic systems, with much of this research driven by the discovery of effective pharmacologic treatments for depression and mania that were shown to alter central amine function in animals (Goodwin and Jamison, 2007). There has also been some evidence for reduced GABAergic activity from post-mortem studies (Benes and Berretta, 2001; Knable et al., 2004; Torrey et al., 2005). Moreover, altered platelet GABA and glutamate uptake was found to be correlated with severity of depression and mania, respectively (Daniele et al., 2012). Despite evidence suggesting the involvement of these circuits, the precise pathophysiology of BD is yet to be identified. In addition, abnormalities of endocrine function, including the hypothalamic-pituitary-axis (HPA), have been reported in patients with mood disorders. For example, there is consistent evidence for elevated cortisol and

corticotrophin releasing hormone (CRH) levels, as well as hypofunction of the glucocorticoid receptor (GR) in patients with major depression (Zunszain et al., 2011). Moreover, it is hypothesised that manic episodes may be preceded by increased adrenocorticotropic hormone (ACTH) and cortisol levels, leading to cognitive and functional impairments (Daban et al., 2005).

Neurophysical abnormalities have also been implicated in BD, for example in the anterior cingulate, hippocampus and amygdala, all of which are involved in the regulation of mood and cognition in humans (Drevets et al., 2008). However, because of limitations in sample sizes and cross-sectional study designs, as well as possible confounding by clinical status and medication effects, it is unknown whether the structural brain changes reported are a result of abnormal development, the disease process itself, or consequences of drug exposure.

Although our understanding of the underlying pathogenesis of BD is limited, a strong body of evidence suggests a substantial contribution of genetic factors in the susceptibility to the disorder. Classic genetic epidemiology in the form of family, twin and adoption studies over the past several decades have provided a wealth of evidence suggesting that BD is a highly heritable disorder. For example, family studies have demonstrated that BD has a tendency to run in families and a meta-analysis of family studies based on more than 6000 first-degree relatives of bipolar probands revealed a weighted summary morbid risk estimate for BD of 8.7% (Smoller and Finn, 2003). Moreover, in a classic family study by Gershon et al. (1982), first-degree relatives of probands with bipolar I disorder (BDI) had similar risks of BDI (4.5%) and bipolar II disorder (BDII) (4.1%), compared to relatives of controls. They also reported that relatives of probands with BDII had increased rates of both BDI (2.6%) and BDII (4.5%).

Evidence from twin studies suggests that the familial aggregation demonstrated by family studies is largely due to genetic factors. Twin studies compare concordance rates of a disorder between monozygotic (MZ) twins, who are genetically identical, with dizygotic twins (DZ), who share approximately half of their genetic material in common. Assuming an equal shared environment (including environmental risk factors for bipolar disorder), any reported differences in the concordance rates for BD between MZ and DZ twin pairs are likely due to the genetic similarity of MZ over DZ

twins. Studies have consistently demonstrated significantly increased concordance rates in MZ compared with DZ twins (Allen et al., 1974; Bertelsen et al., 1977; Cardno et al., 1999; Kendler et al., 1993; Kringlen, 1967; Torgersen, 1986), thus implicating the role of a genetic component in susceptibility to BD. For example, a study by McGuffin et al. (2003) involving 30 monozygotic and 37 dizygotic twin pairs reported a probandwise concordance rate of 67% in MZ twins compared to 19% in DZ twins. Data from twin studies allows for the calculation of heritability: (concordance rate in MZ twins – concordance rate in DZ twins) divided by (100 – concordance rate in DZ twins) (Goodwin and Jamison, 2007). Heritability for BD is estimated to be between 60-85% (Smoller and Finn, 2003). Therefore, whilst it is well established that genetic factors are important in the aetiology of BD, given that heritability estimates do not reach 100%, this suggests that environmental factors may play an important role in contributing to disease susceptibility. For example, the literature is fairly consistent in suggesting that individuals with BD experience increased stressful events prior to onset or subsequent episodes of their disorder (Hosang et al., 2010; Johnson and Roberts, 1995). In addition, it has been shown that adverse childhood life events may increase susceptibility to onset of BD (Fisher and Hosang, 2010) and that early parental loss in particular may be associated with an increased risk for BD in later life (Tsuchiya et al., 2005).

Adoption studies can help to separate the genetic and environmental contributions in the aetiology of a disorder by comparing rates of the disorder in question between offspring of a set of biological parents raised from infancy by unrelated foster parents. Understandably, because of the logistical difficulty in the availability and recruitment of such subjects, only two adoption studies of BD can be found in the literature (Mendlewicz and Rainer, 1977; Wender et al., 1986). Both studies found a greater risk of affective disorder in the bipolar parents of bipolar adoptive relatives, however this was not found to be significantly increased in the study conducted by Wender and colleagues. It is argued that this may be explained by the small sample size involved (based on 10 bipolar probands) likely resulting in a lack of statistical power.

The genetic aetiology of BD is complex, and therefore rather than following a Mendelian mode of inheritance, it is posited that many risk variants, each conferring a small risk, interact to increase risk of the disorder (Craddock and Jones, 1999). Thus, over the past two decades research has focused on identifying susceptibility genes that confer risk for BD. Initial efforts to identify variants associated with BD were made through the use of linkage studies. Linkage studies examine genetic markers spread across the genome to determine chromosomal regions that harbor susceptibility genes, by examining those markers that are co-inherited with disease within biological family members (with more than one affected member). Linkage studies require no prior knowledge of disease pathophysiology, and so were an attractive early method for the study of BD (and psychiatric illness more widely), given the relatively poor understanding of pathogenesis.

Results from a meta-analysis of seven published genome scans for BD identified susceptibility loci on 13q and 22q (Badner and Gershon, 2002). Following this, a meta-analysis of 18 studies conducted by Segurado et al., (2003) did not find genome-wide significant evidence for linkage, however, they did find modest support for regions on chromosomes; 9p22.3–21.1, 10q11.21–22.1, 14q24.1–32.12 and regions of chromosome 18. In 2004, Middleton et al., identified evidence for genome-wide significant linkage for BD in the region of 6q21-25, a region which has received genome-wide suggestive signals in three further independent samples (Dick et al., 2003; Ewald et al., 2002; Lambert et al., 2005). Moreover, this region again showed genome-wide significance in a collaborative analysis of 11 bipolar linkage studies (McQueen et al., 2005). Although several susceptibility regions have been implicated, the limited success of linkage studies to accurately and consistently identify risk loci for BD suggests that genes that confer a relatively large effect on disease risk are not major contributors to the genetic aetiology of BD. Following the limited success of linkage studies, focus shifted to the search for susceptibility genes according to the 'common disease-common variant' (CDCV) model, in which several common variants are thought to confer a small risk and interact to give rise to the disorder (Barnett and Smoller, 2009).

In a candidate gene approach, early association studies focused on serotonin, dopamine, and noradrenaline neurotransmitter systems, based on their involvement in the pharmacological treatment of BD. Several studies investigated genes encoding monoamine oxidase A (MAOA) (Preisig et al., 2000), catechol-O-methyltransferase (COMT) (Jones and Craddock 2001), and the serotonin transporter (5HTT) (Anguelova et al., 2003; Lasky-Su et al., 2005). However, none provided robust support for any of these genes. Genes involved in circadian rhythms have also been a focus of candidate association studies, based on the suggestion that abnormalities of circadian rhythms underlie certain aspects of BD (Harvey, 2008). For example, it has long been known that deprivation of sleep can have both antidepressant qualities (Wehr et al., 1982), and mania-inducing effects (Colombo et al., 1999). Such efforts have yielded inconsistent findings (Benedetti et al., 2003; Mansour et al., 2006; Serretti et al., 2005; Shi et al., 2008) and none have been reliably established as susceptibility genes for BD. A number of studies have also assessed the potential involvement of schizophrenia risk genes in BD, given the clinical and proposed genetic overlap between the two disorders. Initial research provided evidence for the involvement of a number of schizophrenia implicated genes in BD, including; disrupted in schizophrenia 1 (*DISC 1*), d-amino acid oxidase activator (*DAOA*, aka G72), neuregulin1 (*NRG1*), and brain-derived neurotrophic factor (*BDNF*) (Craddock et al., 2006), supporting the hypothesis of an overlap in genetic susceptibility between the two disorders.

It is perhaps the case that the limited success of candidate gene approaches reflects our inadequate understanding of the mechanisms underlying major psychiatric disorders, resulting in poorly informed candidate choices. The relatively disappointing findings from the candidate gene studies, together with major statistical and technological advances, led the way for more hypothesis-free approaches.

Genome-wide association studies (GWAS) allow for the simultaneous analysis of genetic variation across the genome, by assaying hundreds of thousands of genetic markers (single nucleotide polymorphisms, or SNPs) across groups of cases and controls, thus providing an unbiased approach to identifying potential disease associated variation (Corvin et al., 2010). Given the large number of statistical tests

performed in GWAS, this does pose a statistical challenge with regards to multiple testing, and as such a $5x10^{-8}$ threshold for significance is adopted (analogous to a Bonferroni correction of a 0.05 Type 1 error level for 1,000,000 independent tests). Because of the stringent significance threshold enforced, large numbers of cases and controls are required in order to achieve adequate statistical power to detect the small genetic effect sizes typical for human GWAS studies (Corvin et al., 2010). Since the arrival of the GWAS era, the field of bipolar genetics has flourished and has seen the identification of a number of significant risk variants for the disorder, some of which have been robustly replicated.

The first published GWAS for BD involved 1233 cases and 1439 controls (Baum et al., 2008). Using pooled genotyping they reported a genome-wide significant association with *DGKH*, an association that has not since been replicated within later larger studies. During that same year, the Welcome Trust Case Control Consortium (WTCCC) published results of a GWAS looking to identify genetic variation associated with 7 different diseases, one of which was bipolar disorder. Although they did not report any genome-wide significant findings, a region at chromosome 16 showed a strong association with BD. Within a second consortium driven GWAS based on 1461 cases and 2008 controls Sklar et al. (2008) found the strongest signal for a SNP in MY05B ($p=1.66x10^{-7}$). Within the largest collaborative effort at the time, Ferreira et al. (2008), reported results from a meta-analysis of the STEP-UCL and WTCCC GWAS studies, comprising of 4,387 cases and 6,209 controls. The result was a defining moment in the field, identifying ANK3 (ankyrin3) and *CACNA1C* (alpha 1C subunit of the L-type voltage-gated calcium channel) as BD candidate genes. *ANK3* and *CACNA1C* have been replicated in a number of studies (Lee et al., 2011; Schulze et al., 2009; Scott et al., 2009; Sklar et al., 2008; Smith et al., 2009). Both *CACNA1C* and ANK3 encode proteins that influence neuronal excitability through ion channel function, therefore raising the possibility that bipolar disorder may partly result from channelopathies.

In 2008, the Psychiatric GWAS Consortium (PGC) was established in order to facilitate high levels of data-sharing and coordinated analysis on an international level. The Psychiatric GWAS Consortium Bipolar Disorder Working Group (PGC-BD) reported on

a combined GWAS of 11,974 cases and 51,792 controls, making this the largest meta-analysis of BD GWAS to date (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). The primary analysis of 4,496 cases and 42,422 controls identified two SNPs surpassing genome-wide significance in ANK3 and *SYNE1*. When the primary dataset was combined with a further replication sample, these results fell just below genome-wide significance within a meta-analysis, however, an association was confirmed for *CACNA1C* and new evidence was provided for *ODZ4*. In addition, when a GWAS combining data from five psychiatric disorders (BD, schizophrenia, major depressive disorder, autism spectrum disorder, and attention deficit-hyperactivity disorder) was performed, four SNPs with genome-wide significance were identified (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Of these, two were within voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2*. When top SNPs previously identified from bipolar GWAS (*CACNA1C, ANK3, ODZ4*, and *SYNE1*) were assessed for their role in other disorders, all except *CACNA1C* were found to be relatively specific to BD.

More recently, evidence from a further meta-analysis involving 7,773 cases and 9,883 controls, identified a significant GWAS signal near *TRANK1*, a gene which encodes a protein that has shown responsiveness to valproic acid (Chen et al., 2013). Moreover, combining new sets of 2,266 cases and 5,028 controls, and the previously reported PCG-BD dataset (7,481 cases and 9,250 controls), Mühleisen et al. (2014), reported 56 SNPs reaching genome-wide significance at five genomic loci. Among these were the previously identified *ANK3, ODZ4* and *TRANK1* as well as two newly implicated loci, *ADCY2* at 5p15.31 (linked to a common pathway for a number of neurotransmitter systems) and another at 6q16.1 where no specific gene was identified. At the time of writing, analyses were underway in a sample approaching 20, 000 probands with BD, however results were not yet published.

Whilst GWAS have generated major breakthroughs in our understanding of the genetics of BD, and have shown that BD is a highly polygenic disorder, the majority of the genetic risk is yet to be explained. As already explained, GWAS operate on the 'common disease-common variant' model and therefore are designed only to detect

the effects of common SNPs. There is some evidence to suggest the role of rare, copy number variants in BD (Zhang et al., 2009), however, this has not been supported by others (Grozeva et al., 2010). Moreover, it has been suggested that the pathogenicity of these variants may be lower in BD than for schizophrenia (Georgieva et al., 2014). Given the dramatic drop in the cost of DNA sequencing over recent years, it is hoped that this will help to further elucidate the role of rare genetic variants in influencing susceptibility to BD.

1.1.5 Comorbidity

Comorbidity is broadly defined as the co-occurrence of two disorders within the same person (Feinstein, 1970; Scher et al., 2005). Within individuals with bipolar disorder (BD), comorbidity is common and is most likely the rule rather than the exception. The relevance of comorbid conditions is related to their impact, or potential impact, on the clinical course, outcome, choice of treatment, and management of the index disorder. If we consider the long-lasting, chronic course of bipolar disorder, the management of complex comorbid conditions must constitute an important and fundamental part of individualized treatment.

Studies have consistently reported a high rate of psychiatric and non-psychiatric comorbidity in BD. In a Stanley Foundation Bipolar Treatment Outcome Network study of 288 patients with bipolar disorder, 65% were found to meet DSM-IV criteria for at least one other psychiatric comorbidity, 42% had two or more, and 24% were reported to have three or more co-existing psychiatric disorders (McElroy et al., 2001). Comorbid conditions can further complicate the bipolar illness and may influence the course of illness and lead to poorer outcomes and prognosis. For example, Vieta et al. (2001) found that within a sample of 129 patients with bipolar I disorder, presence of psychiatric comorbidity was associated with a greater number of mixed features and depressive episodes, a greater rate of suicidal ideation and higher number of suicide attempts, and poorer social functioning and treatment compliance.

Comorbid anxiety and substance misuse disorders are among the most common psychiatric disorders in BD. Within the Systematic Treatment Enhancement Program

for Bipolar Disorder (STEP-BD), the lifetime and current prevalence of anxiety disorders was reported at 51.2% and 30.5%, respectively (Simon et al., 2004). In a further study, Simon et al. (2007) reported that anxiety disorder comorbidity (and generalized anxiety disorder in particular), was associated with increased risk for suicidal ideation and behavior in patients with BD. Additionally, in an epidemiological survey of 42,000 respondents in the US, mania and hypomania were 14 times more likely to have drug dependence, and 6 times more likely to have experienced alcohol dependence in the preceding 12 month period (Grant et al., 2004). Further epidemiological studies have reported that lifetime presence of alcohol use disorders are present among 46-58% of bipolar I disorder patients, and 19-39% of bipolar II disorder patients (Grant et al., 2005; Merikangas et al., 2007; Regier et al., 1990a).

Moreover, general medical conditions have been found to differentially effect individuals with BD (Kilbourne et al., 2004). Historically, the increased rate of medical illness observed in those with major psychiatric disorders was thought to be a consequence of pharmacologic treatment and unhealthy lifestyle choices. In particular, antipsychotics, antidepressants and mood stabilizers were shown to be associated with an increased risk of metabolic syndromes, such as diabetes and cardiovascular disease (Masand and Gupta, 2002; Nemeroff, 2003). However, a recent study by Khan et al. (2013) suggested that mortality risk was not increased in psychiatric patients that were exposed to psychotropic agents.

In a Canadian, cross-sectional population-based study, McIntyre, et al. (2006a), reported that: chronic fatigue syndrome; migraine; asthma; hypertension; and gastric ulcer were all significantly increased in those with BD. Furthermore, they observed that presence of comorbid conditions was associated with a more severe course of BD, worse functional outcomes and increased use of medical services. Similarly, in a UK study looking to assess the rate of physical illness in a large, well-defined sample of patients with a diagnosis of BD, Forty et al. (2014) reported higher rates of a number of physical health conditions when compared to control subjects. These included: asthma; diabetes type I and II; epilepsy; kidney disease; gastric ulcers; migraine; rheumatoid arthritis; stroke; and kidney disease. In addition, the authors reported that illness burden (defined as a history of three or more medical illnesses), was associated

with a lifetime history of anxiety, a rapid cycling illness pattern, suicide attempt, and an acute onset of mood episodes, when controlling for other associated factors.

It is currently unknown whether medical disorders and BD naturally occur together, whether they are a consequence of treatment or lifetime factors, or a combination of both. However, given the postulated detrimental impact on the course and prognosis of the bipolar illness, it is essential that we gain a better understanding of their relationship and that an awareness of comorbidity and its complications are considered in the management of BD as a means of improving patient outcomes. This is particularly important given that there is evidence to suggest that although individuals with major psychiatric illness appear to be differentially affected by multiple medical comorbidities, such patients receive less screening and fewer preventative interventions (Smith et al., 2013).

The specific relationship and potential overlap between BD with i) migraine, and ii) epilepsy will be discussed further within upcoming sections of this chapter.

1.1.6 Reducing heterogeneity in bipolar disorder

Bipolar disorder (BD) is an overwhelmingly heterogeneous disorder in terms of its clinical presentation, comorbidity, and pathogenesis. There exists a fundamental need to identify more meaningful subgroups within BD that may differ in clinical expression and outcome. Identification of such subgroups may provide clinical benefits, potentially facilitating more effective, targeted treatment and management options. Moreover, it is possible that clinical homogeneity reflects pathophysiological homogeneity, thus making these subgroups a potential useful focus for studies investigating the aetiology of BD.

There have been a number of attempts to reduce the heterogeneity in BD by identifying potential sub-phenotypes that may be more likely to share some common clinical and aetiological basis. These have included: polarity of onset of BD (Forty et al. 2009a); comorbid anxiety disorders, including panic disorder (Forty et al. 2009b); age at onset (Hamshere et al., 2009); and puerperal psychosis (Jones and Craddock, 2001;

Jones and Craddock, 2002). Moreover, lithium responsiveness has also been proposed as a genetically valid subtype of BD (Turecki et al., 2001).

It is proposed that comorbid conditions within BD may offer a further opportunity to increase homogeneity of the disorder. Specifically, this thesis will explore the relationship between BD and the neurological conditions of migraine, and epilepsy, as a means of distinguishing more homogenous subgroups of patients with BD. Subsequent sections within this introductory chapter (Section 1.2 and 1.3) will introduce the topics of migraine and epilepsy, as well as reviewing the evidence for overlap between these disorders and BD.

1.2 Introduction to migraine

Migraine is a chronic, paroxysmal neurological condition, characterised by severe, recurrent and stereotyped headaches. Migraine has a devastating effect on well-being and general functioning, which often lingers following the acute attack and is rated by the World Health Organisation (WHO) as being among the most disabling chronic disorders (Menken et al., 2000). Furthermore, migraine is estimated to be the most costly neurological disorder in Europe (Andlin-Sobocki et al., 2005). Migraine is among the most under-diagnosed and under-treated neurological conditions, with more than half of migraine sufferers not seeking medical care for their headaches (Lipton et al. 2002). For those seeking medical care, the majority of health care for migraine patients is provided in the primary care setting, with only 10-15% of migraineurs seen by neurologists and 4% seen by headache specialists (Lipton et al., 2002).

In 1988, the Headache Classification Committee of the International Headache Society (IHS), published the first internationally accepted headache classification system; The International Classification of Headache Disorders (ICHD), 1st Edition. This classification system allowed for the standardisation of headache diagnosis and although imperfect, these criteria are utilised by researchers and clinicians alike to aid headache disorder diagnosis. The criteria were revised in 2004 (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004) to offer

increased clarity for headache diagnosis by building on the successes of the first edition. Within the classification system (ICHD-II), headaches are differentiated into primary and secondary categories (**see Table 1.1**), where secondary headache disorders are described as those having an identifiable underlying cause such as a brain tumour or infection. In contrast 'primary' refers to a lack of clear underlying causative pathology, trauma or systemic disease. Primary headaches are the most common of the headache disorders and the classification for primary headache is split into four sections: migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias, and other primary headaches.

Table 1.1 International Headache Society classification of primary and secondary headache disorders (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004)

The Primary Headaches
1. Migraine
2. Tension-type headache
3. Cluster headache and other trigeminal autonomic cephalalgias
4. Other primary headaches
The Secondary headaches
5. Headache attributed to head and/or neck trauma
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
12. Headache attributed to psychiatric disorder

Migraine is considered the most burdensome of the primary headache disorders, with considerable impact on both the sufferer and wider society, thus rendering migraine an important public health issue. ICHD-II distinguishes two main types of attack: migraine without aura (MoA), previously referred to as 'common migraine' and migraine with aura (MA), also known as 'classic migraine'. Migraine without aura (MoA) is a clinical syndrome characterised by headache with specific features and associated symptoms. Within an attack of MoA, individuals experience head pain that is: throbbing; unilateral; aggravated by movement; and is severe enough to inhibit or prohibit daily activity. Moreover, migraine without aura (MoA) is associated with nausea, and/or photophobia and phonophobia.

Migraine with aura (MA) is characterised, primarily, by focal neurological aura consisting of fully reversible visual, sensory or language symptoms that either precede or accompany the headache attack and occurs in approximately a third of migraine patients. Visual symptoms can include both positive (i.e. flickering lights, spots or lines) and/or negative features (loss of vision). Similarly, sensory aura can manifest as

positive symptoms in the form of pins and needles, and negative symptoms in the form of numbness. Those experiencing aphasic symptoms may have difficulty thinking logically, finding words or making sentences and suffering from slurred speech. These symptoms are classically transient; their onset is gradual and they persist for no longer than one hour. However, on rare occasions they may persist for days or months. There may also be a symptom-free period of up to one hour before the contralateral headache pain commences. Within MA, individuals may experience more severe neurological symptoms, including hemiparesis. When such motor weakness is experienced as part of the aura spectrum, this is referred to as hemiplegic migraine, of which there are recognised familial and sporadic forms.

In 1996, Russell and Olesen reported a nosological analysis of migraine aura as experienced by 163 patients drawn from a general population sample of 4000 Danish citizens. They observed visual aura to be, overwhelmingly, the most common aura symptom (occurring in 99% of cases), followed by sensory (31%) and aphasic (18%) and motor auras (6%). **Tables 1.2 and 1.3** summarise ICHD-II criteria for MoA and MA.

There is much debate as to whether MA and MoA are part of the same disorder or whether they should be considered as two separate disorders. A common argument for the hypothesis of a single disorder comes from the observation that both types of attack can occur within the same individual; for example, 13% of migraineurs are reported to have attacks of both MoA and MA (Launer et al., 1999). Moreover, the finding that MA and MoA are frequently found within the same family (Ophoff et al., 1994) is often cited as evidence of a shared aetiology between the subtypes. This was supported by Nyholt et al., (2004) who did not find evidence of an aetiological distinction between MA and MoA using latent class analysis to study migraine symptomatology in an Australian twin population (n=6,265). In contrast, reports of clinical differences between the two forms in terms of; duration of the attack, age at onset and resolution, and the frequency and pattern of attacks (Manzoni and Torelli, 2008), argue for the separation of migraine with and without aura. Moreover, Russell and Olesen, (1995) revealed differences in familial patterns of MA and MoA, identifying a greater genetic component for MA and thus providing support for a distinct pathogenic basis.

Table 1.2 Migraine without aura (MoA) criteria defined by the International Headache Society (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004)

Migraine without aura (MoA)
A. At least five attacks fulfilling B-D
B. Attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. At least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache accompanied by at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E. Not attributed to another disorder

Table 1.3 Migraine with aura (MA) criteria defined by the International Headache Society (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004)

Migraine with aura (MA)
A. At least two attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness: 1. Fully reversible visual symptoms, including positive features (e.g., flickering lights, spots or lines) and/or negative features (e.g., loss of vision) 2. Fully reversible sensory symptoms, including positive features (e.g., pins and needles) and/or negative features (e.g., numbness) 3. Fully reversible dysphasic speech disturbances
C. At least two of the following: 1. Homonymous visual symptoms and/or unilateral sensory symptoms 2. At least one aura symptom develops gradually over ≥ 5 min and/or different aura symptoms occur in succession ≥ 5 min 3. Each symptom lasts ≥ 5 and ≤ 60 min
D. Headache fulfilling criteria B-D for *migraine without aura* begins during the aura or follows the aura within 60 min
E. Not attributed to another disorder

It is possible for many headache sufferers to experience migraine-like headaches that do not necessarily meet strict IHS criteria for migraine with or without aura (Russell

and Olesen, 1996). The first edition of the IHS classification (ICHD-I) acknowledged this occurrence of headache attack, coining the term 'migrainous disorder'; a syndrome categorised by all but one of the full migraine diagnostic criteria. Once published, this category was met with criticism from clinicians, who believed such patients should be considered as genuine migraine sufferers. Later research by (Michel et al., 1993) revealed that although the IHS criteria for migraine had excellent specificity, sensitivity was low (<50%), thus indicating that the diagnostic criteria for migraine may perhaps be too restrictive. In similar vein, Rains et al. (2001) reported that of patients presenting to an outpatient headache clinic, 36% were given a diagnosis of 'migrainous disorder'. The validity of this category was questioned due to its exclusion of patients presenting with a symptom pattern so close to that of migraine from the diagnosis of migraine. In light of this criticism, the second edition of the International Classification of Headache Disorders (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004) acknowledged this category of headache sufferers as being an integral part of migraine, introducing the new subtype of 'probable migraine'.

The American Migraine Prevalence and Prevention study (AMPP) (Silberstein et al., 2007) reported probable migraine to be a frequent, undertreated and disabling condition with an epidemiologic profile similar to that of strict migraine. Moreover, Henry et al. (2002) found probable migraine to be more prevalent than strict migraine in a French population study of 10,585 subjects aged 15 years and older (9.1% vs. 7.9%, respectively). Lantéri-Minet et al. (2005) noted the criterion most frequently missing in patients with probable migraine was typical headache duration (4–72 h), with the majority of patients having shorter average headache duration.

Knowledge of migraine epidemiology has increased dramatically over the past two decades, with much of this said to have been driven by the emergence of standardised diagnostic criteria for migraine, the International Headache Society (IHS) classification of 1988 (ICHD-I; Headache Classification Committee of the International Headache Society, 1988) and 2004 (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004). There currently exists no objective marker or diagnostic test for migraine, thus the epidemiological study of migraine has relied

heavily on case definition of migraine. A meta-analysis of 24 studies, only five of which employed IHS classification criteria (ICHD-I; Headache Classification Committee of the International Headache Society, 1988), revealed that case definition accounted for the largest portion of variation in migraine prevalence among studies (36%), followed by gender distribution of the study sample (14.5%) (Stewart et al., 1995). A second meta-analysis attempted to eliminate two of the largest sources of variation by including 18 population-based studies, all of which had utilised IHS criteria and by conducting separate meta-analyses for men and women (Scher et al., 1999). Following standardisation of case definition, a substantial proportion of variation in prevalence was explained by very few factors, such as age and geographic location of the study population. Some of the variation, however, remained unexplained with the authors postulating that socioeconomic status, cultural differences in symptom reporting or other unmeasured factors may explain part of the residual variance in migraine prevalence. Thus, introduction and adoption of IHS classification for migraine has helped to clarify our understanding of the scope of the public health problem posed by migraine.

The American Migraine Study conducted in 1989 (Stewart et al., 1992) and the American Migraine Study II conducted in 1999 (Lipton et al., 2001) looked to describe the prevalence, sociodemographic profile, and burden of migraine in the United States. Another key objective of the AMS II was to make comparisons with the first study to assess changes in the epidemiology of migraine over time. Within the AMS II, a validated, self-report questionnaire was disseminated to 20, 000 households to identify IHS-based migraine in individuals aged 12 years and above. Of 43,527 eligible individuals, 29,727 responded to the questionnaire, providing a response rate of 68.3%. The 1-year prevalence of migraine in the United States was reported to be 13%; 18.2% in females and 6.5% in males and it was noted that 23% of respondent households had at least one member with migraine. These estimates were very similar to the 11.7%, 17.6% and 5.7% (respectively) results reported in the original and methodologically identical American Migraine Study, conducted ten years previously. Such findings suggested that within the United States, migraine prevalence had remained stable over time. This finding was in contrast to the results of the National Health Interview Survey data that reported a 60% increase in migraine prevalence in

the United States between 1980 and 1989 (Lipton et al., 2001). However, the measure of self-reported migraine within the survey data was not validated against IHS diagnostic criteria. Rather, migraine was defined by asking the following; "During the past 12 months, did anyone in the family have a migraine headache?" Thus, using this case definition, the increase in proposed prevalence of migraine may in fact be reflecting changes in the awareness of migraine over time.

Interestingly and reassuringly, the rate of migraine sufferers that had received a medical diagnosis of migraine had increased from 38% in 1989 to 48% in 1999. Despite these improvements, it is notable that approximately half of migraine sufferers never receive a diagnosis of migraine (Lipton et al., 2001). Such findings may be explained by the proportion of migraine sufferers seeking medical care for their headaches. In the original American Migraine Study, 16% of migraineurs were currently visiting a physician for headache, 50% had previously seen a physician but had lapsed from care and 34% had never seen a physician for headache. When the study was repeated in 1999, they found that the percentage of individuals currently seeing a physician had tripled to 47%, the percentage of those who had lapsed from care had declined by more than half to 21%, and the percentage of those who had never visited a physician had remained approximately the same at 32%. The increase in the rate of migraine sufferers currently seeking medical care is encouraging. However, with figures from the most recent study suggesting that more than half of sufferers are not seeking care (21% of those who had lapsed and 32% of those never seeking care), it is clear that migraine remains under-diagnosed and under-treated.

Migraine prevalence in European populations has also been reported. As part of the Eurolight project; a project supported by the EC Public Health Executive Agency, Stovner and Andree (2010) aimed to provide an update on headache epidemiology as a preparation for the multinational European study on the prevalence and burden of headache. Across 33 studies of migraine prevalence in selected European countries (Austria, France, Germany, Italy, Lithuania, Netherlands, Spain, UK, Ireland and Luxembourg), the mean prevalence of current (in the last year or less) migraine among 170,000 adults was 14.7% (8% in men and 17.6% in females), similar to the 1-year prevalence rates reported in the American Migraine Studies. Additionally, Steiner et

al. (2003) reported estimates of 1-year prevalence of migraine in the UK by surveying a representative sample of the population of mainland England. Steiner and colleagues conducted a telephone survey of a random sample (n=4007) of those aged 16-65 years using a previously validated diagnostic interview. They revealed a response rate of 76.5% and reported an overall 1-year prevalence rate of migraine of 7.6% for males and 18.3% of females.

Migraine prevalence follows an inverted-U curve with increasing age, commonly arising during adolescence and young adulthood. Prevalence peaks in mid-life and declines thereafter (Lipton et al., 1999). Overall, prevalence is highest between the ages of 25-55 years, the peak years of economic productivity, which may explain the significant socioeconomic impact of migraine. The gap between peak incidence of migraine in adolescence and peak prevalence in middle life highlights the long duration of the condition.

Women are particularly prone to migraine headaches, with a sex ratio for lifetime migraine being two to threefold greater among women, a finding consistent across countries (Low et al., 2007). However, the lifetime pattern of sex differences in migraine does appear to vary with age. Prior to puberty, prevalence of migraine in males is found to be equal to or greater than that reported in females. During and following adolescence, however, prevalence and incidence of migraine increases more rapidly among women. This increased prevalence continues until its peak in the fortieth and fiftieth decades and subsequently declines thereafter. The female preponderance of migraine has previously been explained, in part, by hormonal changes and more specifically, with falling levels or withdrawal of oestrogen (Lichten et al., 1996; Whitty et al., 1966).

Research has suggested that migraine is associated with various psychiatric conditions, including BD, major depression and anxiety spectrum disorders (Antonaci et al., 2011). For example, a large UK study conducted by Samaan et al. (2009), looked to compare the rate of IHS-defined migraine between 1259 individuals with recurrent depression and 851 psychiatrically healthy controls, and found migraine to be more prevalent in cases than in controls (15% vs. 5.1%, respectively). Moreover, Baptista et al. (2012) looked to describe the prevalence of migraine in a clinical sample of

psychiatric patients compared to the general population of Venezuela. The authors reported an increased rate of migraine within a clinical sample of individuals with depression and dysthymia (n=82) (24.5%), and BD (n=191) (15.7%), compared to the general population (n=516) (14.9%). Baptista et al., (2012) also reported that the rate of migraine in a sample of 132 participants with schizophrenia was significantly lower than that reported in the general population (8.3% vs. 14.9%, p=.008). Rates of IHS-defined migraine were reported to be even higher in a clinical sample of 62 inpatients with major affective disorders in a study conducted by Fasmer (2001), who reported migraine to be common in both those with unipolar depression (46%) and BD (44%). In addition, within their large study exploring the rates of a number of medical illnesses in patients with BD (n=1720), major depressive disorder (n=1737) and psychiatrically healthy controls (n=1340), Forty et al. (2014) reported increased rates of migraine in those with BD (23.7%) and major depression (21.9%) compared to controls (16.5%). Whilst these increased rates were found to be significantly increased in the BD group only, migraine was noted as being the most prevalent medical condition in those with major depressive disorder.

The risk of suicide may also be increased in individuals with migraine (Arciniegas and Anderson, 2002; Breslau, 1992). The presence of psychiatric comorbidity in migraine patients has been identified as a risk factor for the transformation of migraine into a chronic form (Lipton, 2009). Moreover, migraine with psychiatric comorbidity is associated with increased use of healthcare resources. Therefore, identifying these comorbidities may result in improved patient management and provide the opportunity for individualized treatment targeted at both conditions. The next section of this chapter will explore both the clinical and aetiological evidence for overlap between migraine and BD.

1.2.1 Evidence of overlap between migraine and bipolar disorder

1.2.1.1 Clinical and epidemiological studies

As discussed above, an association between migraine and affective disorder has long been recognised, with a wealth of clinical and genetic studies supporting a

bidirectional association between unipolar depression and migraine (Bruti et al., 2012). Although much of the research within this field traditionally focused on the study of unipolar depression, there has been an emerging body of evidence suggesting that individuals with bipolar disorder (BD) may also be disproportionately affected by migraine.

In a cross-sectional study involving 62 Norwegian outpatients, Fasmer (2001) looked to investigate the prevalence of migraine (diagnosed according to International Headache Society criteria) in patients with major affective disorders. Migraine was found to be common in both those with major depressive disorder (MDD) (46%), and BD (44%). Moreover, within patients with BD, rates of migraine were found to be significantly increased in those with bipolar II disorder (BDII) compared to those with bipolar I disorder (BDI) (77% vs. 14%, respectively). Whilst rates of migraine were found to be similar amongst those with MDD and BD, a later study by Dilsaver et al. (2009) in a group of Latino adults with affective disorders (87 with BD and 123 with MDD) revealed that patients with BD were 2.9 times more likely to have migraine than those with MDD, suggesting that migraine may be more strongly associated with bipolarity. In that same year, Dilsaver et al. (2009) reported that a family history of BD (and not MDD) was associated with an increased risk of having migraine headaches, regardless of the patient's diagnosis of BD or MDD.

A number of studies have reported prevalence rates of migraine among individuals with BD to be approximately 25%. For example, Mahmood et al. (1999) reported a lifetime prevalence of International Headache Society (IHS)-defined migraine of 25.9% (27% among BD women, 25% among BD men), based on their clinical sample of 117 bipolar patients attending a psychiatric outpatient unit. It is important to note, however, the 69% response rate of their mail in questionnaire. Whilst this is considered an excellent response rate within a psychiatric population, it is possible that a response bias exists potentially leading to an over or under-estimation of migraine prevalence. However, it is important to note that similar rates of migraine were also observed within Ortiz et al's. (2010) community-based study of 323 individuals with BD. They described a migraine prevalence of 24.5%, and found a higher prevalence of migraine among those with BDII compared to those with BDI (34.8% vs. 19.1%, p=.003).

Moreover, they reported that of the 79 subjects with comorbid migraine, 73% had migraine with aura (n=58, 17.9% of total sample), two times higher than that reported in the general population (Russell and Olesen, 1996).

Using data derived from the Canadian Community Health Survey, McIntyre et al. (2006b) identified 2.4% of the sample as screening positively for BD, and of these, 24.8% had received a diagnosis of migraine from a physician. Moreover, this was found to be significantly higher than the 10.3% of physician-diagnosed migraine observed in the general population. The sex-specific prevalence for bipolar subjects was 14.9% for males and 34.7% for females; more than twice that of the rate of physician-diagnosed migraine among males and females without BD (5.8% and 14.7%, respectively. Using data drawn from the Bipolar Disorder Research Network (BDRN); the same participant cohort that is reported on in the current thesis, Forty et al. (2014) also explored the rate of doctor or health professional-diagnosed migraine within their study of general medical comorbidity within BD. Forty and colleagues reported a migraine prevalence of 23.7% which was statistically significantly higher than the 16.5% prevalence identified within a control group. The reliance on a doctor diagnosis for the identification of migraine in the above two studies may have resulted in an underestimation of migraine, given that, as already discussed, more than half of migraine suffers do not seek medical care for their headaches.

Low et al. (2003) reported one of the highest rates of migraine within a sample of 108 individuals with BD, identifying a lifetime prevalence of 39.8%, with an overall migraine rate of 64.7% in a subgroup of patients with BDII (11 of 17). However, it is important to note that this finding was based on a clinical sample, where subjects were currently receiving treatment in an outpatient psychiatric unit, and so may not be generalizable to community settings. Moreover, the clinical population sampled within this study may have given rise to inflated rates of migraine due to the increased risk of Berkson's bias, whereby individuals reporting a diagnosis of one disorder are more likely to report a diagnosis of (or be diagnosed with) other disorders because of their more frequent contact with health professionals (Berkson, 1946). In addition, the overrepresentation of women in the sample (67.6%), and the fact that the mean age

of the sample matched the peak age of migraine noted with within the general population (approximately 40 years), may explain the high rate of migraine reported.

A recent meta-analysis pooling data from 14 studies, encompassing 3976 individuals with BD (mean age 35.5 years, SD 7.6, 71% female), established an overall prevalence of migraine of 34.8% (95%CI: 25.54–44.69) (Fornaro and Stubbs 2015). Moreover, as suggested by the literature, the meta-analysis corroborated the finding that individuals with BDII may be particularly susceptible to migraine, reporting a higher prevalence of migraine among those with BDII (54.17%, 95% CI: 31.52–75.95) compared to BDI (32.7%, 95% CI: 18.16–49.19, p<.0001). However, Fornaro and Stubbs (2015) made a point of emphasizing the inconsistency across studies in their definition of BDII, with some broadening the criteria to include those with affective temperaments. The meta-analytic study also established higher rates of migraine in BD within studies identifying migraine using standardised criteria (e.g. International Headache Society) compared to non-standardised criteria/self-report measures (47.9% vs. 20%, p=.0001), emphasizing the importance of using recognised criteria in order to maximise sensitivity.

Studies have also revealed differences in the clinical course of the bipolar illness in BD patients according to the presence or absence of migraine. A summary of key studies exploring the impact of migraine in a bipolar sample can be found in **Table 1.4**. Within Mahmood et al's. (1999) study, mentioned above, an association was found for an earlier onset of BD and comorbidity with migraine. An earlier age of onset has been associated with a more severe course and poor outcomes in BD (Post et al., 2010), suggesting that comorbid migraine in BD may be associated with a more severe illness course. A younger age of onset of BD with comorbid migraine was also reported by McIntyre et al. (2006b), however, this finding was true for bipolar males only. Within this study, bipolar males were also more likely to have a higher lifetime prevalence of comorbid anxiety disorders, and to utilize primary and mental health services. When bipolar females with migraine were compared to bipolar females without migraine, they were not found to significantly differ on these variables however they did experience more comorbid medical disorders, and were more likely to require help with personal or instrumental activities of daily living. The sex-specific implications of

the BD-migraine comorbidity identified in this study suggest more serious implications for males with BD than females.

Within their 2003 study of the sociodemographic and clinical characteristics associated with migraine in BD, Low et al. (2003) found that bipolar subjects with migraine: were younger; were more educated; were more likely to be employed or studying; had fewer psychiatric admissions; and were more likely to have a family history of migraine, and psychiatric disorders. Low et al. (2003) also reported that bipolar subjects with comorbid migraine were more likely to have had an index episode of depression and to have been treated with an antidepressant. These findings, combined with the previously mentioned higher rate of migraine among subjects with BDII in this study, suggest that bipolar subjects with comorbid migraine may be more vulnerable to the 'depressions' of bipolarity. This hypothesis is further supported by a more recent study by Brietzke et al. (2012b) who found that in a group of 339 subjects with bipolar disorder, those with comorbid migraine experienced more mood episodes, particularly those of depressive polarity.

In an attempt to identify factors and outcomes associated with migraine in BD, Saunders et al. (2014) explored clinical correlates associated with self-reported doctor-diagnosed migraine in 412 individuals with BD. Female sex increased the odds of migraine (OR: 3.5, 95% CI: 2.1-5.8), as did a BDII diagnosis (OR: 2.1, 95% CI: 1.2-3.6), and a history of mixed symptoms (OR: 2.0, 95% CI: 1.3-3.0). Comorbid migraine was also correlated with a greater number of episodes of depression reported at baseline ($r=0.26$, $p<.001$). Psychosocial factors including emotional and sexual abuse were also found to be correlated with migraine in the bipolar sample. Saunders et al. (2014) identified gender differences in the clinical correlates of migraine in BD. They reported that in bipolar men, comorbid migraine was associated with; BDII (OR: 4.2, 95% CI: 1.4-12.4), rapid cycling (OR: 3.5, 95% CI: 1.4-8.8), and more depressive symptoms ($r=0.29$, $p=.02$). Conversely, these associations were not observed in bipolar women with comorbid migraine.

In another study based on a sample of individuals from the Bipolar Disorder Research Network (BDRN), Gordon-Smith et al. (2015), also identified rapid cycling as a feature of BD and comorbid migraine, supporting the finding observed in males only in the

above study (Saunders et al., 2004). In their large study of 1488 individuals with BD, Gordon-Smith et al. (2015) reported that those with comorbid migraine (n=375) were nearly twice as likely to have a rapid cycling illness course. In addition, authors reported that being female (OR: 2.099, 95% CI: 1.254-3.515, p=0.005), having a rapid cycling illness course (OR: 1.888, 95% CI: 1.251-2.848, p=0.002), and a history of panic attacks (OR: 1.842, 95% CI: 1.221-2.779 p=0.004) best predicted the presence of comorbid migraine in a multivariate model.

In the study by Ortiz et al. (2010) introduced above, the authors looked to further evaluate the relationship between migraine and psychiatric disorders by conducting two studies. The first examined clinical and demographic characteristics of BD patients with respect to their migraine status, with the second exploring psychiatric correlates in a sample of migraine patients. The first study included 323 subjects with BD (n=204 with BDI; n=92 with BDII; and n=27 with bipolar spectrum disorders; bipolar not otherwise specified, or schizoaffective disorder bipolar type). Migraine comorbidity within BD was associated with higher rates of suicidal behavior, social phobia, panic disorder and generalized anxiety disorder. Within their second study of 102 individuals with migraine, Ortiz et al. (2010) identified a 34.4% prevalence of current psychiatric diagnosis, increasing to 73.5% for lifetime psychiatric diagnosis. A wide range of psychopathology was reported by migraine sufferers, particularly mood and anxiety disorders. The authors described an increased frequency in the lifetime prevalence of BD in migraine subjects compared to that reported in the general population (7.8% for BDII, and 4.9% for BDI). Given that increased rates of migraine are reported in BD, and that there is evidence to suggest that rates of BD are increased in individuals with migraine, this suggests the potential for a bidirectional relationship between migraine and BD, which raises the possibility of a common predisposition to both disorders. Moreover, this study also commented on the temporal relationship between migraine and psychiatric disorders, noting that a diagnosis of migraine preceded psychiatric diagnosis in 78.6% of cases (n=59), whereas a prior psychiatric diagnosis was found in only 14.6%, with the remaining 6.7% of diagnoses made within the same year.

In a large Canadian nationally representative (n=26,984) population-based study, Nguyen and Low (2012) examined the association of migraine with different combinations of mood episodes (manic episodes alone; depressive episodes alone; manic and depressive episodes; controls with no lifetime history of mood episodes), as well as exploring sociodemographic and clinical correlates of migraine for each migraine–mood episode combination. Compared to the control group who had no history of mood episodes, the adjusted odds ratio of having migraine was 2.0 (95% CI = 1.4–2.8) for manic episodes alone, 1.9 (95% CI = 1.6–2.1) for depressive episodes alone, and 3.0 (95% CI = 2.3–3.9) for subjects with both manic and depressive episodes. Moreover, when compared to those subjects with; i) manic episodes alone, and ii) depressive episodes alone, the odds of having migraine were significantly increased in subjects with both manic and depressive episodes (OR 1.5 vs. manic episodes alone; 1.8 vs. depressive episodes alone). When focusing on the clinical correlates associated with migraine within each mood combination, migraine comorbidity was associated with an earlier age of onset of psychiatric illness in subjects with both manic and depressive episodes, whereas in those with either manic or depressive episodes alone, migraine comorbidity was associated with increased suicidality and anxiety. Such differences in the clinical correlates associated with migraine emphasize the importance of considering the specific mood episodes experienced when examining this comorbid relationship.

Table 1.4 Summary of key clinical studies exploring the relationship between comorbid migraine and bipolar disorder

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
Mahmood et al. (1999)	To estimate the prevalence of migraine in people suffering from bipolar disorder (BD)	Cross-sectional. Self-report questionnaire incorporating IHS criteria for migraine mailed to 117 individuals with bipolar disorder attending a psychiatric hospital.	21 (25.9%) of BD patients met IHS criteria for migraine (27% in BD women and 25% in BD men). 57% (12/21)) of BD patients with migraine had their first mood episode before the age of 25 years compared to 36% (16/44) of BD patients without migraine.	Migraine is increased in patients with BD compared to those within the general population and may indicate a more severe variant of BD.	Unrepresentative clinical sample. Relatively small sample size. 69% response rate, therefore there is a possibility a response bias exists. Self-report measure of migraine.
McIntyre et al. (2006b)	To report on the prevalence of comorbid migraine in BD and examine the implications for bipolar age of onset, psychiatric comorbidity, illness course,	Cross-sectional, population-based survey from the Canadian Community Health Survey – Mental Health and Well-Being (CCHS) (n=36,984).	2.4% of the sample met criteria for bipolar I disorder. Migraine prevalence was significantly greater in those with BD compared to those in the general population (24.8% vs. 10.3%). The sex-specific prevalence of comorbid	Migraine differentially affects people with BD in the general population and may have more serious implications for males with BD than females with BD.	Self-report measure of BD and migraine. Doctor diagnosis of migraine (did not adhere to IHS criteria for

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
	functional outcome, and medical service utilization.		migraine in BD was 14.9% for males and 34.7% for females. Bipolar males with migraine had greater psychosocial impairment, reported an earlier age of onset of bipolar disorder, and had a higher lifetime prevalence of comorbid anxiety disorders. Bipolar females with comorbid migraine had more comorbid medical disorders and were more likely to require help with daily living compared to BD females without migraine.		migraine diagnosis). Assessed individuals with bipolar I disorder only. Analysis was conducted post-hoc
Low et al. (2003)	To investigate the prevalence, clinical correlates and treatment of migraine in BD.	Cross-sectional survey employing a face-to-face interview involving the completion of a questionnaire based on diagnostic criteria of the IHS to 108 patients within an outpatient psychiatric facility.	39% (n=43) BD patients met criteria for migraine (43.5% of women and 31.4% of men). Prevalence of migraine in the bipolar II disorder (BDII) group was 64.7%. 23 BD patients 53.5% of those with migraine) met criteria for migraine with aura.	BD with migraine is associated with a distinct set of clinical characteristics and may represent a subtype of BD. BD patients with migraine may suffer more from the 'depressions' of bipolarity as indicated by the	Unrepresentative nature of the clinical sample. Relatively small sample size. Overrepresentation of women in the sample (67.6%).

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
			BD patients with migraine were: younger; more likely to be educated and employed; more likely to have an index episode of depression and to be treated with antidepressants; and had fewer psychiatric admissions.	higher rate of BDII and the high proportion of patients initially presenting with depression.	Potential for recall bias.
Brietzke et al. (2012b)	To evaluate the difference in severity of clinical course between BD subjects with and without migraine.	Cross-sectional study of 339 individuals with BD. Data was collected from baseline assessments of individuals with BD, enrolled in a standardized programme of naturalistic BD follow-up, from 3 outpatient specialist treatment centers in Brazil. Presence of migraine was defined	33.9% (n=115) BD subjects had received a diagnosis of migraine from a doctor. Significantly higher rate of women in the BD with comorbid migraine group. BD subjects with comorbid migraine experienced more mood episodes, particularly those of a depressive polarity. More severe illness course in BD subjects with comorbid migraine defined by: presence of a rapid cycling illness course, number of overall mood episodes, number of depressive episodes, and lifetime number of psychiatric hospitalizations.	Comorbid migraine alters the clinical course of the bipolar illness and is a correlate of BD severity. The adequate treatment of migraine may have a beneficial long-term impact for patients who have both conditions.	Doctor diagnosis of migraine determined by self-report. Analysis was conducted post-hoc. Findings based on an unrepresentative clinical sample.

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
		according to whether the subject had a previous diagnosis from a doctor.	However, these differences were not observed after correction for multiple comparisons.		
Saunders et al. (2014)	To examine gender differences in the impact of migraine on the clinical course and outcomes in BD.	A retrospective study of 412 patients with BD (bipolar I and II disorder, schizoaffective bipolar type) and 157 healthy controls from the Pretcher Longitudinal Study of Bipolar Disorder 2005-2009. Presence of migraine was determined according to a self-reported diagnosis of migraine from a doctor.	Migraine was significantly more likely in subjects with BD compared to controls (31% vs. 6%). Female sex increased odds of migraine (OR 3.5, 95% CI 2.1-5.8), as did a bipolar II diagnosis (OR 2.1, 95% CI 1.2-3.6), and a history of mixed symptoms (OR 2.0, 95% CI 1.3-3.0). Comorbid migraine was correlated with a greater number of episodes of depression reported at baseline and psychosocial factors including emotional, and sexual abuse. In bipolar men, comorbid migraine was associated with; bipolar II disorder (OR 4.2, 95%	Migraine is highly prevalent in BD, particularly in females with BD and particularly in those with BDII. Clinicians should be encouraged to recognise migraine in BD in an attempt to improve the long-term prognosis of the disorder.	Self-report doctor diagnosis of migraine. Subjects were part of a longitudinal study and thus may not represent more severe forms of the disorder.

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
			CI 1.4-12.4), rapid cycling (OR 3.5, 95% CI 1.4-8.8), and more depressive symptoms (r=0.29, p=.02). These associations were not observed in bipolar women with comorbid migraine.		
Gordon-Smith et al. (2015)	To determine clinical characteristics associated with comorbid migraine in a large, representative, UK sample of individuals with clinically well-characterised BD.	Cross-sectional study of 1488 individuals with BD; n=1120 with BDI and n=368 with BDII History of migraine was assessed via two different methods: a) doctor diagnosis of migraine and b) self-report questionnaire designed to incorporate IHS criteria for migraine diagnosis.	25.2% (n=375) BD subjects had a diagnosis of migraine (n=118 according to the self-report questionnaire, and n=257 according to a self-reported doctor diagnosis. A multivariate model revealed that BD subjects with comorbid migraine were significantly more likely to be female (OR=2.099, p=0.005), have comorbid panic attacks (OR=1.842, p=0.004), and have a rapid cycling illness course (OR=1.888, p=0.002).	Comorbid migraine in BD may delineate a more homogenous subtype of BD with an unstable rapid cycling course. Identifying individuals with BD and comorbid migraine may be of use in a clinical setting and this subgroup could be the focus of future aetiological studies.	Migraine was assessed using self-report methods and the measurement of migraine was not consistent, with the study employing two different measures of migraine. Overrepresentation of BDI cases.
Ortiz et al. (2010)	To evaluate the relationship between migraine and psychiatric	Community-based, cross-sectional studies:	Study 1: 24.5% of the BD sample had comorbid migraine and this was significantly greater in those with BDII	There exists a bidirectional relationship between migraine and BD.	Diagnosis of migraine in study 1 was made via means of a self-

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
	disorders by conducting two related studies. The first looked to explore clinical and demographic characteristics of BD patients with respect to their migraine status. The second study examined psychiatric correlates in a sample of migraine patients.	Study 1: 323 subjects with BD (n=204 with bipolar I disorder; n=92 with bipolar II disorder; and n=27 with bipolar spectrum disorders; bipolar not otherwise specified, or schizoaffective disorder bipolar type). Diagnosis of migraine was made via a self-report standardized questionnaire following guidelines of the IHS. Study 2: 102 individuals with migraine interviewed at a specialty migraine clinic where the migraine	compared to BDI (34.8% vs. 19.1%, respectively). 73% of migraine subjects (n=58, 17.9% of total sample had migraine with aura). Migraine comorbidity within BD was associated with higher rates of; suicidal behavior, social phobia, panic disorder and generalized anxiety disorder. Study 2: 34.4% of the migraine sample had a current psychiatric diagnosis, with 73.5% having a lifetime psychiatric diagnosis. A wide range of psychopathology was reported, particularly for mood and anxiety disorders. There was an increased rate of lifetime BD migraine subjects compared to that reported in the general population (7.8% for	Migraine comorbidity in BD is associated with an increased risk of suicidal behaviour and comorbid anxiety disorders	report questionnaire. Study 2 was conducted in a clinical setting and therefore may represent more chronic and severe forms of migraine.

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
		diagnosis is based on the IHS criteria.	bipolar II disorder, and 4.9% for bipolar I disorder).		
Nguyen and Low (2012)	To examine the lifetime comorbidity and clinical correlates of migraine with different combinations of mood episodes: (1) manic episodes alone; (2) depressive episodes alone; (3) manic and depressive episodes; (4) controls with no lifetime history of mood episodes.	Cross-sectional, population-based sample from the Canadian Community Health Survey 1.2 (n = 36,984). BD was diagnosed according to DSM-IV criteria using the World Mental Health Composite International Diagnostic Interview (CIDI). Presence of migraine was indicated by the presence of a self-reported prior diagnosis from a health professional.	The lifetime prevalence of migraine in BD (groups 1 and 3 combined) was 24.3%. Compared with controls (groups 4), the odds of having migraine were 2.0 (95% CI = 1.4–2.8) for manic episodes alone, 1.9 (95% CI = 1.6–2.1) for depressive episodes alone, and 3.0 (95% CI = 2.3–3.9) for subjects with both manic and depressive episodes. When compared with those with; manic episodes alone, and depressive episodes alone, the odds of having migraine were significantly increased in subjects with both manic and depressive episodes (OR 1.5 vs. manic episodes alone; 1.8 vs. depressive episodes alone).	Migraine comorbidity in BD identifies a subset of individuals with earlier onset of affective illness and more psychiatric comorbidity and suggests that migraine may be used as an indicator of illness severity. Differences were found in the clinical correlates of migraine comorbidity depending on the specific combination of mood episodes experienced.	Migraine status was not assessed according to IHS criteria. Post-hoc retrospective design.

Study	Aims	Sample size and study design	Main results	Conclusions	Limitations
			Migraine comorbidity was associated with an earlier onset of psychiatric illness in subjects with both manic and depressive episodes (group 3), whereas in those with either manic or depressive episodes alone 9groups 1 and 2), migraine comorbidity was associated with increased suicidality and anxiety		

BD=bipolar disorder; BDI=bipolar I disorder; BDII=bipolar II disorder; IHS=International Headache Society; MA=migraine with aura.

To summarise, it can be seen from the above studies that varying rates of migraine have been reported within individuals with BD (not specifying bipolar subtype), ranging from approximately 24% to 44% (Ortiz et al., 2010; McIntyre et al., 2006b; Mahmood et al., 1999; Gordon-Smith et al., 2015; Low et al., 2003; Fasmer, 2001). A recent meta-analysis reported a pooled prevalence of migraine of 34.8% based on 14 studies and accounting for 3976 individuals with BD (Fornaro and Stubbs, 2015). A more consistent finding is the increased prevalence of migraine in individuals with BDII compared to those with BDI (Fasmer, 2001; Ortiz et al., 2010; Saunders et al., 2014), a finding supported by the recent meta-analysis reported by Fornaro and Stubbs (2015). A number of studies have also identified differences in the clinical profile of bipolar patients according to their history of migraine. The reported clinical characteristics associated with migraine comorbidity within BD include: an earlier onset of the bipolar illness (McIntyre et al., 2006b; Mahmood et al., 1999); an increased number of mood episodes (Brietzke et al., 2012b; Saunders et al., 2014); a history of comorbid anxiety disorder (Ortiz et al., 2010; Gordon-Smith et al., 2015; McIntyre et al., 2006b); and a rapid cycling course of illness (Gordon-Smith et al., 2015; Saunders et al., 2014).

Interestingly, previous studies have identified differences in the psychiatric comorbidity of the migraine subtypes, migraine with aura (MA) and migraine without aura (MoA), where it has been suggested that MA may have a stronger association with psychiatric disorders than MoA (Breslau et al., 1991; Samaan et al., 2009). For example, in a prospective study, MA was reported to have a stronger association with major depression than MoA (OR 4.9; 95% CI 3.34-7.19 vs. OR 3, 95% CI 2.23-4.14, respectively) (Breslau et al., 2000). Similarly, Oedegaard et al. (2005a) found that depression alone, and depression with comorbid anxiety were more likely in women having MA than MoA, however there was no difference in the prevalence of depression and anxiety disorders between MA and MoA in men. In addition, Breslau et al. (1991) observed significantly increased rates of BD and panic disorder in patients with MA when compared to migraine free individuals; however, this was not the case for the MoA group. Of particular concern is the association of MA with suicide attempt. In 1991, Breslau et al. reported an association of MA and MoA with suicide attempt when associated with major depressive disorder (MDD). However, after

adjusting for the presence of MDD and other psychiatric and substance use disorders, the association remained significant for the MA group only. In a later study, Breslau (1992) observed an increased risk for both suicidal ideation and suicide attempt in patients with MA alone and patients with MA with coexisting MDD, compared to those with neither MDD nor migraine. Thus, it appears that there are important differences in the comorbid expression of migraine and psychopathology, particularly for affective pathology, dependent on migraine subtype.

To date, much of the research exploring the clinical characteristics of BD associated with migraine (described above) has not distinguished between migraine with (MA) and without aura (MoA). In 2005, Oedegaard and colleagues looked to further characterise the relationship of migraine with affective disorders (including unipolar, BDI and BDII subjects) by exploring the clinical correlates of MA, migraine aura without subsequent headache, MoA, and no migraine (Oedegaard et al., 2005b). Whilst the authors reported overall group differences across the four migraine subtypes, the main focus of the paper was to make comparisons between individuals with MA vs. migraine aura without headache. When comparing the four groups of migraine sufferers, significant differences were found for gender distribution, the distribution of unipolar, bipolar I and II disorders, rate of affective temperaments, suicide attempt and frequencies of reported irritability during depression. When differentiating MA from migraine aura without headache, significant differences were found for age of migraine onset, affective temperament and suicide attempt, with multivariate analysis revealing a significant association between age of migraine onset and affective temperament.

1.2.1.2 Pathophysiology and genetics

One potential explanation for the association between bipolar disorder (BD) and migraine could be a shared underlying pathophysiology. The possibility of common neurobiological pathways between BD and migraine are suggested by the overlap in the pharmacological treatment used to treat both disorders. For example, valproate, an anti-epileptic drug well-established for the maintenance treatment in BD, has also been shown to have a prophylactic effect in migraine,

reducing the number of attacks, duration of headache and intensity of pain (Silberstein, 1996). The neurobiological mechanisms underlying the association between these disorders remain unknown, however both have been linked to disturbances in the serotonergic (Hamel, 2007; Mahmood and Silverstone, 2001; Silberstein, 1994), dopaminergic (Emilien et al., 1999; Peroutka, 1997), and glutaminergic systems (Vaccaro et al., 2007). Moreover, Brietzke et al. (2012a) reviewed evidence implicating disturbances in inflammatory cytokines within both disorders.

Further evidence of common biological mechanisms has come from research demonstrating the involvement of ion channels within both BD, and migraine. The aetiology of migraine is not fully understood, however, like BD it is considered to be a complex polygenic multifactorial disorder, with estimates of heritability ranging between 40%-65% (Larsson et al., 1995; Ziegler et al., 1998). Much of the progress in identifying genetic susceptibility to migraine has come from findings from the genetic architecture of the autosomal dominantly inherited migraine subtype, familial hemiplegic migraine (FHM). As previously described, hemiplegic migraine (HM) is a subtype of migraine with aura, in which migraine attacks are associated with motor weakness and may present in isolation (sporadic; SHM) or with a family history (at least one first or second-degree relative) of similar attacks (familial; FHM). Hemiplegic migraine is rare, with a Danish population-based epidemiological survey indicating the prevalence of sporadic hemiplegic migraine to be approximately 0.002% and familial hemiplegic migraine 0.003% (Thomsen et al., 2002). FHM is genetically heterogeneous, and variants in at least three genes have so far been implicated. FHM1 is caused by mutations in the calcium channel gene *CACNA1A* (Ophoff et al., 1996), and is estimated to account for approximately 50% of all FHM families (Ducros et al., 2001). In 2003, a second locus was discovered with the identification of more than 30 mutations identified in the sodium/potassium pump gene *ATP1A2* (FHM2) (DeFusco et al., 2003). Finally, mutations on chromosome 2q24 within the neuronal voltage-gates sodium channel gene *SCN1A* were identified in 2005 (FHM3) (Dichgans et al., 2005). All three FHM genes either encode ion channels or are involved in ion transportation, thus highlighting the importance of ion channels in the molecular mechanism of migraine and supporting the hypothesis of migraine as a 'channelopathy'.

Whilst these specific FHM genes have not been implicated in studies of BD, as already described within this chapter, two of the strongest associations to come out of genome-wide association studies of BD have been for two genes involved in ion transportation (*ANK3* and *CACNA1C)*, suggesting that disturbances in ion channel function are relevant for both migraine and BD.

It has been discovered that individuals with hemiplegic migraine (HM) are found within the same families as those with non-hemiplegic forms of migraine (Launer et al., 1999), and that HM patients can also experience non-HM attacks (Carrera et al., 2001). It is therefore plausible to postulate that hemiplegic and common migraine subtypes share pathogenic mechanisms, making the Mendelian model of FHM useful in the study of non-hemiplegic migraine. Whilst the known FHM genes have been studied in the more common forms of migraine, with (MA) and without aura (MoA), their role is debated, and strong evidence is currently lacking to implicate them in common migraine subtypes (Wessman et al., 2007).

A small number of studies have been conducted to explore potential genetic susceptibility regions for the combined migraine-bipolar phenotype. For example, a genome-wide linkage study on 31 families (n=202) identified an overlapping locus on chromosome 20p11 for both BD and migraine, a region harbouring a gene involved in calcium homeostasis (*SLC24A3*) (Oedegaard et al. 2010b). To date, two genome-wide association studies (GWAS) have been published using the BD-migraine phenotype. The first found evidence of association for several single-nucleotide polymorphisms approaching the threshold for genome-wide significance ($p=5 \times 10^{-8}$) on chromosome 13q14.1, in a region containing the uncharacterised gene KIAA0564 (Oedegaard et al. 2010a), suggesting that the BD-migraine combined phenotype has the potential to reclassify individuals into a more homogeneous genetic subgroup. However, these findings must be treated with caution given that they are based on a very small sample of 56 bipolar subjects with a doctor diagnosis of migraine. A second GWAS involved 460 bipolar subjects with self-reported migraine (cases) and 914 bipolar subjects without migraine (controls) (Jacobsen et al., 2015). This study identified a genome-wide significant association for rs1160720 in the *NBEA* gene ($p= 2.97\times10^{-8}$). This variant failed to show association with migraine or BD individually, leading authors to speculate the aetiological specificity of

this gene to the combined phenotype and to hypothesize that BD with comorbid migraine may be a distinct syndrome with different genetic risk factors than for either migraine, or BD alone.

1.2.2 Summary

The evidence reviewed above suggests that migraine is frequently comorbid with bipolar disorder (BD), and that migraine comorbidity may delineate a subset of BD patients with a distinct set of clinical outcomes. Recognition and targeted treatment for migraine in bipolar patients may improve course of illness and prognosis in BD. Further research unravelling the complex relationship between migraine and BD, with a particular focus on the individual subtypes of migraine, will help us to better understand and characterise the clinical features of this comorbidity and to identify subpopulations of individuals with BD that could benefit clinically from more effective, targeted diagnostic and treatment strategies. Current evidence also provides support for the use of a refined bipolar phenotype including comorbid migraine, pointing to common biological mechanisms between the two disorders. However, given the caveats of small samples and the lack of standardised criteria for migraine diagnosis involved in these studies, it is clear that more work in this area is needed.

1.3 Introduction to epilepsy

Epilepsy is a chronic disorder of the brain, where there is a tendency for the occurrence of unprovoked epileptic seizures. Epilepsy is one of the most common neurological conditions in the world, affecting approximately 50 million people worldwide (WHO, 2016, fact sheet updated February 2016). Eight percent of those affected by epilepsy are in developing countries and within these countries approximately 75% of people with epilepsy are not receiving appropriate treatment (WHO, 2016; fact sheet updated February 2016). In the UK, approximately 600,000 people have a diagnosis of epilepsy and take anti-epileptic drugs, which is equivalent to approximately 1 in 103 people. The prevalence rate of epilepsy in the UK is approximately 9.7 per 1000 or 0.97%

(Joint Epilepsy Council, 2011). Using a meta-analytic approach, (Ngugi et al., 2010) estimated the median prevalence of active epilepsy within developed countries to be 4.9 per 1000, and the median lifetime prevalence to be 5.8 per 1000. The lifetime prevalence of seizures (i.e. the risk of having a non-febrile epileptic seizure at some point in an individual's lifetime) is higher, and is noted to be between 2 and 5% (Neligan and Saunder, 2009). The incidence of epilepsy is consistently reported to be higher in males than in females, however this difference is rarely found to reach statistical significance (Banerjee and Hauser, 2008). A systematic review of incidence studies reported the median annual incidence of epilepsy to be 50.7 per 100,000 for males and 46.2 per 100,000 for females (Kotsopoulos et al., 2002). Although epilepsy is found in all age groups, it is said to more frequently affect people within the first two decades of life, and people over the age of 60 years (Sander, 2003). **Figure 1.1** illustrates the UK incidence of epilepsy by age, for males and females.

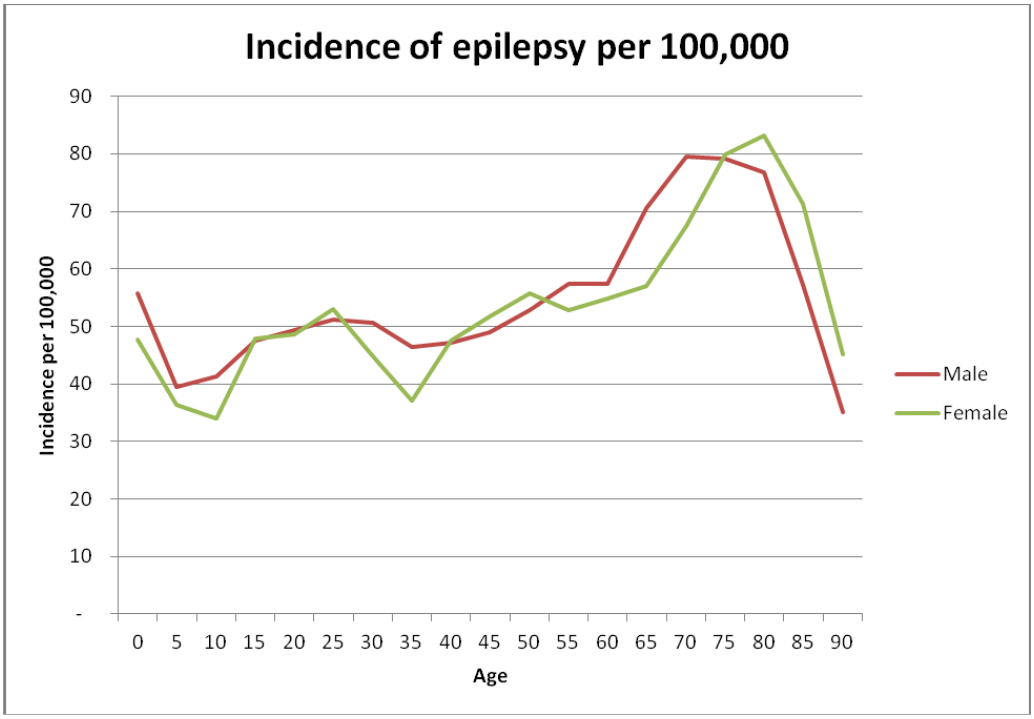


Figure 1.1 Incidence of epilepsy by age for males and females. (Image taken from: Joint Epilepsy Council. 2011. Epilepsy prevalence, incidence and other statistics [online]. http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf).

There is no test for epilepsy; consequently, a diagnosis of epilepsy relies largely on history taking, and patient and eyewitness accounts of the seizure.

Investigations conducted at the time of examination such as, neuroimaging techniques including magnetic resonance imaging (MRI) and computerised tomography (CT) scans, and electroencephalogram (EEG), can be helpful in establishing epilepsy as the likely cause of the seizure, or for the localization of the epileptogenic zone. However, the results of these tests can often be normal despite certainty in the diagnosis of epilepsy. For example, within a prospective study of 158 patients attending a neurology outpatients (referred following a loss of consciousness, or on the basis of having possible epilepsy), neuroimaging revealed a relevant abnormality in 12/43 (27.9%) patients, and the yield from EEG was 7/25 (28%) of those with epilepsy (although EEG result changed the diagnosis in only one case) (Angus-Leppan, 2008). Such findings emphasize the invaluable clinical contribution in the diagnosis of epilepsy. Given the lack of any form of diagnostic test, it is unsurprising that diagnostic accuracy is a problem. Within a population-based study of 214 individuals with a primary diagnosis of epilepsy, misdiagnosis rates of 23% were reported (Scheepers et al., 1998). Moreover, within a retrospective study of n=184 adults referred with 'refractory epilepsy' to a UK specialist clinic, Smith et al. (1999) estimated the rate of misdiagnosis to be 26.1%. Psychogenic non-epileptic attacks, and syncope are two of the most common conditions misdiagnosed as epilepsy. Other differential diagnoses of epilepsy include: hypoglycemia; panic attacks; paroxysmal movement disorders; paroxysmal sleep disorders; transient ischemic attacks (TIA); migraines; and transient global amnesia (TGA) (Benbadis, 2009).

Epilepsy is not a single condition, but rather a large and diverse group of disorders, having in common an abnormally increased predisposition to seizures, and as such many people prefer to use the term 'the epilepsies'. Whilst recognising the diversity of the disorder, the singular term 'epilepsy' will continue to be used throughout this thesis. The International League against Epilepsy (ILAE) made a major contribution to the field when it first introduced standardized classifications and terminology for seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), which were largely based on

seizure manifestations and EEG findings. Since their introduction, advances in neuroimaging and genetics have had a substantial impact on our understanding of epilepsy and as such, facilitated the need for a revision of the original classification systems. In 2010, the first radical overhaul of the organization of epilepsy was published, focusing on updating terminology in line with current understanding (Berg et al., 2010). Moreover, in 2005, the ILAE commissioned a Task Force to formulate conceptual definitions of "seizure" and "epilepsy" recognising the need for purposes of clinical diagnosis (Fisher et al., 2005). These definitions can be found in **Table 1.5**.

Table 1.5 International League Against Epilepsy conceptual definition of a seizure and epilepsy (Fisher et al., 2005)

Epileptic seizure	A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epilepsy	A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition.

The above definition of epilepsy was traditionally applied as having two unprovoked seizures occurring at least 24 hours apart (Hauser et al., 1991). However, this operational definition was considered too restrictive and the ILAE Task Force were encouraged to consider altering the definition to include circumstances that do not meet the two unprovoked seizures criteria. In response to this, the task force proposed that epilepsy should be considered under any of the following conditions: 1. At least two unprovoked seizures occurring more than 24 hours apart; 2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (approximately 75% or more) (circumstances occurring with remote structural lesions, such as stroke, central nervous system infection and certain types of traumatic brain injury) and; 3. At least two seizures in a setting of reflex epilepsy (for example photosensitive seizures). The new definition was introduced in order to encourage clinicians to give greater

consideration to recurrence risk following a single unprovoked seizure, making it more acceptable to begin treatment in the special circumstances outlined above. However, the task force did acknowledge that whilst the revised operational definition may be useful for clinical purposes, it may not be suitable for all research studies that may lack sufficient evidence or knowledge of risk of recurrence. Therefore, it is recognised that within any scientific study or publication most diagnoses of epilepsy are likely to still be made using the traditional 'two unprovoked seizure' criterion.

According to the 2010 organisation of epilepsy (Berg et al., 2010), seizures are broadly categorised into two main groups; focal and generalised (support for which has been provided from ictal and inter-ictal EEG*).* Generalised seizures are described as "originating at some point within, and rapidly engage, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex" (Berg et al., 2010). Focal seizures are described as "originating within networks limited to one hemisphere, which may be discretely localized or more widely distributed" (Berg et al., 2010). Focal seizures can spread within the same hemisphere, and to areas in the contralateral hemisphere, evolving into a generalized seizure. The initial presenting symptomatology of focal seizures depends on where in the brain the seizure activity originates, and will often reflect the functional role of that part of the cortex. For example, a patient experiencing a seizure originating from the temporal lobe may experience sensory changes including, amnestic sensations (for example, déjà vu or jamais vu), hallucinations (including visual, auditory and olfactory), and emotional disturbance (for example intense feelings of euphoria, fear or anger). Within the 1989 classification, focal seizures were further classified into 'simple' or 'complex', depending on the impairment of consciousness. However, in Berg et al.'s (2010) reorganization, these terms were abandoned due to the difficulty in the judgment of awareness during a seizure. The distinction between focal and generalised seizures was first introduced within the original 1989 classification, and whilst Berg et al. (2010) considered it useful to maintain this terminology, they acknowledged its restrictions and accepted that there are many cases where this dichotomy is not meaningful (Berg and Scheffer, 2011). **Figure 1.2** depicts the ILAE 2010 classification of seizures (Berg et al., 2010).

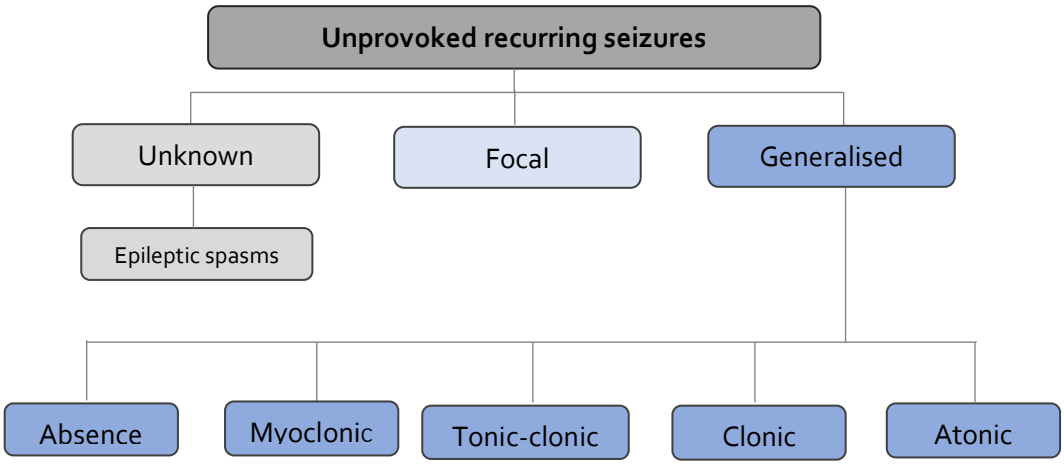


Figure 1.2 International League Against Epilepsy classification of seizures (Berg et al., 2010)

The 2010 classification also looked to update the aetiological categories proposed by the original classification, to reflect our increased understanding of epilepsy. Berg et al. (2010) introduced the aetiological categories of; genetic, structural/metabolic, and unknown, replacing the outdated 'idiopathic', 'symptomatic' and 'cryptogenic' categories. A comparison of these aetiological categories is outlined in **Table 1.6**. Within the 2010 classification, Berg et al. (2010) also re-established the concept of 'electroclinical syndromes' defined as a complex set of clinical features, signs, and symptoms that together constitute a distinctive, recognizable clinical disorder. Electroclinical syndromes are characterized on the basis of a typical age at onset, seizure types, and EEG characteristics, permitting this specific diagnosis which has implications for treatment and management.

Table 1.6 Comparison of aetiological categories proposed by the 1989 Classification and Terminology, and the newly proposed Terminology and Concepts (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Berg et al., 2010)

ILAE 1989 Classification		ILAE 2010 Classification	
Idiopathic	No underlying cause other than a possible hereditary predisposition.	Genetic	A direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder.
Symptomatic	A consequence of a known/suspected disorder of the central nervous system	Structural/ metabolic	A distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. These disorders may be of acquired or genetic origin. When of genetic origin, there is a separate disorder interposed between the gene defect and the epilepsy.
Cryptogenic	A disorder whose cause is hidden. Cryptogenic epilepsies are presumed to be symptomatic	Unknown	The nature of the underlying cause is as yet unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate metabolic/structural disorder not yet identified.

Epilepsy is a chronic but treatable condition. Although some epilepsies remit at puberty (for example childhood absence and benign rolandic epilepsy), most are long-term, meaning that treatment is often lifelong. The goal of treatment is to achieve a seizure-free status without adverse effects and the mainstay of treatment is the use of antiepileptic drugs (AEDs). In the UK, up to 70% of people

developing epilepsy should expect to become seizure free with optimum antiepileptic drug (AED) treatment (Sander, 2004). However, a population-based community study by Moran et al. (2004) revealed that of 1652 people with epilepsy in the UK, only 52% had been seizure-free in the preceding year, with seizures remaining uncontrolled in 48%, and these individuals reporting significant impact on their work, family and social life. These figures suggest that approximately 18% of epilepsy patients who could potentially be seizure-free may be receiving suboptimal treatment. Within this same study, Moran et al. (2004) assessed the pattern of utilization of AEDs for epilepsy in the community sample, revealing that the most commonly used AEDs were: carbamazepine (37.4%); valproate (35.7%); phenytoin (29.4%); phenobarbitone (14.2%); and lamotrigine (10.3%). Moreover, monotherapy was used in 68% of patients. Within an earlier study by Hart and Shorvon (1995) that described AED utilization in 1051 patients with epilepsy from UK primary care services, the most frequently used drugs were: phenytoin (33%); carbamazepine (30%), valproate (25%); and phenobarbital (9%). Sixty-five percent of epilepsy patients were on monotherapy in this study, a figure very similar to that reported by Moran and colleagues 20 years later. However, it does appear that there was considerable difference in the particular agents used within monotherapy. Moran et al. (2004) noted that valproate (33%) and carbamazepine (31%) were the most commonly used drugs in monotherapy, followed by phenytoin (24%) and phenobarbital (5%), and that these accounted for 93% of all AEDs used for monotherapy. In Hart and Shorvon's (1995) study, these four AEDs accounted for 97%, suggesting that the introduction of newer AEDs such as, topiramate and gabapentin, had only a modest impact.

As described above, not all of those treated with AEDs will achieve seizure freedom. The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2010). One option for those that do not respond to AED therapy is epilepsy surgery, which aims to eliminate or reduce the frequency of epileptic seizures by removing the epileptogenic zone.

Epilepsy imposes a substantial burden on both the individual and wider society. For example, Begley et al. (2000) estimated the total cost of epilepsy in the United States to be $12.5 billion, with the majority of the expenditure attributable to indirect costs; such as those related to other disabilities and socioeconomic losses. Research also suggests that people with epilepsy are high users of healthcare services (Wiebe et al., 1999) contributing to the high economic burden associated with the disorder. In addition to the measurable impact of these disorders on society, it is also essential to consider the intangible costs and devastating consequences on the individual and their family. The impact of epilepsy extends far further than the clear adverse implications on health. Seizures, and importantly the potential for recurrence of seizures have considerable cognitive, psychological, and social effects. Seizure control, or ideally, freedom from seizures has been shown to be vital in improving the quality of life of patients. For example, (Leidy et al., 1999) demonstrated that patients with well-controlled epilepsy had a similar health-related quality of life (HRQOL) to the general population; however those whose seizures were uncontrolled showed a significantly impaired HRQOL. Moreover, epilepsy has a long history of being a stigmatizing disorder; one that is often associated with fear and exclusion. Sadly, such misconceptions and negative stereotypes still remain today, placing considerable burden on the quality of life of those affected by the disorder (Jacoby, 2002).

Comorbidity is common in epilepsy and research indicates higher rates of both somatic and psychiatric conditions in individuals with epilepsy compared to the general population (Gaitatzis et al., 2004). Mood disorders have long been considered frequent psychiatric comorbid conditions in people with epilepsy, occurring at much greater rates in those with epilepsy compared to the general population; estimates vary due to sampling strategies, between 20-50% (Kanner, 2003). Depression is often noted as the most frequent psychiatric disorder in people with epilepsy, with incidences ranging from 20-30% in community-based epilepsy samples, and 20-55% in specialist epilepsy clinics (Baker et al., 1996; Kanner and Balabanov, 2002; Blum et al., 2003; Eden and Toone, 1987; Robertson et al., 1994; Ottman et al., 2011). Depression is often regarded as an understandable consequence of the epileptic disorder, given the

socially disadvantageous nature of epilepsy. However, a more complex, bidirectional relationship between the two disorders has also been proposed, in light of evidence suggesting an increased risk for developing epilepsy in individuals with depression. For example, a population-based case-control study of patients with late onset epilepsy (first seizure after the age of 54 years), found that major depression was associated with a six-fold increased risk for unprovoked seizures (Hesdorffer et al., 2000). Authors also reported that this increased risk remained even when controlling for age, sex, length of medical follow-up and treatment for depression. Moreover, in a large (n=11,741) Danish population-based study using hospital registry data, (Nilsson, 2003), reported a relative risk for epilepsy among patients with depression of 1.32, compared with controls (patients with diabetes or osteoarthritis). However, this observed increased risk seemed to be due to the effect of comorbid alcohol abuse within depressed patients, given that the relative risk was 9.9 in patients with depression plus alcohol abuse, but only 0.9 in patients with depression without alcohol abuse.

To date, much of the neuropsychiatric literature has focused on the study of unipolar depression, with investigation into bipolar disorder (BD) remaining limited. The following section will review the evidence for overlap between epilepsy and BD.

1.3.1 Evidence of overlap between epilepsy and bipolar disorder

1.3.1.1 Clinical studies

Traditionally, it was stated that symptoms of bipolar disorder (BD) within epilepsy were less common than symptoms of depression and certainly classic BD was thought to be rare (Wolf, 1982). It has previously been said that "*Classic BD type I is rarely seen in epilepsy, and manic episodes occur almost exclusively in the setting of postictal psychosis or after epilepsy surgery"* (Mazza et al., 2007). This notion has since been challenged, with authors now more likely to support a putative bidirectional relationship.

One of the first systematic assessments of BD symptomatology within epilepsy revealed bipolar symptoms to be evident in a sixth of epilepsy patients (Ettinger et al., 2005). Within this study, Ettinger et al. (2005) utilized the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000) (a validated screening instrument for symptoms of bipolar I and II disorder) with a sample of 127,800 people selected to represent the US adult population. Of the 85,358 subjects (67%) who returned the survey, 12% of those with epilepsy reported bipolar symptoms (not bipolar disorder *per se*). Bipolar symptoms were reported 1.6 to 2.2 times more often in subjects with epilepsy than in those groups with other chronic disorders. People with migraine were the second largest group, in terms of their reporting of bipolar symptomatology (7%), with rates of bipolar symptomatology also higher in those with asthma (6%) and diabetes (3%). A further population-based survey conducted more recently, focusing specifically on epilepsy and a spectrum of potential neuropsychiatric and pain disorder comorbidities demonstrated significant comorbidity for a number of psychiatric disorders (including BD), with epilepsy. Specifically, BD was found to be more than twice as prevalent among individuals with self-reported epilepsy as those without (prevalence ratio = 2.11, 95% CI 1.82-2.45) (Ottman et al., 2011).

In a case-control study to identify epilepsy-related characteristics associated with the presence of mood disorders in epilepsy, Jagadheesan et al. (2003) compared 44 patients with epilepsy with a history of mood disorder, and 44 epilepsy patients with no such history. They identified 5 (11.4%) of those with a comorbid mood disorder as having bipolar disorder, whilst the rest (88.6%) had major depressive disorder. Epileptic patients with a history of mood disorders: were more likely to be educated (88.6% vs. 65.9% $p<.05$); had a later onset of epilepsy (21.44 vs. 12.19 years, $p<.01$); had a higher frequency of cluster attacks 54.5% vs. 31.8%, $p<.05$); and a longer duration of epilepsy illness (7.58 vs. 4.76 years, $p<.05$). However, epileptic patients with and without a history of mood disorders were found to be similar in terms of seizure frequency, seizure type, EEG abnormalities and family history of affective disorder.

An important distinction to consider in the evaluation of BD within epilepsy is whether it is 'true' BD that is found to be more frequent in people with epilepsy,

or whether the symptoms observed are in fact related to phenotypic mimics, misdiagnosed as BD. For example, Ettinger et al. (2005), above, suggested that the mood disorder questionnaire used in their study may in fact be identifying individuals with the controversial interictal dysphoric disorder (IDD). Blumer et al. (2004) coined this term to refer to a presentation of chronic depression or dysthymia that tends to run an intermittent course and fails to meet criteria for a DSM based diagnosis. Blumer and colleagues (2004) described this proposed pleomorphic disorder as being characterized by eight key symptoms: fluctuating dysthymia, irritability, alternation with occasional euphoric periods, fear, anxiety, anergia, pain and insomnia. This frequently observed atypical presentation of depressive disorders in patients with epilepsy led clinicians to believe that such disorders were clinically different to those seen in non-epileptic patients (Kanner and Barry, 2001).

Mula et al. (2008) identified major depressive disorder as being the most strongly correlated DSM-IV Axis 1 disorder with IDD. However, in their efforts to investigate the psychopathological features of IDD using clinical instruments designed to measure manic (MDQ: Mood Disorder Questionnaire) and depressive (BDI: Beck Depression Inventory) symptomology, Mula et al. (2008) noted a higher specificity for IDD diagnosis by the MDQ compared to that of the BDI (86% vs. 65.9%, respectively), adding support to the hypothesised close relationship between IDD and the bipolar spectrum. Moreover, features of IDD relating to mood instability and irritability are symptoms traditionally belonging to the spectrum of bipolar disorders, rather than unipolar depression (Moller and Curtis, 2004). Others have speculated a relationship with BD, suggesting that IDD represents a form of cyclothymic disorder that sometimes exacerbates and meets criteria for major depression. IDD remains a controversial concept (Mula, 2013) with some authors arguing that the definitions are too broad and the psychometric tools not specific enough to differentiate from anxiety and depressive symptoms (Amiri and Hansen, 2015). While an overlap with this proposed syndrome may have explained the symptomatology in some cases, it is notable that nearly half of Ettinger et al's. (2005) respondents with positive MDQ scores in fact had a formal diagnosis of BD.

In addition, in the evaluation of BD in people with epilepsy, it is essential to take into account the number of behavioural changes that can occur around the ictus and the features of postictal or prodromal phases associated with seizures, as well as the occurrence of manic symptoms as a side effect of antiepileptic pharmacology (Mula and Monaco, 2006). **Figure 1.3** displays the number of behavioural and affective psychiatric disturbances that can occur throughout the ictal, postictal and interictal phases of seizure activity. Mula et al. (2008), looked to address this distinction, aiming to describe prevalence of both BD and bipolar symptoms in adult outpatients with epilepsy, whilst also considering the role of potential confounding variables, such as relation to seizures and drug therapy. They identified 12% (n=17) of epilepsy patients as having a DSM-based diagnosis of BD and 15% (n=21) screening positive for bipolar symptoms with the MDQ. However, following consideration of potential confounders, prevalence of 'true' BD and bipolar symptoms were found to be 1.4% and 2%, respectively. In the remaining cases, symptoms were found to be related to phenotypic copies such as IDD or related to behavioural manifestations occurring around the ictus.

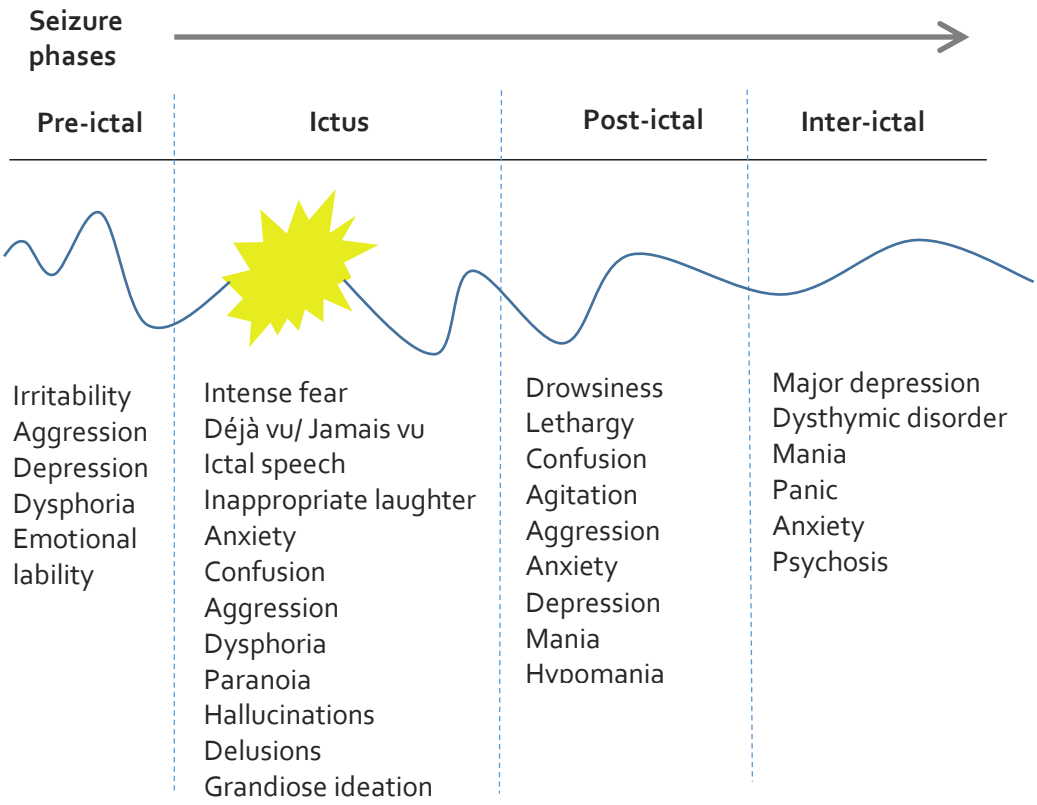


Figure 1.3 Examples of behavioural and affective changes during seizure phases. (Figure reproduced from Knott et al., 2015)

It is well known that temporal lobe epilepsy (TLE) plays an important role in the genesis of ictal and post-ictal mania and moreover, that manic episodes can develop following injury to the temporal or frontal lobes (Starkstein et al., 1988). Seizure activity associated with the temporal and frontal epileptogenic zones is often referred to as 'secondary mania', thought to be caused by a disturbance in the limbic system. Due to the role of the limbic system in regulating emotion, mood and behaviour, patients with TLE are noted as having a high propensity to develop psychiatric disorders (particularly affective disorders) and can present a diagnostic challenge as they blur the interface between psychiatry and neurology. In this instance, patients with TLE and those with focal seizures more generally, may represent a diagnostic challenge given their overlap of symptoms such as: olfactory, auditory and gustatory illusions and hallucinations; feelings of depersonalisation or detachment; and panic, fear and anxiety. Psychiatric classification manuals, such as the DSM-IV (American

Psychiatric Association, 2000), define this as 'mood disorder due to general medical condition', and in such cases psychiatric disorder is not considered to be comorbid with the medical disorder, but rather an expression of it. However, it has been argued that such classification systems are superficial and perhaps overlook the neuropsychiatric diversity found in epilepsy. For example, De Oliveira et al's. (2010) observation of the neuropsychiatric profile of patients with TLE revealed high rates of BD (10%) and any mood disorder (49%), even when considering clinical variables related to epilepsy.

Following consideration of phenotypic copies of BD and potential manifestations of epilepsy, an important question remaining is whether the interictal manic episode within epilepsy is comparable to the manic episode of BD patients. A case-control study exploring this question compared the clinical features of interictal manic episodes with those of bipolar I disorder (BDI) (Kudo et al., 2001). It was reported that compared to BD controls, epilepsy patients with interictal manic episodes experienced less severe manic and depressive episodes and 62% experienced a rapid cycling course of the bipolar illness. However, the study did not control for confounding factors, such as medication use, which may have influenced the bipolar illness given the known anti-manic properties of epileptic pharmacotherapy.

A fundamental issue needing further exploration is whether it is bipolar symptomology or a clinical picture meeting full diagnostic criteria for BD that is found at increased rates in people with epilepsy. In an effort to assess rates of bipolar symptoms versus BD in epilepsy, Lau et al. (2012) found that of ten individuals who met criteria for bipolar symptomology assessed by the MDQ, only one had a diagnosis of BD, suggesting that symptomology is not synonymous to formal disorder. This appears to be in stark contrast to the 50% of positive screens for bipolar symptomology confirmed to have a diagnosis of BD in Ettinger et al.'s (2005) study. It is important to emphasize that the MDQ (the main tool used to formally assess bipolar symptomology in epilepsy cohorts) has not been validated for use within an epilepsy population and so its sensitivity within this population is unknown.

To date, there has been a distinct lack of studies exploring the systematic assessment of well-characterized epilepsy within a bipolar population. Rather, much of the research to date has focused on the assessment of multiple physical health disorders concurrently, with studies often grouping disorders together by organ system (i.e. neurologic disorders). Such studies have identified an increased prevalence of neurologic disorders within BD, compared to controls subjects (Carney and Jones, 2006; Evans-Lacko et al., 2009). However, whilst this has acted to increase our knowledge of medical burden, and broadly defined neurologic disorders within BD, it has not allowed for comprehensive investigation of epilepsy within BD.

Moreira et al. (2011) aimed to describe the prevalence of nine general medical conditions, including epilepsy in a Brazilian sample of outpatients with bipolar I disorder. Nearly 69% of subjects were reported to have at least one general medical condition, with epilepsy prevalence estimated at 8%. An additional study that specifically included epilepsy in their assessment of general medical comorbidities used a nationally representative data set to review comorbid conditions in hospital discharge records that noted BD. Epilepsy was not stated as one of the fifteen most prevalent comorbid conditions in discharge records of those with a primary diagnosis of BD. However, they did report an increased prevalence of epilepsy among the discharges with a primary diagnosis of BD, compared to discharges with a different primary diagnosis (Weber et al., 2011). A further study to utilize hospital medical records examined rates of comorbid medical disorders in patients with BD and schizophrenia (Oreški et al., 2012). Within BD patients, the prevalence of general neurological disorders was 8% and an epilepsy prevalence of 1%. These rates were not found to be significantly different to those reported in the schizophrenia patient group, although neurological disorders were found to be the most prevalent somatic condition in schizophrenia patients (11%). Finally, Forty et al. (2014) looked to examine rates of a number of medical illnesses, including epilepsy, in a large, well-defined sample of patients with BD, and to make comparisons with a control group and with a sample of patients with recurrent depression. They found a significantly increased rate of self-reported epilepsy in the bipolar group when compared to both the control (3.4% vs. 0.5%, $p<.001$) and the recurrent depression group

(3.4% vs. 2.0%, p<.05). They also explored the rate of self-reported epilepsy across bipolar subtypes, finding no significant difference between bipolar I disorder and bipolar II disorder groups (2.1% vs. 2.2%).

In a clinical sample of 40 first degree relatives of bipolar probands, 60 first degree relatives of epilepsy probands and 50 control subjects, Jidda et al., (2014) found an increased rate of epilepsy among relatives of individuals with BD compared to controls (15.2% vs. 2.0%, p<.001), providing evidence for the familial clustering of BD and epilepsy. However, an association between BD and parental epilepsy was not reported in a large Finnish study of national registry data (Sucksdorff et al., 2015). The authors did, however, observe an association between BD and comorbid epilepsy even after adjusting for parental psychopathology (OR: 2.53, 95% CI: 1.73-3.70).

Given that very few studies have explicitly assessed epilepsy within a bipolar sample, it is clear that this is an area in need of further investigation. It is important for future work to focus on the assessment of well-defined epilepsy within bipolar subjects, not reliant on self-report measures; as well as exploring the temporal relationship of the two disorders, to uncover the true nature and direction of their association.

1.3.1.2 Pathophysiology and genetics

Several converging lines of research suggest a relationship between bipolar disorder (BD) and epilepsy. Both conditions are substantially heritable, follow an episodic course, can be chronic, and respond to anticonvulsant medications, all of which point to a common underlying pathophysiology.

One of the pathophysiological mechanisms hypothesized to underpin both epilepsy and BD, is the kindling phenomenon. Kindling was first described in an experimental animal model of epileptogenesis (Goddard et al., 1969) as a means of describing the evolution of seizure development and progression. Kindling is a process whereby repetitive stimulation involving sub-threshold stimuli induces seizures until they start to occur spontaneously. The kindling phenomenon results in lasting (and potentially permanent) functional and structural changes in the brain and can be modified by pharmacological

treatment. Many anti-epileptic drugs (which are also known to have mood-stabilizing properties), such as carbamazepine, lamotrigine and phenytoin successfully block completed kindled seizures, however are unable to block their development (Post, 2004). The kindling phenomenon has also been applied to explain the episodic nature of BD (Post and Wiess, 1996). Post and Weiss (1996) postulated that in a genetically susceptible individual, particular repeated (psychosocial) stressors experienced within a vulnerable period and environment can lead to the development of mood symptoms occurring with increasing intensity and duration, until the occurrence of a full-blown depressive or manic episode. It is also proposed that each episode leaves a 'trace' and increases vulnerability for subsequent episodes, a mechanism referred to as 'episode sensitization' (Huber et al., 2001).

A further possible common pathogenic mechanism between epilepsy and BD involves abnormalities of common neurotransmitter systems (for which their role in BD has already been discussed) including; serotonin (5HT), norepinephrine (NE), dopamine (DA), glutamate, and gamma-amino-butyric acid (GABA). The hypothesis for the involvement of neurotransmitter systems has largely been derived from the fact that many antiepileptic drugs (AEDs) are known to act on these systems. For example, in the case of GABA: carbamazepine is known to modulate the $GABA_A$ receptor (Granger et al., 1995); valproate increases the release of GABA through the upregulation of $GABA_B$ receptors (Laeng et al., 2004); and phenytoin has been found to increase GABAergic transmission (Cunningham et al., 2000). However, it has also been observed that although the AEDs topiramate and retigabine show strong effects on GABAergic transmission, they do not demonstrate any anti-manic properties (Amann and Grunze, 2005). Moreover, glutamate; the main excitatory transmitter in epileptogenesis, is known to be the target of a number of AEDs. For example, carbamazepine, valproate and lamotrigine, have all been shown to exhibit anti-glutamatergic actions (Lampe and Bigalke, 1990; Löscherr, 1993; Teoh et al., 1995; Waldmeier et al., 1995).

The roles of 5HT and NE have been established through the use of animal models and humans with temporal lobe epilepsy. Jobe et al. (1999) noted the involvement of 5HT and NE in genetically prone rat strains (GEPR-3 and GEPR-

9), who have a predisposition to sound-induced generalized tonic-clonic seizures and were shown to have deficits in serotonergic and noradrenergic pre and postsynaptic transmission. Moreover, an increase of extracellular serotonin has been identified with valproate (Whitton et al., 1985), lamotrigine (Southam et al., 1998) and carbamazepine (Dailey et al., 1997). Finally, evidence for the involvement of 5HT and DA in epilepsy is reflected by the finding that low doses of these are protective against limbic seizures, and conversely, high concentrations demonstrate pro-convulsive properties in some animal models, whereby receptor blockades significantly aggravate seizures (Clinckers et al., 2004).

Detailed twin studies and familial aggregation analysis have made a compelling case that both generalized and focal epilepsies have a sizable genetic contribution (Thomas and Berkovic, 2014). Similarly, and as already discussed, the heredity of bipolar disorder has been estimated to be between 60-85%, for which a complex polygenic genetic basis is postulated. Two of the strongest associations to come out of genome-wide association studies of BD are for the involvement of *CACNA1C* and *ANK3*, leading to the hypothesis that BD may be, at least in part, an ion channelopathy. Some of the most convincing evidence for the involvement of ion channels in epilepsy has come from the identification of mutations within voltage-gated sodium channel genes leading to rare monogenic epileptic syndromes (Harkin et al., 2007; Meisler and Kearney, 2005; Mulley et al., 2005). For example, over 80% of cases with severe myoclonic epilepsy of infancy (SMEI), also known as Dravet's syndrome, have mutations within the voltage-gated sodium channel gene *SCN1A* (Claes et al., 2001; Harkin et al., 2007). The SCN1A gene has also been implicated in generalized epilepsy with febrile seizures plus (GEFS+) (Escayg et al., 2000; Wallace et al., 1998), intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTCS) (Fujiwara et al., 2003), and was most recently implicated within a large meta-analysis of genome-wide associations studies in focal and generalized epilepsies including 8696 cases and 26157 controls (International League Against Epilepsy Consortium on Complex Epilepsies, 2014). In addition, in 1998, mutations of the two potassium channel subunit genes, *KCNQ2* and *KCNQ3*, were identified as the underlying genetic abnormality in benign familial neonatal convulsions

(BFNC), a condition characterized by recurrent seizures in newborn babies (Biervert et al., 1998; Charlier et al., 1998; Singh et al., 1998).

Whilst the association between mutations in sodium and potassium channel genes and both epileptic encephalopathies and adult epilepsies is well-established, the role of the calcium channel in the aetiology of human epilepsy is less clear (Thomas and Berkovic, 2014). Mutations in *CACNA1H* (neuronal voltage-gated T-type calcium channel subunit) have not been proven to cause epilepsy independently, but are better considered to be susceptibility variants (Heinzen et al., 2012). Nineteen single nucleotide polymorphisms (SNPs) identified in 240 cases identified in CACNA1H have been linked to the genetic generalized epilepsies and childhood absence epilepsy in particular (Heron et al., 2007). Like many candidate gene analyses, the findings from parallel sequencing studies did not support a major role for *CACNA1H* in the genetic generalized epilepsies (Heinzen et al., 2012). In contrast, there is a much more supportive literature for the role of calcium channel dysfunction in the rodent literature. Mouse models where serendipitous mutation produces seizures include stargazer (*CACNG2*), lethargic (*CACNB4*) and ducky (*CACNA2D2*) (Cain and Snutch, 2012). There is a wealth of literature on the epileptic encephalopathies, however, again the relevance of calcium channel gene mutation is unknown. De novo mutagenesis is the important mechanism in this devastating childhood epilepsy (Epi4K Consortium, 2013). Of the other bipolar disorder associated genes only *ANK3* has been linked to epilepsy. A *de novo* missense mutation in *ANK3* was shown in a child with Lennox-Gastaut syndrome and autism spectrum disorder in the Epi4K series (Epi4K Consortium, 2013). *ANK3* has an important regulatory function at the AMPA receptor (Smith et al., 2014). Finally, ion channels are pharmacologically related to epilepsy, in that several AEDs are known to exert action on sodium, calcium and potassium channels (Löscher, 2002; Rogawski and Löscher, 2004).

1.3.2 Summary

There exists a wealth of both clinical and aetiological-based research suggesting a link between bipolar disorder (BD) and epilepsy. However, this relationship is far from clear and further research is necessary to clarify the nature, impact and

mechanism of the co-occurrence of these disorders. A number of studies suggest that it is no longer appropriate to consider bipolar symptoms or bipolar spectrum disorders to be rare in epilepsy. Whether or not the bipolar symptomology identified within epilepsy should be considered to be in a spectrum with a disorder fulfilling diagnostic criteria, is currently unknown. However, it is important to stress the value of recognising all forms of bipolar symptomology, regardless of aetiology and whether or not they meet strict diagnostic criteria for classic BD, given their potential for profound negative impact on the individual (particularly given the known association between bipolar symptoms and suicidality). Variation in the epidemiological data available, in terms of the methodology employed, case definition of BD and bipolar symptomology, heterogeneous patient populations and scientific rigour, means that currently it remains difficult to make any robust statements regarding the risk and comorbidity of bipolar spectrum disorders in epilepsy. Although the assessment of psychiatric symptoms within epilepsy is a complicated endeavour, it appears there is a clear need to screen for bipolar symptomology within people with epilepsy and ensure appropriate integrated psychiatric care.

Conversely, there is a distinct lack of studies examining the reverse association; comorbid epilepsy within a sample of individuals with BD. As such, there is a clear need to assess whether epilepsy is overrepresented in BD, as well as to explore the potential clinical impact of epilepsy in BD. These lines of research will help us to clarify the potential bidirectional relationship between these two disorders and will shed some light on the true nature and direction of their association.

Whilst it is clear that more research is needed to unravel the clinical relationship between epilepsy and BD, there are a number of undeniable similarities between the two disorders. These include, their episodic nature, potential to run a chronic course, high heritability, and the efficacy of some anti-epileptic medications in the prophylaxis of both disorders. These lines of research are often cited as evidence of potential common underlying pathophysiology

between BD and epilepsy and ignite interest in the mechanisms surrounding this relationship.

The final section of this chapter will discuss the general aims and outline of the current thesis.

1.4 Aims and outline of the current thesis

The overall aim of this thesis is to further explore the relationship between bipolar disorder (BD) and the neurological conditions of migraine, and epilepsy, within a large, well-characterised sample of individuals with BD. The specific aims of this thesis are summarised below.

Given the caveats discussed in this introductory chapter of many existing studies examining the relationship between migraine and BD, ***the first aim of this thesis is to explore the rate of migraine (as defined by standardised International Headache Society criteria) within a large sample of bipolar subjects and to assess this rate across the bipolar diagnostic subtypes; bipolar I disorder (BDI), bipolar II disorder (BDII) and schizoaffective, bipolar type (SABP) (Chapter 3).*** It is hypothesized that the rate of migraine within the bipolar cohort will be higher than the approximate 12% rate reported in the general population (Breslau et al., 1991). In line with current literature (Fornaro, 2015), it is also hypothesised that the rate of migraine will be higher among those with bipolar II disorder (BPII) compared to those with bipolar I disorder (BPII). The current chapter presented evidence suggesting that the psychiatric comorbidity of migraine is dependent on migraine subtype, with migraine with aura (MA) suggested to have a stronger association with psychiatric disorders than migraine without aura (MoA) (Breslau et al., 1991; Samaan et al., 2009). Therefore, ***the second aim of this thesis is to extend existing literature by exploring the association between the migraine subtypes; migraine with aura (MA) and migraine without aura (MoA), and BD (Chapter 3).*** In addition, the current thesis employed various definitions of classifying migraine diagnosis (which will be described in detail in Chapter 2). Therefore, ***the third aim of this***

thesis is to assess the concurrent validity of these methods in deriving a diagnosis of migraine within individuals with BD.

Previous small-scale research has revealed differences in the clinical course of the bipolar illness according to the presence or absence of migraine (Mahmood et al., 1999; Low et al., 2003; Brietzke et al., 2012b; Saunders et al., 2014; Ortiz et al., 2010). Therefore, ***the fourth aim of this thesis looks to explore the impact of migraine comorbidity on course of illness in BD***, by establishing whether the presence of migraine defines a clinical subtype of bipolar subjects who experience a distinct set of lifetime clinical characteristics (Chapter 4). It is hypothesized that the clinical presentation of the bipolar illness will differ according to the presence of comorbid migraine. Despite the proposal that MA may have a stronger association with psychiatric disorder than MoA, to date no studies exploring the relationship of migraine with the clinical features of BD have differentiated between these subtypes. Therefore, the second part of Chapter 4, and ***the fifth aim of this thesis, will examine whether there exist differences in the lifetime bipolar clinical characteristics associated with MA and MoA, separately.***

As discussed within the current chapter, a potential explanation for the association between BD and migraine could be a shared underlying pathophysiology. Previous research suggesting that migraine comorbidity is associated with a distinct clinical profile within BD provides further support for the proposal that migraine may provide a useful tool for stratifying individuals with BD, potentially identifying subgroups of patients for which there may be shared genetic variation. Therefore, ***the sixth aim of this thesis is to examine genetic susceptibility to BD with comorbid migraine, through a genome-wide association study (GWAS) (Chapter 5).***

Whilst mood disorders have long been considered frequent psychiatric comorbid conditions in people with epilepsy, to date much of the neuropsychiatric literature has focused on the study of unipolar depression, with investigation in to BD remaining limited (Baker et al., 1996; Kanner and Balabanov, 2002; Blum et al., 2003; Eden and Toone, 1987; Robertson et al., 1994; Ottman et al., 2011). This is particularly surprising given the phenotypically similar symptom profile between epilepsy and BD, and the

efficacy of some anti-epileptic medications in the prophylaxis of both disorders. Therefore, within Chapter 6, I look to further explore the comorbid relationship between bipolar disorder and epilepsy. Firstly, ***Chapter 6 will assess the rate of self-reported epilepsy within a large, well-characterised sample of UK participants with a diagnosis of BD, which will constitute the 7th aim of this thesis.*** It is hypothesized that the rate of self-reported epilepsy identified in the bipolar sample will exceed the 1% rate reported in the general population (Ottman et al., 2011; Rai et al., 2012). The chapter will then describe a process for identifying a cohort of bipolar individuals with well-defined, expert-confirmed epilepsy. Using these two definitions of epilepsy (self-report and expert-confirmed), ***the 8th and final aim of this thesis will explore the relationship between epilepsy and the clinical features and course of illness within BD***, by examining lifetime clinical characteristics of illness in individuals with bipolar disorder according to their lifetime history of epilepsy. It is hypothesized that the clinical features of illness experienced will differ between bipolar subjects with and without comorbid epilepsy.

Chapter 2 will describe the methodological approach for studying each of the above aims.

Chapter 2

Methodology

2.1 Summary

This chapter describes the sample used throughout this thesis, including details of recruitment and clinical assessment procedures, and describes the main measures used within subsequent chapters. Details regarding specific methodology, sample characteristics and statistical analyses will be outlined within the appropriate chapters.

The sample and data utilized throughout this thesis originated from the Bipolar Disorder Research Network (BDRN; www.bdrn.org). I have been a member of BDRN since 2012, when, prior to my postgraduate studies, I joined the team as a Research Officer where I was responsible for the identification and recruitment of NHS patients into the research network.

2.2 Bipolar Disorder Research Network (BDRN)

The Bipolar Disorder Research Network (BDRN) is a large, ongoing programme of molecular genetic and clinical studies of affective disorders, with the overall aim of investigating biological, psychological and social determinants of mood disorders, including bipolar disorder (BD). BDRN was established in 2008 and is led by Principal Investigators Professor Ian Jones, Professor Lisa Jones and Professor Nick Craddock. BDRN was originally based both at Cardiff University and the University of Birmingham. In 2015, the research group based at the University of Birmingham moved to the University of Worcester, where the group continue to work in close collaboration with Cardiff University. The research programme is funded by the Wellcome Trust and the Stanley Medical Research Institute and has UK National Health Service (NHS) Research Ethics

Committee approval and Local Research and Development approval in all participating NHS trusts/health boards.

2.3 Sample recruitment

The Bipolar Disorder Research Network (BDRN) uses a number of methods to recruit research participants, including both systematic and non-systematic methods. At the time of writing, BDRN had recruited approximately 6150 participants to its network.

2.3.1 Systematic

Systematic recruitment methods involve screening for eligible participants through NHS services (e.g. Community Mental Health Teams and lithium clinics). With the approval of the treating Consultant, suitable patients are invited to participate in the study. Patients are not approached when acutely psychiatrically ill.

2.3.2 Non-systematic

Non-systematic recruitment methods involve promotion of the research within local and national media (including television, radio, press and internet coverage), advertisements on the research team's website (www.bdrn.org), and through patient support organisations, such as Bipolar UK (www.bipolaruk.org.uk).

2.4 Inclusion/exclusion criteria

Inclusion criteria of the research programme stipulate that individuals must be: 18 years or over; meet DSM-IV criteria for major affective disorder; and be able to provide written informed consent. Individuals are excluded from the study if they: have a lifetime diagnosis of intravenous drug dependency; have only experienced mood episodes as a result of alcohol/substance dependence, or medical illness; or are biologically related to another study participant.

2.5 Clinical assessment of the Bipolar Disorder Research Network

Participating subjects are interviewed in person by a trained psychiatrist or research psychologist. Following a complete description of the study, voluntary consent is obtained. Subjects then undergo a structured clinical assessment lasting approximately an hour and a half (described below), and provide a 30ml venous blood sample. Subjects are interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing JK et al., 1990). The SCAN was developed by the World Health Organisation as a set of instruments and manuals designed to assess, measure and classify psychopathology and behaviour across adult life that is associated with major psychiatric disorders. The SCAN sections assessing symptoms of mania, depression and psychosis were included within the BDRN interview. The SCAN assessment is supplemented by the OPCRIT (OPerational CRITeria) symptom checklist (Craddock et al., 1996; McGuffin et al., 1991); which is used to rate the presence or absence of manic, depressive and psychotic symptomatology, along with some other clinical features. Symptom items are rated on both a lifetime ever and worst-episode basis. Where possible, subjects' psychiatric and general practice case notes are reviewed and all available information is combined and best-estimate lifetime diagnoses are made according to the Diagnostic and Statistical Manual of mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000), and International Classification of Diseases, Tenth Revision (ICD-10; World Health Organisation, 1992). As discussed within the introduction of this thesis, the most recent edition of the DSM was introduced in 2013 (DSM-5; American Psychiatric Association, 2013). All of the cases involved in this thesis were rated prior to the publication of the most recent edition, and so were rated according to DSM-IV criteria (American Psychiatric Association, 2000).

Both the Global Assessment Scale (GAS) (Endicott et al., 1976) and Bipolar Affective Disorder Dimension Scale (BADDS) (Craddock et al., 2004) are rated using all available participant information, including information obtained from the SCAN interview and available case notes. GAS is a rating scale to measuring

overall severity of psychiatric disturbance and evaluates a subject's functioning during a specified time period on a continuum from 1 to 100, where 1 represents the hypothetically most unwell individual and 100 represents the hypothetically healthiest. GAS is rated according to three timeframes; i) lifetime worst in a depressive episode; ii) lifetime worst in a manic episode; and iii) functioning over the past week. BADDS is a rating system comprised of four dimensions measuring lifetime experience of psychopathology in each of these dimensions (Mania, Depression, Psychosis and Incongruence). Both the Mania and Depression dimensions are composite measures that take into account both the severity and frequency of episodes. Both dimensions are rated on a scale of 0 to 100, where 0 represents no evidence of manic/depressive symptoms and 100 represents evidence of more than ten incapacitating episodes of mania/depression. The Psychosis dimension rates the prominence of lifetime psychotic symptoms throughout illness, where 'illness' refers to both affective and non-affective periods of psychopathology. The final Incongruence dimension is a measure of the congruence of psychotic symptoms with affective state, where zero represents complete mood congruence (i.e. psychotic symptoms occur only during affective episodes) and 100 represents complete incongruence (i.e. psychotic symptoms have predominated the illness course and occur chronically outside, or in the absence of, affective episodes). The quantitative measure offered by the BADDS offers a dimensional system that complements traditional diagnostic classification systems.

2.5.1 Inter-rater reliability of lifetime psychiatric ratings

Consistency in diagnostic and rating procedures is assessed regularly by the BDRN research team through inter-rater reliability meetings. Inter-rater reliability was formally assessed for 20 randomly selected cases with a range of mood disorder diagnoses. Mean overall Cohen's kappa of 0.85 and 0.83 were obtained for DSM-IV and ICD10 diagnoses, respectively. Consistency in the rating of other key psychiatric clinical variables, including suicidal ideation, age of onset of psychiatric disorder and the number of episodes of mania and depression was also assessed. Inter-rater reliability for these key variables was high with mean kappa statistics (categorical variables) and intra-class

correlation coefficients (continuous variables) ranging from 0.81-0.99, and 0.85-0.97, respectively (Jones et al., 2005).

2.5.2 Questionnaire measures

Following interview, participants are left with a set of self-report questionnaires to complete. Written instructions request that participants complete all of the questionnaires at the same time and return them within one week in the stamped, addressed enveloped provided. Participants who do not return the questionnaire pack within one month receive a reminder letter which includes another copy of the questionnaire pack and a return envelope. Participants who do not return the questionnaire pack following a further two weeks receive a reminder telephone call.

The questionnaire pack left with participants includes the following measures:

- Beck Depression Inventory (BDI) (Beck et al., 1961).
- Altman Self-Rating Mania Scale (AMS) (Altman et al., 1997).
- Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975).
- Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) (Akiskal et al., 2005).
- Brief Life Events Questionnaire (BLEQ) (Brugha and Cragg, 1990).

Both the BDI and AMS were included to provide a measure of current mood state as residual affective symptoms have been shown to have a confounding effect on measures of underlying cognitive style and neuropsychological functioning (Ferrier et al., 1999; Jones et al., 2005). The questionnaire pack also asks participants about both their psychiatric and medical history. In order to establish the lifetime prevalence of physical health and psychiatric disorders, participants are asked the following question:

"Has a doctor or health professional ever told you that you have any of the following?"

Twenty physical health disorders are included in the questionnaire. These are: asthma, cancer, diabetes type 1, diabetes type 2, elevated lipids/high cholesterol, epilepsy, gastric ulcers, heart disease, hypertension, kidney

disease, liver disease, memory loss/dementia, migraine headaches, multiple sclerosis, osteoarthritis, osteoporosis, Parkinson's disease, rheumatoid arthritis, stroke, thyroid disease. The questionnaire also asks about the presence of 14 psychiatric disorders: attention deficit disorder (ADHD), autism, depression, bipolar disorder, obsessive compulsive disorder (OCD), agoraphobia, schizophrenia, panic disorder, phobias, anxiety, alcohol abuse, other substance abuse, anorexia and bulimia. For each disorder, participants can choose from three responses; 'yes', 'no', or 'not sure'.

2.6 BDRN newsletter and questionnaire follow-up assessment

As a means of keeping in contact with participants, BDRN produce an annual newsletter, enabling the group to share recent work and update participants on the progress of the research. The newsletter also allows participants to let us know of any changes to their contact details, thus keeping the contact details for the sample up to date. This newsletter is disseminated to all participants that have consented to future contact from BDRN. The newsletter also provides an opportunity to gather further information from participants and as such, at regular intervals (yearly to two yearly), BDRN send a questionnaire pack with the newsletter for participants to complete and return in a stamped, addressed envelope.

2.7 Assessment of migraine in the Bipolar Disorder Research Network

In 2011, Bipolar Disorder Research Network (BDRN) participants were sent a pack of 9 self-report questionnaires along with an annual newsletter, which included a 'headache' questionnaire to assess the lifetime history of migraine (**Appendix A**). The headache questionnaire included in the pack was a modified version of the Structured Migraine Interview (Samaan et al., 2009). The SMI was designed according to International Headache Society criteria (ICHD-II; Headache Classification Subcommittee of the International Headache Society,

2004) to assess the lifetime presence of migraine. The SMI consists of 10 questions to assess each of the individual items outlined in the criteria and evaluates; the presence of headache, severity, frequency, distribution, site, character and visual aura. When compared with consultant neurologists' diagnosis in 41 patients attending the London Migraine Clinic, face-to-face administration of the SMI was found to be highly sensitive (0.87) and moderately specific (0.58). In addition, the misclassification rate was reported to be 0.15, positive predictive value was 0.97, and negative predictive value was 0.26 (Samaan et al., 2010). The authors suggested that an explanation for the measure achieving only a moderate specificity may be that all subjects in the validation study had been referred to the London Migraine Clinical for headache, and so the sample was unbalanced by the lack of subjects without headache.

BDRN administered a modified version of the SMI self-report questionnaire to the research cohort. BDRN included seven additional questions to the original 10-item questionnaire to assess: headache frequency; additional aura symptoms; aura progression; aura succession; medical explanation for headaches; medical investigation; and family history of migraine. Not only did these additional questions provide further clinical information, but they also allowed for the assessment of sensory and speech-related aura symptoms, and for the diagnosis of both familial and sporadic hemiplegic migraine.

Responses from the headache questionnaire were scored to generate the following migraine diagnoses: migraine without aura (MoA); migraine with aura (MA) (including hemiplegic migraine); and probable migraine. The criteria used for deriving migraine diagnoses within the current thesis and are defined below:

1. Migraine without aura (MoA): Recurrent headache attacks fulfilling a-c:

   a) lasting between 4-72 hours; b) at least two of: pulsating/one-sided/moderate to severe pain intensity/aggravated by physical activity; c) associated with either nausea and/or vomiting, and/or hypersensitivity to sound or light.

2. Migraine with aura (MA): At least 2 episodes of aura symptoms including visual, sensory or speech disturbances accompanied by or followed by (within 60 minutes) a headache fulfilling criteria for migraine without aura (below). Aura symptoms must also meet at least two of the following:
   a) homonymous visual symptoms and/or unilateral sensory symptoms; b) at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes; or c) each symptom lasts ≥5 and ≤60 minutes.

3. Probable Migraine (PM): Recurrent headache meeting only 2 of criteria A-C for migraine without aura.

4. No migraine: Does not meet criteria for the above migraine diagnoses.

The criteria outlined above for diagnosing migraine within this thesis are based on those of the International Headache Society, however due to the design of the SMI, there do exist some minor discrepancies. Firstly, question 3 of the SMI asks about hypersensitivity to sound 'or' light, whereas International Headache Society Criteria (IHS) requires both photophobia 'and' phonophobia, for this feature to be scored as present. Within the original SMI, it has been argued that the change of wording of this question is unlikely to over-diagnose cases of migraine given that it has been shown that a quarter of patients with migraine tend to under report these symptoms during routine questioning (Evans et al., 2008). Secondly, IHS criteria stipulate that the headache should not be attributed to any of the following: head and/or neck trauma; cranial or cervical vascular disorder; non-vascular intracranial disorder; a substance or its withdrawal; infection; disorder of homeostasis; disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial cranial structures; or psychiatric disorder. Psychiatric disorder was not used as an exclusion factor for the diagnosis of migraine in the current thesis, given that an overall aim of the thesis was to explore the relationship between migraine and BD. Moreover, given the difficulty of attributing secondary effects and that the certainty of diagnosis of

secondary headache could not be guaranteed using the questionnaire methods employed, this criterion was omitted from the derivation of migraine diagnosis within the current thesis.

The headache questionnaire used by BDRN was designed and disseminated to the research cohort prior to my joining of the group and commencement of postgraduate studies. However, the coding of responses, derivation of migraine diagnoses and all subsequent analyses were all conducted by myself.

Chapter 3 of this thesis focuses on assessing the validity of the self-report headache questionnaire in screening for lifetime presence of migraine within a bipolar population. In order to achieve this, a random sub-sample of subjects were selected to complete a follow-up telephone interview. The telephone interview used within this thesis is a modified version of that employed by the Epilepsy Phenome Genome Project (EPGP) (Winawer and Connors, 2013). The EPGP is an international consortium of 27 clinical centers worldwide with the objective of collecting detailed phenotypic and genetic data on a large number of epilepsy participants. Within their clinical interview, the EPGP also gather information regarding migraine headaches. The migraine instrument used by the EPGP is a revision of a standardised and validated interview (Lipton et al., 2001), as recommended in the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements Project. The NINDS Common Data Elements Project set about developing data standards for clinical research and the first set of Common Data Elements (CDEs) for headache were developed in 2011. Validation of this tool in a population sample of 112 migraineurs and 62 control subjects with other types of headache (mostly tension type headache), revealed a sensitivity of 1 and specificity of .82 (Lipton et al., 2001).

The modified migraine interview used within this thesis can be found within **Appendix B**. One of the primary modifications made to this interview concerned the assessment of aura symptoms. The original interview included questions for the assessment of visual aura only. When I contacted the authors, they explained that this decision was justified by the finding that visual symptoms appear to be the most frequent (occurring in 99% of individuals with migraine with aura) and that those with several types of aura symptoms have been found to experience visual aura in virtually every attack (Russell and

Olesen, 1996). Within the BDRN sample we wanted a measure that assessed the full range of possible aura symptoms, and so included additional questions for the assessment of sensory, speech and motor-based aura symptoms. Moreover, it was not possible to map the questions included in the original interview regarding aura symptoms to criteria of the IHS, regarding its development and duration. Therefore, I included further questions to assess these detailed characteristics of the aura. Further additions to the interview included questions to assess: medical explanation for headaches, investigation and treatment for migraine; frequency of headaches; and family history of migraine. Finally, as telephone interviews were completed approximately three years following completion of the initial screening questionnaire (in the eight-month period between April-November, 2014), it was possible that participants could have experienced migraine headaches for the first time after completion of the initial questionnaire. Therefore, when participants were asked the age at which they first experienced severe headaches (question 2, **Appendix B**), the interviewer also noted whether this was before or after completion of the original migraine questionnaire in 2011, to account for such circumstances that could have acted to skew validation of the questionnaire tool.

All subjects were interviewed by myself. I was blind to the subject's original migraine diagnosis derived from the self-report questionnaire at the time of telephone interview.

2.8 Assessment of epilepsy in the Bipolar Disorder Research Network

Lifetime history of epilepsy was assessed in the Bipolar Disorder Research Network (BDRN) cohort via a staged screening strategy. Within stage 1 of this screening strategy, a self-report questionnaire measure was disseminated to BDRN participants as part of a larger questionnaire pack, in the summer of 2013, by myself and the rest of the BDRN research team during the second year of my PhD study (**Appendix C**).

The self-report epilepsy questionnaire utilized by BDRN was a modified version of a brief screening instrument to identify individuals with epilepsy, designed by Ottman et al. (2010). The original instrument consisted of 9 questions and included items that targeted recognised seizures, as well as symptom-based questions targeting possible unrecognised seizures (**figure 2.1**).

1. Did anyone ever tell you that you had a seizure or convulsion caused by a high fever when you were a child?
2. [Other than the seizure[s] you had because of a high fever] Have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?

Ask the following questions only if subject said "no" to epilepsy or a seizure disorder in q2. Otherwise go to next part of interview.

3. [Other than the seizure[s] you had because of a high fever] Have you ever had, or as anyone ever told you that you had, any of the following…

A. A seizure, convulsion, fit or spell under any circumstances?
B. Uncontrolled movements of part or all of your body such as twitching, jerking, shaking or going limp?
C. An unexplained change in your mental state or level of awareness; or an episode of "spacing out" that you could not control?
D. Did anyone ever tell you that when you were a small child, you would daydream or stare into space more than other children?
E. Have you ever noticed any unusual body movements or feelings when exposed to strobe lights, video games, flickering lights, or sun glare?
F. Shortly after waking up, either in the morning or after a nap, have you ever noticed uncontrollable jerking or clumsiness, such as dropping things or things suddenly "flying" from your hands?
G. Have you ever had any other type of repeated unusual spells?

Figure 2.1 Nine question screening instrument for the ascertainment of epilepsy (Ottman et al., 2010).

Each question within the screening instrument could be answered 'no', 'yes', 'possible', or 'don't know', where a response was classified as positive if the subject answered 'yes' or 'possible'. Ottman et al. (2010) validated their screening instrument by administering it through a telephone interview to individuals with medical record–documented epilepsy (n=168) or isolated unprovoked seizure (n=54), and individuals who were seizure-free on medical record review (n=120), from the Rochester Epidemiology Project population-

based study. Within their validation study, Ottman et al. (2010) considered four definitions of a positive screen which consisted of a positive response to: (1) any question in the screening instrument (any positive); (2) any of Q2 through Q3G (any positive excluding febrile seizure); (3) Q2 or Q3A (epilepsy or any seizure); and (4) Q2 only (epilepsy only). For each screen definition, sensitivity was defined as the proportion of subjects with medical record–documented unprovoked seizures who screened positive, and the false-positive rate (1-specificity) was defined as the proportion of subjects who screened positive among subjects found to be seizure-free on record review. Of those individuals identified as having epilepsy on record review, 76% responded positively to the 'epilepsy' screening question (Q2), compared to only 46% of those with isolated unprovoked seizure on record review. Among those who did not respond positively to Q2, 15% of those with epilepsy and 35% of those with isolated unprovoked seizure responded positively to the 'any seizure' question (Q3A). Only a small number of subjects responded positively to the symptom-based questions (Q3B-G). The only possible exception was Q3C which asked about "a change in mental state or level of awareness", in which both subjects with and without unprovoked seizures were equally likely to respond positively.

Sensitivity was highest for the broadest screen definition (positive response to any screen question) among both those with medical record documented epilepsy (96%) and isolated unprovoked seizure (87%). However, it is important to note that 7% of seizure-free subjects also screened positive according to this definition. Sensitivity declined when the febrile seizure question was excluded, both for subjects with epilepsy (94%) and those with an isolated unprovoked seizure (85%). Next, when the screen definition of "epilepsy or any seizure" (Q2 or Q3A) was employed, sensitivity was slightly lower and the false-positive rate declined to 3%. Finally, using the "epilepsy only" screen definition (Q2), sensitivity declined to 76% among epilepsy patients however the false positive rate also declined considerably to 0.8%. Ottman et al. (2010) also calculated the positive predictive value (PPV; the proportion of screen-positive individuals subsequently confirmed to be affected), based on an epilepsy prevalence of 2%. They revealed PPV to be the lowest for the broadest screen definition. Therefore, although this group yielded the highest sensitivity, an expected PPV of 23% suggests that approximately only one in four positive screens would be

confirmed as having epilepsy within subsequent stages of screening, using this broad screen definition of epilepsy. In contrast, Ottman et al. (2010) reported that use of the epilepsy question alone produced the highest PPV, estimating that 66% of screen-positive individuals would be confirmed to have epilepsy using this question. Ottman et al. (2010) argue that the optimal choice for screening depends on the resources available and the purpose of a particular study. For example, if the objective is to estimate the prevalence of epilepsy, then it is essential that sensitivity is maximised to avoid underestimation. However, it must also be acknowledged that the rate of false positives will be high and positive screens will need to be evaluated in a second stage of screening to confirm true epilepsy cases. Conversely, if the objective of a study is to identify individuals likely to have epilepsy for further analysis (for example, comorbidity studies; Kobau et al., 2006; Ottman et al., 2011) it is suggested that the use of the epilepsy question alone (Q2) may be sufficient at minimal cost (i.e. lowest false positive rate).

Within Chapter 6 of this thesis, the objective was to identify individuals with epilepsy within a cohort of individuals with bipolar disorder to examine potential differences in lifetime bipolar clinical characteristics according to presence of epilepsy. Therefore, it was decided that a screening definition of epilepsy with the highest specificity (lowest false positive rates) was required. Consequently, for the purposes this thesis, self-reported epilepsy/seizures was defined as anyone who screened positively (answering either 'yes' or 'possible') to the main seizure disorder/epilepsy question:

'Other than the seizure[s] you had because of a high fever (so other than febrile seizures), have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?'

Although it was anticipated that use of the above screening question to identify epilepsy cases within the bipolar sample would provide a low false positive rate, this thesis looks to more definitely define epilepsy within the cohort through the use of a detailed telephone interview, in order to separate true from false positives. Details of this process are described fully in Chapter 6. The telephone interview utilised within this thesis was an adaptation of a standardised, structured diagnostic inventory employed by the Epilepsy Phenome Genome

Project (EPGP) and can be found in **Appendix D**. The interview used by the EPGP was modified from a previously validated instrument; the Seizure Classification Interview (SCI) which was originally developed as part of the Epilepsy Family Study Proband Interview Form (Ottman et al., 1993, 1990). The SCI contains both structured questions in discrete categories (e.g. 'yes', 'no', or 'don't know'), as well as open-ended free verbatim questions. The SCI contains separate sections to assess four categories of seizures: 1) 'big seizures' or grand mal seizures; 2) 'small seizures' or partial seizures; 3) 'sudden jerking of part or all of your body'; and 4) 'episodes in which part or all of your body suddenly goes limp, causing you to fall or drop things'. The section on grand mal seizures is designed to distinguish between primary and secondary generalization, and includes questions on age at onset, history of aura, unilateral onset of convulsions, postictal unilateral weakness and numbness, and postictal aphasia. A verbatim section asks participants to describe what happens before, during, and after the seizure. Loss of consciousness is assessed with questions asking about history of postictal confusion and drowsiness, and inability to recall events during the seizure.

The next section on 'small seizures' includes questions on age at onset, seizure duration, changes in awareness and ability to communicate with surroundings, focal motor activity, automatisms, eye-fluttering, postictal confusion, and postictal drowsiness. A verbatim description of what happens before, during, and after a small seizure is also requested. If the patient has had more than one type of small seizure, they are asked to name these in the order of most to least frequent and the questions included in this section of the interview are repeated for each type. The primary aim of the section on episodes of sudden jerking is to confirm history of myoclonic seizures, and includes questions on age at onset, extent of body involvement (i.e., part or all), unilateral or bilateral involvement, restriction of episodes to the same side, and usual timing (i.e., only before sleep, only before a big seizure, only on awakening).

The final section on episodes of going limp aims to ascertain history of atonic seizures and includes questions on age at onset, loss of consciousness, and postictal confusion. A validation study of the SCI based on 50 patients confirmed to have a lifetime history of epilepsy (defined as the lifetime history of two or more unprovoked seizures, in line with the International League Against

Epilepsy; ILAE), compared interview-based diagnoses with independent diagnoses made by neurologists (also using the ILAE system for seizure classification) (Ottman et al., 1990). The study revealed that interview diagnoses agreed with those of the neurologist for broad seizure-type classifications (i.e., partial vs. generalized onset) in 88% of patients, and for the diagnosis of specific seizure type in 64% of patients. Sensitivity ranged from 0.60 to 1.0 for partial onset seizures, and from 0.43 to 0.67 for generalized onset seizures. Specificity ranged from 0.60 to 0.87 for partial onset seizures, and was 1.0 for generalized onset seizures. Positive predictive value was 0.95 for any partial onset and 1.0 for any generalized onset seizure. These results suggest that the SCI can be used to produce accurate diagnoses of major seizure categories.

Within their assessment, the EPGP employed a modified version of the SCI which no longer included separate sections for the third and fourth seizure categories of 'sudden jerking' and 'going limp', and rather incorporated these within a 'small seizures' section. The semi-structured interview used by the EPGP was designed to ascertain seizure type, symptomatology, seizure frequency, age at onset, history of status epilepticus, epilepsy syndrome, anticonvulsant response, and additional medical conditions including migraine. The interview comprised of the following sections: grand mal seizure overview (which mirrored the 'big seizures' section in the SCI); a small seizure overview; a section asking about seizure triggers; a screen for status epilepticus, prolonged seizures and recurrent seizures; a section to assess the lifetime history of migraine headaches (described in Section 2.7 of this chapter); and a final section asking about alcohol intake and its relation to seizures.

The telephone interview employed within this thesis was an adapted version of that used by the EPGP. One of the main differences between these two interviews involved the structure of sections to ascertain an overview of seizure types. As outlined above, the EPGP employed separate sections to assess 'big seizures' and 'small seizures'. The modified interview used within the current thesis did not separately assess these. Rather, in line with the structure of the EPGP interview section for 'small' seizures, we asked participants to name each different seizure type they had experienced (where a different 'type' was described as one where they feel different during the event, or if what happens

before, during or after the event is different from other types). We then asked participants to list these in the order from most to least frequent, and participants were asked about each of their seizure types in turn. As per the EPGP interview, we asked participants questions to assess age at onset, seizure duration, changes in awareness and ability to communicate with surroundings, postictal confusion, and postictal drowsiness, as well as a verbatim description of what happens before, during, and after the seizure. We did not, however, ask participants the specific symptom questions included in the EPGP interview. This decision was made as it was thought that the purpose of these questions were to determine the type of epilepsy experienced, whereas the aim of the study reported in the current thesis was to identify the presence of epilepsy (of any kind).

Further differences between the EPGP interview and modified interview used within this thesis include the omission of sections assessing status epilepticus, as well as other medical conditions (migraine). Moreover, within the section relating to alcohol intake, the interview used within this thesis asked participants more generally about their intake and its relation to their seizures, rather than asking about alcohol intake prior to and following the onset of their epilepsy/seizures as per EPGP interview. Finally, the interview employed within this thesis included additional sections that were not included in the original interview. These included sections to assess; any medical examinations/investigations the participant had received in relation to their seizures, medication prescribed, and family history of seizures and epilepsy.

In order to determine a diagnosis of epilepsy, all interviews were reviewed together by myself and Consultant Epileptologist, Professor Mike Kerr. In the instance of complex cases, these were blind reviewed by a second Epileptologist, Dr Rhys Thomas, and a consensus diagnosis was reached.

2.9 Data capture – Formic

The BDRN interview and questionnaire measures described above are designed using the data capture system Formic Fusion (Formic Ltd: Middlesex, UK). This system allows completed forms to be scanned so that the data are electronically

recorded. The scanning procedure also allows data verification checks to be performed. Following data capture, the data can then be viewed and exported for further use.

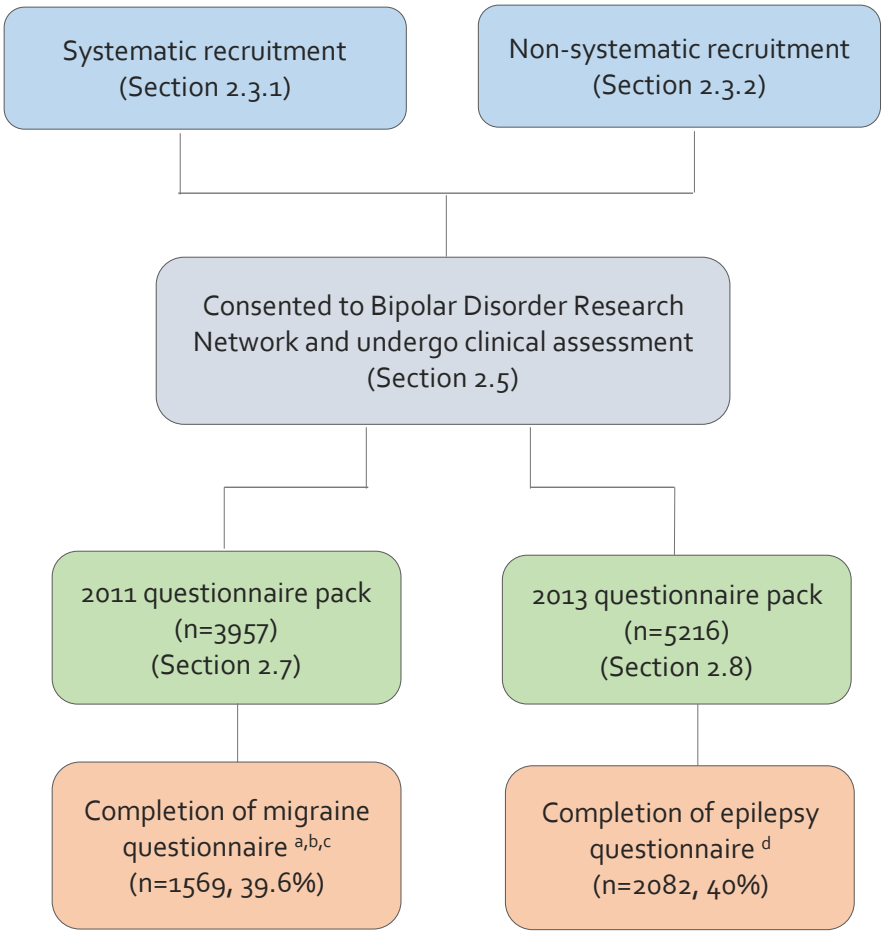
Whilst the headache questionnaire used by BDRN was designed and disseminated to the research cohort prior to my joining of the group, the questionnaire pack including the epilepsy questionnaire, as well as both migraine and epilepsy telephone interviews were designed by myself using the formic system. Completed questionnaire packs of the entire BDRN cohort were also scanned and validated by myself.

2.10 Statistical analysis

Details regarding specific analyses employed will be described within each chapter. Analyses were performed using SPSS version 20 (IBM Corp, 2011) unless stated otherwise. Normality of the data was assessed using the Kolmogorov-Smirnov test. The majority of the data analysed were not normally distributed and so non-parametric tests were employed. Statistical tests were considered significant at the $p<0.05$ level (two tailed) unless stated otherwise.

2.11 Overview of samples used within the present thesis

Figure 2.2 shows the derivation of the samples used within each chapter of this thesis.



[a] Chapter 3; [b] Chapter 4; [c] Chapter 5; [d] Chapter 6

Figure 2.2 Diagram to show the derivation of the samples used within each chapter of this thesis.

Chapter 3

Examination of migraine in a bipolar disorder sample

3.1 Introduction

The introductory chapter of this thesis explored evidence for overlap between the neurological disorder of migraine, and bipolar disorder (BD), and outlined a number of clinical and population studies reporting an increased prevalence of migraine among BD sufferers (Mahmood et al., 1999; McIntyre et al., 2006b; Ortiz et al., 2010; Gordon-Smith et al., 2015). It was also reported that individuals with bipolar II disorder (BDII) may be disproportionately affected by migraine (Fasmer, 2001; Ortiz et al., 2010; Saunders et al., 2014); a finding supported by a recent meta-analysis exploring the prevalence and moderators of migraine in BD (Fornaro and Stubbs, 2015). Chapter 1 also outlined differences in the psychiatric comorbidity of migraine that were dependent on migraine subtype, with migraine with aura (MA) observed to have a stronger association with psychiatric disorders than migraine without aura (MoA) (Ball et al., 2009; Breslau et al., 1991). Taken together, this evidence suggests that migraine is frequently comorbid with BD and that the strength of this association varies according to the particular subtype of migraine, and of BD, under study. Further evidence identifying differences in the clinical course of the bipolar illness in those with comorbid migraine, and the possibility of common pathophysiological mechanisms between the two disorders, suggest that migraine may delineate a distinct subset of individuals with BD. However, given the caveats of a number of existing studies regarding: small sample sizes; lack of standardised criteria for migraine; unrepresentative clinical samples; and inconsistency across studies in their definition of bipolar subtypes (in particular

BDII), further research is required to examine the complex relationship between migraine and BD.

The current chapter looks to extend existing literature by identifying the rate of migraine within a large, well-defined UK sample of individuals with a Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV; American Psychiatric Association 2000) diagnosis of BD. This study will also assess the rate of migraine across the bipolar diagnostic subtypes; bipolar I disorder (BDI), bipolar II disorder (BDII) and schizoaffective, bipolar type (SABP). A further focus of this study is to explore the association between the migraine subtypes; migraine with aura (MA) and migraine without aura (MoA), and BD. Chapter 2 described the different methods employed by the Bipolar Disorder Research Network (BDRN) for the case definition of migraine, and so the final aim of this chapter will assess the concurrent validity of these methods for the measurement of migraine within the bipolar sample.

3.2 Methods

3.2.1 Subjects

Participants were drawn from the Bipolar Disorder Research Network (BDRN), a clinical and genetic study of individuals across the United Kingdom with mood disorders, described in detail within Chapter 2.

A questionnaire pack including a self-report questionnaire assessing lifetime history of migraine (detailed within Chapter 2; **Appendix A**) was disseminated to 3957 BDRN participants. Of these, 1583 individuals completed and returned the questionnaire pack (response rate of 40%). Of these, 1569 (99%) individuals had completed the migraine questionnaire. Individuals were included in the current study if they met DSM-IV (American Psychiatric Association, 2000) diagnostic criteria for bipolar I disorder (BDI), bipolar II disorder (BDII), or schizoaffective, bipolar type (SABP), leaving 1428 participants in the current study.

3.2.2 Assessment of migraine

3.2.2.1 Self-report questionnaire

The lifetime history of migraine within the bipolar sample was primarily assessed using the self-report questionnaire. The questionnaire was a modified version of The Structured Migraine Interview (SMI) (Samaan et al., 2009) and is outlined within Chapter 2. Using this measure, a diagnosis of migraine was assigned according to criteria of the International Headache Society (IHS) (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004) for migraine without aura (MoA), migraine with aura (MA) (including hemiplegic migraine, HM), and probable migraine.

3.2.2.2 Telephone interview

In order to assess the concurrent validity of the self-report questionnaire in screening for the lifetime presence of migraine within a bipolar population, a random sub-sample of subjects were selected to complete a follow-up telephone interview. This sub-sample was chosen to comprise of 100 subjects; 20 individuals identified as having no history of migraine according to the self-report questionnaire, 60 individuals identified as having probable migraine, and 20 individuals identified as having a lifetime history of migraine. The majority of cases were selected from the 'probable migraine' group because this was the group where it was expected there was likely to be less concordance between actual diagnosis and that derived from the screening measure compared to those identified as definitely having or not having migraine. Individuals with probable migraine are missing just one criterion for a full migraine diagnosis and so it is likely that a number of these represent true migraine cases. Thus, the proportion of individuals to be contacted within each diagnostic group was chosen to allow for further investigation into the probable migraine group, to explore the appropriateness of adopting a broader definition of migraine, incorporating those with probable migraine. Participants from each diagnostic group (migraine, probable migraine and no migraine) were randomly selected to be contacted for telephone interview.

In order to be considered for selection for telephone interview, participants were required to have address and contact number details recorded on the study

database. Once these participants had been identified, their unique study identifier was listed in ascending order in an excel spreadsheet (participants from each migraine group; migraine, probable migraine, no migraine, were listed in separate spreadsheets). In order to assign random numbers to each participant, the excel command "=RAND()" was used. Participants were then ordered according to their assigned random number. From the ordered and randomised list for each migraine group, the top 20 were selected to be contacted for telephone interview from the migraine and no migraine groups, and the top 60 were selected from the probable migraine group, as discussed above. Once telephone interviews had commenced, it was decided that a further 10 individuals would be randomly selected to be contacted for telephone interview to allow for the likelihood that a 100% response rate would not be achieved. These 10 individuals were selected in line with the process and group proportions detailed above; 2 from the no migraine group, 6 from the probable migraine group and 2 from the migraine group.

Individuals selected for telephone interview were sent an initial contact letter, which provided brief details about the research and informed individuals that a researcher would be in contact over the next few weeks. Individuals were also given the opportunity to refuse any further contact regarding this research, by contacting the study team by telephone or email. If the individual did not contact the team, I called the participant to answer any questions they may have had regarding the research and to discuss whether they would be interested in taking part.

The telephone interview employed was an adaptation of a standardized and validated interview, developed by (Lipton et al., 2001) (**Appendix B**) and is described in detail in Chapter 2. All subjects were interviewed by myself and I was blind to the subject's original migraine diagnosis derived from the self-report questionnaire at the time of telephone interview.

3.2.2.3 Single item checklist

As described in Chapter 2, as part of the BDRN clinical assessment, individuals were asked about their history of a variety of medical illnesses on a brief self-report medical history checklist. Specifically, information regarding lifetime history of medical illness was assessed by asking participants if a doctor or

health professional had ever told them that they had ever had any of twenty medical disorders, including migraine headaches.

3.2.3 Statistical analysis

3.2.3.1 Migraine prevalence according to BD diagnostic subtype

Lifetime prevalence of migraine was compared across bipolar I disorder (BDI), bipolar II disorder (BDII), and schizoaffective bipolar type (SABP) diagnostic groups, with chi-square tests, to determine whether rates significantly differed between groups. To assess the association of each bipolar diagnostic subtype (BDI, BDII and SABP) with migraine, binary logistic regression analysis was conducted for each bipolar subtype (against other diagnoses combined as a reference group) with migraine status as the outcome variable. Due to the known increased rate of migraine among women, sex was also entered in to the logistic regression models as a covariate. In addition, a significant difference in age at interview was found between bipolar diagnostic groups (p=.027) with the median age at interview being highest within the BPI group (49 years), followed by the BPII group (47 years), followed by the SABP group (44 years). Migraine prevalence is known to peak in mid-life and decline thereafter, therefore given the age range observed across bipolar diagnostic groups, age was also included as a covariate.

3.2.3.2 Association of migraine subtypes across BD diagnostic subtypes

To assess the association of each migraine subtype; migraine with aura (MA) and migraine without aura (MoA), with bipolar diagnostic groups (BDI, BDII, and SABP), a binary logistic regression was conducted for each BD diagnostic group; firstly with MoA vs. no migraine, and secondly with MA vs. no migraine, as the outcome variable. As above, age and sex were entered into the logistic regression models as covariates.

3.2.3.3 Comparison of BDRN methods for determining a migraine diagnosis

The primary method used to determine migraine diagnosis within the current study was the interpretation of responses to the self-report migraine questionnaire, according to IHS criteria. However, in order to clarify symptoms of migraine and to provide an extra degree of certainty about the diagnosis, telephone interviews were conducted on a sub-sample individuals (described in Section 3.2.2.2). As described in the 'Assessments' section (Section 3.2.2), BDRN also have data available from a single item checklist asking whether individuals had ever been told by a doctor or health professional whether they had a variety of medical illnesses, including migraine. This study will compare the performance of these methods in establishing a diagnosis of migraine within subjects with BD.

Firstly, the study aims to assess concurrent validity of the single item checklist measure of migraine diagnosis, using the diagnosis established with the self-report questionnaire as the reference diagnosis. Secondly, the study aims to assess validity of the self-report questionnaire, using the diagnosis derived from telephone interviews as the reference diagnosis.

For both of the above comparisons, validity was assessed by calculating sensitivity, specificity, positive and negative predictive value. Sensitivity of an instrument refers to the ability of the tool to correctly identify individuals with a particular disease and is calculated as follows:

$$Sensitivity = \frac{true\ positive}{true\ positive + false\ negative)}$$

Specificity refers to an instrument's ability to correctly identify those without the disease in question:

$$Specificity = \frac{true\ negative}{(true\ negative\ + false\ positive)}$$

Measures of sensitivity and specificity are computed in order to evaluate the ability of a test to discriminate between individuals with and without a particular disease. Both parameters are population measures and so summarise characteristics of a test over a particular population. Consequently, they have limited clinical usefulness in determining an individual patients' probability of having the disease in question. Alternatively, when we know a patient's test result and want to interpret that to assess the likelihood of them having the disease, predictive values are considered to be more appropriate. Positive predictive value (PPV) is defined as the probability that the disease is present when the test is positive:

$$PPV = \frac{true\ positive}{(true\ positive + false\ positive)}$$

Conversely, negative predictive value (NPV) is the probability that the disease is not present when the test is negative:

$$NPV = \frac{true\ negative}{(true\ negative + false\ negative)}$$

3.3 Results

3.3.1 Completion of BDRN questionnaire pack

Of the 3957 questionnaire packs disseminated to BDRN participants, 1583 were completed and returned, providing a response rate of 40%. Of those who returned their questionnaires, 1569 (99.1%, 39.6% of total) had completed the migraine questionnaire and of these, 1428 met DSM-IV diagnostic criteria for bipolar disorder, with 993 (69.5%) having a diagnosis of bipolar I disorder (BDI), 380 (26.6%) of bipolar II disorder (BDII), and 55 (3.9%) of schizoaffective, bipolar type (SABP). Of the 1428 subjects included in the current study, 1049 (73.5%) were female. The mean age of participants at interview was 48.03 ± 11.7 years (range 18-83 years).

Given that the self-report migraine questionnaire was disseminated to BDRN participants as part of a larger questionnaire pack, it is possible that participants with a history of migraine may have been more likely to complete the migraine questionnaire, potentially biasing the sample. To further explore this, I examined completion rates of the additional eight questionnaires included in the questionnaire pack, by those who completed the migraine questionnaire (**Table 3.1**).

Table 3.1 Completion rates of additional questionnaires by participants completing the migraine questionnaire

Number of additional questionnaires completed by participants completing the migraine questionnaire	**N (%)**
All 8 additional questionnaires	1137 (72.5%)
7 additional questionnaires	415 (26.4%)
6 additional questionnaires	15 (1%)
5 additional questionnaires	1 (0.05%)
4 additional questionnaires	1 (0.05%)
3 additional questionnaires	0
2 additional questionnaires	0
1 additional questionnaires	0
Migraine questionnaire only	0

Of the 1569 subjects who completed the migraine questionnaire: 1137 individuals (72.5%) completed the additional 8 questionnaires included within

the pack, and a further 415 individuals (26.4%) completed 7 questionnaires. No individuals completed the migraine questionnaire only.

As mentioned above, 99.1% of the 1583 BDRN subjects who returned the questionnaire pack completed the migraine questionnaire. Examination of the 14 subjects (0.9%) who returned their questionnaire pack but did not complete the migraine questionnaire revealed that: 28.6% (n=4) completed all of the further 8 questionnaires included in the pack; 42.9% (n=6) completed 7 other questionnaires; 14.3% (n=2) completed 6 other questionnaires; 7.1% (n=1) completed 5 other questionnaires; and finally, 7.1% (n=1) completed 4 other questionnaires included in the pack.

3.3.2 Migraine prevalence within the BD sample

According to the self-report questionnaire, a total of 277 (19.4%) individuals were identified as having comorbid migraine according to IHS criteria (21.7% among women and 12.9% among men). A further 304 (21.3%) met criteria for probable migraine, which as stated previously, is an attack or headache missing one of the features needed to fulfil all IHS criteria for a migraine disorder. 65 (4.5%) individuals were found to have typical aura with non-migraine headache, and 4 (0.3%) were classified as having typical aura without headache. Finally, 778 (54.5%) individuals were found to have no migraine. **Figure 3.1** depicts the breakdown of these categories within the total sample.

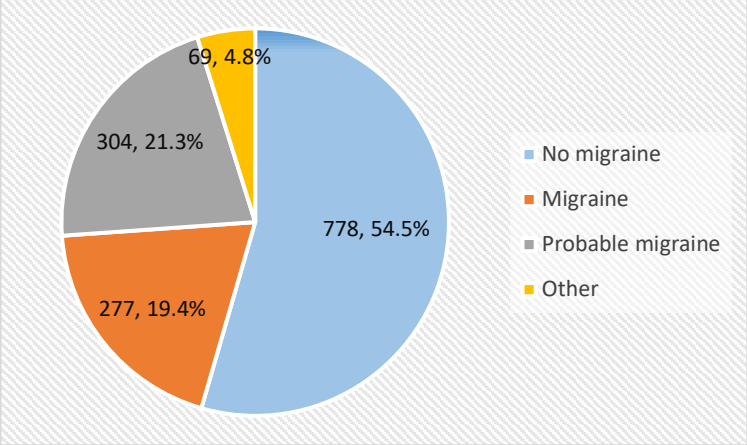


Figure 3.1 Migraine prevalence within the bipolar sample (N=1428).

Note: 'Other' consists of typical aura with non-migraine headache n=65 (4.5%) and typical aura without headache n=4 (0.3%)

Figure 3.2 shows the breakdown of migraine diagnoses within the 277 individuals meeting IHS criteria for migraine.

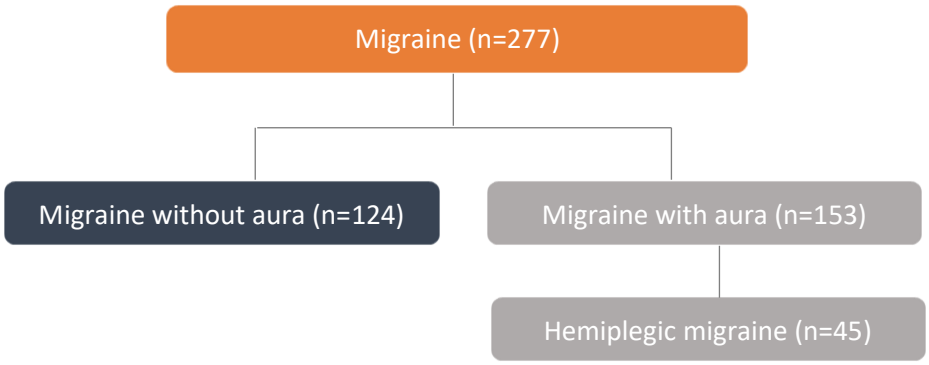


Figure 3.2 Breakdown of International Headache Society (IHS) migraine diagnoses of the 277 individuals identified as having migraine according to the self-report questionnaire.

Of the 277 (19.4%) individuals meeting IHS criteria for migraine; 153 (55.2%; 10.7% of total sample) met criteria for migraine with aura (MA); 46.9% in males and 57% in females. Forty-five individuals with MA met criteria for hemiplegic

migraine (HM) (16.2%; 3.1% of total sample). One-hundred and twenty-four individuals (44.8%; 8.7% total sample) met criteria for migraine without aura (MoA); 53.1% in males and 43% in females.

3.3.2.1 Migraine prevalence according to bipolar diagnostic subtypes

Figure 3.3 displays the rate of migraine across bipolar diagnostic subtypes (BDI, BDII and SABP).

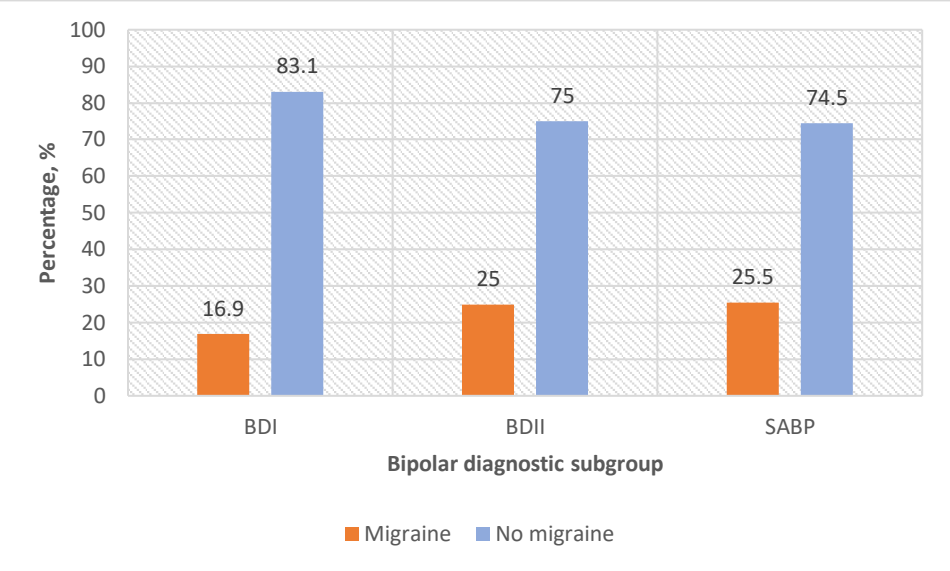


Figure 3.3 Rate of migraine (%) across bipolar diagnostic subtypes, bipolar I disorder (BDI) (n=993), bipolar II disorder (BDII) (n=380), and schizoaffective bipolar type (SABP) (n=55).

Figure 3.3 reveals that migraine prevalence was found to be highest among individuals with SABP (25.5%) and those with BDII (25%). Individual chi-square tests revealed that the rate of migraine was statistically significantly higher in those with BDII when compared to those with BDI (p=.000004).

To assess the association of migraine with each bipolar diagnostic subtype (against other diagnoses combined) individual logistic regression models were constructed with presence or absence of migraine as the outcome variable (**Table 3.2**). Analyses included age and gender as covariates as described in the methods section (Section 3.2.3).

Table3.2 Association of migraine with bipolar diagnostic subtypes

Bipolar subtype	Adjusted odds Ratio (OR)	95% CI		P-value
		Lower	Upper	
BDI	.487	.361	.657	.000002*
BDII	2.027	1.486	2.765	.000008*
SABP	1.439	.730	2.836	.293

**p<.01. AOR=adjusted odds ratio controlling for age and sex; CI=confidence interval; BDI=bipolar I disorder; BDII=bipolar II disorder; SABP=schizoaffective bipolar type*

A significant negative association was found to exist between migraine and BDI (OR: .487; 95% CI: .361-.657), and a significant positive association was found between migraine and BDII (OR: 2.765; 95% CI: 1.486-2.765). A positive association was also found between migraine and the SABP patient group; however this association failed to reach statistical significance, which may be due to the small number of cases in this group (n=55).

3.3.3 Migraine subtypes and their association with BD

Figure 3.4 displays the rate of migraine without aura (MoA), and migraine with aura (MA) across bipolar diagnostic subtypes. Rates of MA were higher than MoA in each of the bipolar diagnostic subtypes and were highest in the schizoaffective bipolar (SABP) group (64.3%), followed by the bipolar II disorder (BDII) group (57.9%), followed by the bipolar I disorder (BDI) group (53%).

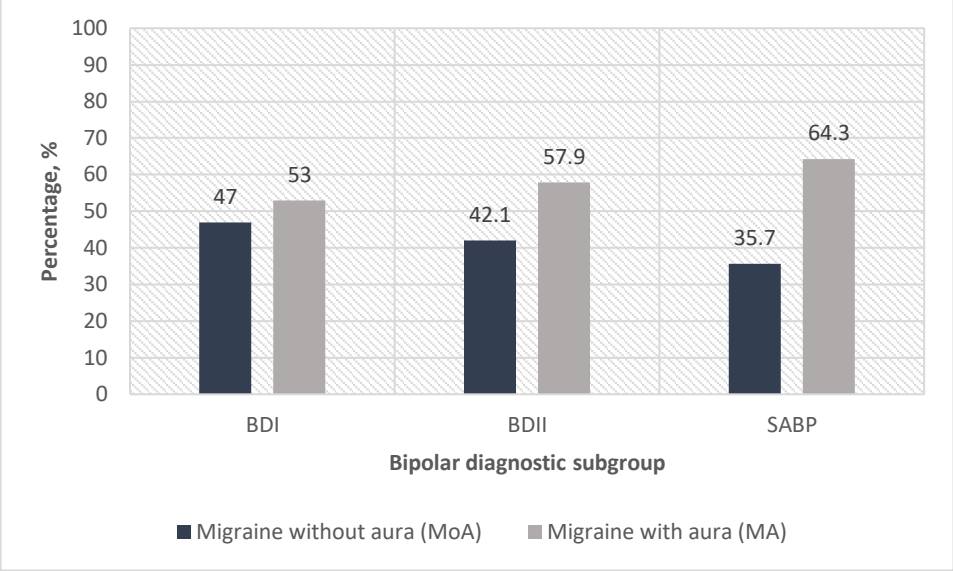


Figure 3.4 Rate of migraine with aura and migraine without aura across bipolar diagnostic subtypes, bipolar I disorder (BDI), bipolar II disorder (BDII), and schizoaffective bipolar type (SABP)

It was also of interest to determine the association of each migraine subtype (MA and MoA) with individual bipolar diagnostic subgroups (BDI, BDII and SABP). To explore this, individual logistic regressions were computed to examine the specific association of each of the bipolar diagnostic subtypes (compared with all other diagnoses combined) with; i) migraine with aura (MA) vs. no migraine, and ii) migraine without aura (MoA) vs. no migraine. **Table 3.3** displays adjusted odds ratios (OR) including age and gender as covariates, 95% confidence intervals (95% CI), and p-values for each migraine subtype (compared to no migraine) across bipolar diagnostic groups.

Table 3.3 Association of bipolar disorder subtypes in individuals with aura (MA) and without aura (MoA) compared with individuals with no migraine

Bipolar subtype	Migraine without aura (MoA), n (%)		Migraine with aura (MA), n (%)	
	AOR (95% CI)	P-value (95% CI)	AOR (95% CI)	P-value
BDI	.555 (.369-.834)*	.005*	.436 (.302-.631)*	.00001*
BDII	1.875 (1.231-2.858)*	.003*	2.183 (1.491-3.194)*	.000059*
SABP	1.066 (.397-2.867)	.899	1.740 (.784-3.863)	.174

** p<.01. AOR=adjusted odds ratio controlling for age and sex; 95% CI=95% confidence interval; BDI=bipolar I disorder; BDII=bipolar II disorder; SABP=schizoaffective bipolar type*

Table 3.3 shows that the same direction of effects that were observed with any migraine vs no migraine are seen with both migraine subtypes, in terms of a significant negative association of MoA and MA with BDI, and a significant positive association with BDII. Moreover, it can be seen that the strength of the association with BDII is larger for MA than for MoA, and is also larger than the association with any migraine (**Table 3.2**).

3.3.4 Validation of measures for migraine diagnosis

3.3.4.1 Single item checklist vs. self-report questionnaire for migraine diagnosis

Table 3.4 shows the breakdown of migraine and no migraine diagnoses according to the single item checklist measure of migraine and the self-report migraine questionnaire. This table also shows calculated values for sensitivity, specificity, positive predictive value and negative predictive value for the single item checklist measure compared to the self-report questionnaire measure as the reference diagnosis.

Table 3.4 Relationship between the single item checklist measure and self-report questionnaire for the diagnosis of migraine

Single item checklist	Self-report questionnaire		
	Migraine	No migraine	Total
Migraine	125 (56.6%)	35 (6.2%)	160 (20.3%)
No migraine	96 (43.3%)	532 (93.8%)	628 (79.7%)
Total	221 (100%)	567 (100%)	788 (100%)

Sensitivity = true+ (true+ + false-) = 125/(125+96) = 0.566 = 56.6%

Specificity = true - (true- + false+) = 532/(532+35) = 0.938 = 93.8%

Positive predictive value = true+/(true+ + false+) = 125/(125+35) = 0.78 = 78%

Negative predictive value = true-/(true- + false-) = 532/(532+96) = 0.85 = 85%

A moderate sensitivity (56.6%) and high specificity (93.8%) was found for the single-item measure of 'doctor diagnosed' migraine, when compared to a diagnosis derived from the self-report questionnaire. Such a combination suggests that although the measure was very effective in correctly identifying those without the disorder, this came at a cost in sensitivity, with 43.3% of those identified as having migraine according to the self-report questionnaire, going undetected. Thus, the high specificity implies that one is unlikely to obtain a positive screen for a patient who does not truly have the disease; however a negative screen is likely to include false negatives, given the relatively modest sensitivity. Moreover, the positive predictive value (PPV) was 0.78 and negative predictive value (NPV) 0.85, indicating that 78% of those who screened positive for migraine with the single item measure actually had migraine (according to the self-report questionnaire) and 85% of individuals who screened negatively for migraine with the measure, were found not to have migraine with the self-report questionnaire. Thus, it seems that the single item measure may be better at ruling out migraine (NPV 0.85) than it is as ruling in migraine (PPV 0.78).

3.3.4.2 Self-report questionnaire vs. telephone interview for migraine diagnosis

As described within the methods section of this chapter, a total sub-sample of 110 individuals were selected from the 1428 that had completed the self-report migraine questionnaire, to be contacted to complete a follow-up telephone interview. Of the 110 maximum possible interviews, I completed a total of 80 (72.7%). The number of individuals successfully contacted and the number of interviews completed throughout the telephone interview process are summarised in **Figure 3.5**.

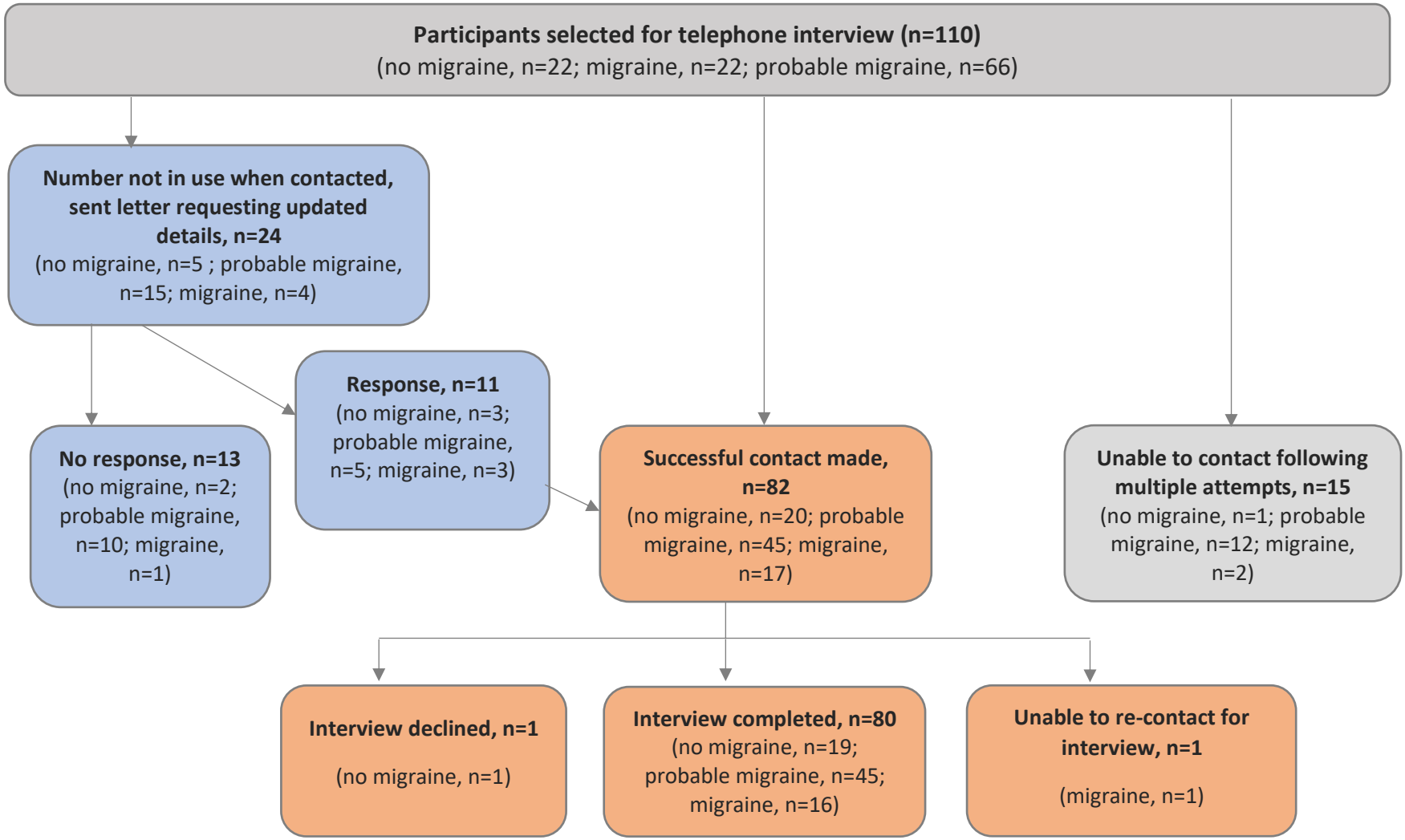


Figure 3.5 Flow chart of participants selected and contacted for telephone interview

Of the individuals selected for telephone interview (n=110), 22% (n=24) were found not to have working numbers when contacted. These individuals were sent a follow-up letter asking them to complete a form updating the research team with their contact details if they were interested in hearing more about the research and to return this form in the stamped addressed envelope provided. Thirteen individuals (54.2%) responded to this letter and provided the research team with their up to date contact details. A total of 82 individuals (including the 13 that replied to the request for updated details) were successfully contacted to discuss details regarding the research and to enquire whether they would like to complete the telephone interview. Of these, 80 (73% of the total possible number of participants, n=110) individuals completed the telephone interview. One individual declined the interview and one individual was unable to be contacted at the arranged time to complete the telephone interview (nor were they available on multiple subsequent attempts). **Table 3.5** shows the total number of interviews completed across the migraine groups. The proportion of interviews completed across migraine groups is similar to those we were originally aiming for (i.e. 20% from the migraine group, 60% from the probable migraine group, and 20% from the no migraine group).

Table 3.5 Number and percentage of telephone interviews completed across migraine groups

Migraine group	**N (%)**
No migraine	19 (23.7%)
Probable migraine	45 (56.3%)
Migraine	16 (20%)
Total	80 (100%)

Table 3.6 shows the breakdown of migraine and no migraine diagnoses according to the self-report migraine questionnaire and the telephone interview. This table also shows calculated values for sensitivity, specificity, positive predictive value and negative predictive value for the self-report questionnaire compared to diagnoses derived from the telephone interview as the reference diagnosis.

Table 3.6 Relationship between self-report questionnaire and interview diagnosis of migraine

Self-report questionnaire	Telephone interview		
	Migraine	No migraine	Total
Migraine	12 (92.3%)	1 (6.7%)	13 (46.4%)
No migraine	1 (7.7%)	14 (93.3%)	15 (53.6%)
Total	12 (100%)	15 (100%)	28 (100%)

Sensitivity = true + (true+ + false-) = 12/ (12+1) = 0.923 = 92.3%

Specificity = true - (true- + false+) = 14/ (14+1) = 0.933 = 93.3%

Positive predictive value = true + / (true+ + false+) = 12/ (12+1) =0. 92= 92%

Negative predictive value = true - / (true- + false-) = 14/ (14+1) = 0.93 = 93%

The self-report questionnaire was found to have high sensitivity (92.3%) and high specificity (93.3%), when compared to migraine status derived from the telephone interview. Moreover, positive predictive value (PPV) was 0.92 and negative predictive value (NPV) 0.93, indicating that the questionnaire is equally effective in ruling in migraine (PPV 0.92) as it is ruling out migraine (NPV 0.93). As described in Chapter 2, the telephone interviews were completed approximately three years following completion of the initial screening questionnaire, making it possible for participants to have experienced migraine headaches for the first time after completion of the initial questionnaire, thus potentially skewing validation figures. It is important to note, however, that no participants during the telephone interview stage reported an onset of severe headaches after completion of the original migraine questionnaire in 2011.

Validity of the self-report questionnaire shown above is for a definition of strictly-defined migraine; however within the questionnaire and telephone interview a number of individuals meeting criteria for probable migraine were also identified. **Table 3.7** shows the breakdown of probable migraine and no migraine diagnoses according to the self-report migraine questionnaire and the telephone interview. This table also shows calculated values for sensitivity, specificity, positive predictive value and negative predictive value for the self-report questionnaire compared to diagnoses derived from the telephone interview as the reference diagnosis.

Table 3.7 Relationship between the self-report questionnaire and telephone interview for the diagnosis of probable migraine

Self-report questionnaire	Telephone interview		
	Probable migraine	No migraine	Total
Probable migraine	9 (75%)	4 (22.2%)	13 (43.3%)
No migraine	3 (25%)	14 (77.8%)	17 (56.7%)
Total	12 (100%)	18 (100%)	30 (100%)

Sensitivity = true + (true+ + false-) = 9/ (9+3) = 0.75 = 75%

Specificity = true - (true- + false+) = 14/ (14+4) =0.778 = 77.8%

Positive predictive value = true + / (true+ + false+) = 9/ (9+4) = 0.69 = 69%

Negative predictive value = true - / (true- + false-) = 14/ (14+3) = 0.82 82%

The self-report questionnaire was found to be much less sensitive (75%) and specific (77.8%) for the diagnosis of probable migraine, compared to that of strictly-defined migraine (92.3% and 93.3%, respectively). The reason for the lowered sensitivity and specificity of the questionnaire for the diagnosis of probable migraine is likely due to the fact that 29 of the 45 (64.4%) individuals identified as having probable migraine according to the questionnaire were in fact found to meet full criteria for migraine diagnosis following telephone interview. **Table 3.8** shows the breakdown of all migraine diagnoses across the self-report questionnaire and telephone interview.

Table 3.8 Breakdown of migraine diagnoses according to the self-report questionnaire and telephone interview measures

Self-report questionnaire	Telephone interview				
	Migraine	Probable migraine	No migraine	Other*	Total
Migraine	12	3	1	0	16
Probable migraine	29	9	4	3	45
No migraine	1	3	14	1	19
Total	42	15	19	4	80
**'Other' represents individuals meeting criteria for typical aura with a non-migraine headache*					

Table 3.8 shows that 75% (n=12) of those initially identified as having migraine according to the self-report questionnaire, were confirmed to have migraine

following telephone interview; and 19% (n=3) were subsequently reclassified as having probable migraine. Only one individual originally identified as having migraine according to the self-report questionnaire was found not to have migraine following telephone interview. In addition, whilst 4 individuals (8.8%) originally identified as having probable migraine according to the self-report questionnaire were later found to not have migraine following telephone interview, the majority (n=29, 64.4%) were actually reclassified as meeting full IHS criteria for migraine. Finally, of those who did not meet criteria for migraine according to the self-report questionnaire, this was confirmed in n=14 cases (74%) following telephone interview, 3 cases (16%) were reclassified as having probable migraine, 1 case (5%) now met full criteria for migraine, and the remaining case (5%) met criteria for typical aura with a non-migraine headache.

When considering a broad diagnosis of migraine (including both strictly-defined and probable migraine cases) derived from the self-report questionnaire compared to a reference diagnosis derived from the telephone interview, a sensitivity and specificity of 93% and 74%, respectively, were observed. In addition, a positive predictive value of 0.91 and negative predictive value of 0.78, indicated that 91% of those who screened positive for broadly-defined migraine with the self-report questionnaire were confirmed to have broad migraine, and 78% of individuals who screened negatively for broadly-defined migraine were found not to have migraine at the telephone interview stage.

3.4 Discussion

Results from this study are consistent with a number of population-based studies that demonstrate an increased prevalence of migraine in bipolar disorder (BD), compared to that reported within the general population (Fasmer, 2001; Mahmood et al., 1999; Ortiz et al., 2010). Using a similar questionnaire-based method for identifying migraine within the general population, Breslau et al. (1991) reported a lifetime prevalence of migraine of 12.8%. Within the current study, I report a migraine prevalence of 19.4% based on a self-report questionnaire measure diagnosed in line with International Headache Society (IHS) criteria. It is important to note that migraine prevalence described here is slightly lower than the approximate 25% prevalence stated in a number of previous studies investigating migraine within a sample of individuals with BD (McIntyre et al., 2006b; Low et al., 2003). Reasons for such discrepancy could be explained by methodological differences between studies in terms of sample population, study definitions of migraine and BD, and differences in the proportion of bipolar I (BDI) and bipolar II (BDII) disorder subjects included.

For example, McIntyre et al. (2006b) studied a community sample and reported a migraine prevalence of 24.8%. However presence of migraine was determined by physician-diagnosed migraine rather than being based on standardised criteria of the IHS. Low et al. (2003) reported one of the highest rates of migraine prevalence (39%) within individuals with BD. This finding was based on a clinical sample, where subjects were currently receiving treatment in an outpatient psychiatric unit. Furthermore, the mean age of their sample matched the peak age of migraine noted within the general population (approximately 40 years). A final key difference is that the migraine questionnaire used to assess IHS-defined criteria by Low et al. (2003) was administered through a face-to-face semi-structured interview.

Given the slightly reduced migraine prevalence reported here compared with previous studies, it is important to note the high rate of probable migraine observed. In addition to the 277 (19.4%) individuals identified as having migraine, a further 304 (21.3%) were found to have probable migraine (PM); a headache fulfilling all but one criterion for migraine with or without aura. Within

the general population, estimates of the 1-year prevalence of PM vary widely, from 2.6%-9.1% (Henry et al., 2002; Lipton et al., 2002; Rains et al., 2001; Russell and Olesen, 1996). In 2004, Patel et al. reported similar 1-year prevalence rates of strict and probable migraine (14.7% and 14.6%, respectively) and revealed an overlap in symptom profiles between strict and probable migraine, supporting the concept that PM is a form of migraine. Moreover, within a French population study of 10,585 subjects aged 15 years and older, Henry et al. (2002) revealed PM to be more prevalent than strict migraine (9.1% vs. 7.9%, respectively).

Recognising and diagnosing PM is important within clinical practice. Given the overlap in profiles of features and treatment response it is likely that PM involves the same pathophysiological processes as strictly defined migraine. Consequently, if PM is indeed a prevalent form of migraine, population studies that focus solely on narrow definitions of migraine may be underestimating both the prevalence and impact of migraine. If this study was to incorporate a broad definition of migraine (including both strict and probable migraine), prevalence would increase to 40.7%. In support of a broader or more inclusive definition of migraine, the current study found that a large proportion (64.4%) of interviewed probable migraine cases that were interviewed (n=45), were in fact reclassified as meeting criteria for strict migraine following telephone interview. If these findings generalised so that 64.4% of all of those identified as having probable migraine according to the self-report questionnaire (n=304) were to be confirmed to meet criteria for strictly-defined migraine, rates of migraine within the current sample would increase to 30% (n=473).

Consistent with previous studies (Fasmer, 2001; Ortiz et al., 2010), I found a higher prevalence of migraine among subjects with BDII compared to BDI (25% vs. 16.9%, respectively); a difference that was found to be statistically significant (OR: 2.054, 95% CI 1.508-2.798, p = .000004). A similarly high prevalence of migraine was also observed within the schizoaffective, bipolar type group (SABP) (25.5%). This was not found to be significantly different compared to those with BDI, however, the small sample size of this group (n=55) may mean that there was not sufficient power to detect a significant difference. The only study to report rates of migraine within SABP is Baptista et al. (2012), who found

higher rates of migraine among this group (20.6%), when compared to either BDI (16.7%), BDII (6.3%), or with a bipolar non-specified group (17.1%). Interestingly, Baptista et al. (2012) report a higher rate of migraine among those with BDI compared to BDII, which is in contrast to existing literature. The finding of this chapter of an increased prevalence of migraine among BDII subjects provides support for the hypothesis that bipolar I and II may be distinct nosological conditions, and that the mechanisms involved in the aetiology of BDII may also be involved in the aetiology of migraine. As both BDII and migraine are found to be more common in women, it could be argued that the increase in migraine prevalence within BDII is possibly due an effect of gender. The current study included sex as a covariate in analysis, therefore controlling for any effect of gender. Moreover, within the current study, male subjects with BDII were also found to have elevated rates of migraine.

Within our bipolar cohort of migraine sufferers, we identified a greater number of patients with migraine with aura (MA) than those without aura (MoA). One-hundred and fifty-three migraine sufferers (55.2%; 10.7% of total sample) had experienced MA, compared to the 124 (44.8%; 8.7% of total sample) subjects that had suffered with MoA. This becomes even more prominent if the 69 subjects identified as having typical migraine with non-migraine headache (n=65) and typical aura with no headache (n=4) are included within the former group. This finding is in contrast to the third of migraine patients generally reported to experience aura symptoms (Silberstein and Lipton, 1993). However, this is not the only study to report such a finding. For example, in their cross-sectional study of 62 Norwegian outpatients with affective disorders, Fasmer, (2001) observed a greater number of patients with MA (n=12, 43% of migraine group, 19% of total sample) compared to MoA (n=10, 35.7% of migraine group, 16% of total sample). Similarly, in their community-based study of 323 individuals with BD, Ortiz et al. (2010) reported a two-fold prevalence of MA compared to that reported in the general population (Russell and Olesen, 1996). The larger proportion of those with MA compared to MoA in this study is not surprising given the statistically significant association found between MA and BD, particularly for BDII subjects. Such a finding is in line with previous research indicating a stronger association between affective disorders and MA, compared to MoA (Breslau et al., 1991; Oedegaard et al., 2005a).

Forty-five individuals within the MA group met criteria for hemiplegic migraine (HM) (16.2%; 3.1% of total sample). Within the general population, the occurrence of HM is said to be rare, however only one population-based epidemiological survey of sporadic and familial HM has been conducted to date. In 2002, Thomsen et al. (2002) estimated the prevalence of HM to be 0.01%, with the familial and sporadic forms being equally prevalent. This estimate is much lower than the 3.1% rate of HM observed reported in the current study. As introduced within Chapter 1 of this thesis, FHM is an autosomal dominantly inherited subtype of migraine, for which polymorphisms in at least three genes have been implicated; *CACNA1A* (Ophoff et al., 1996), A*TP1A2* (DeFusco et al., 2003), and *SCN1A* (Dichgans et al., 2005). All three FHM genes either encode ion channels or are involved in ion transportation, and therefore support the hypothesis of migraine as a 'channelopathy'. Disturbances in ion channel function are also implicated in BD, with two of the strongest associations to come out of genome-wide association studies of bipolar disorder (BD) being for two genes involved in ion transportation; *ANK3* and *CACNA1C* (Ferreira et al., 2008; Lee et al., 2011; Schulze et al., 2009; Scott et al., 2009; Sklar et al., 2008; Smith et al., 2009). Given the proposed similarity in the underlying mechanisms of FHM and BD, this may suggest a greater likelihood of genetic overlap between the two disorders, which may in turn explain the high rate of HM observed in the current bipolar sample.

Evaluation of the different methods utilised by the BDRN to ascertain a migraine diagnosis, revealed a moderate level of agreement between the single item checklist measure of migraine and the self-report questionnaire. Sensitivity of the single-item 'doctor diagnosed' migraine was found to be 56.6%, suggesting that 43.3% of those identified as having migraine with the questionnaire, were undetected. Therefore, although the questionnaire disseminated within this study is also based on self-report methods, it appears that asking about migraine symptomology in more detail in self-report measures, rather than asking a single question about the lifetime presence of migraine (as diagnosed by a health professional), is advantageous for increasing sensitivity. The combination of high specificity and modest sensitivity observed for the single

item measure implies that a positive screen is unlikely in a patient who does not truly have the disease, however false negatives are likely in the event of a negative screen, suggesting the measure will lead to an under-reporting of true migraine cases.

Results of the validity testing of the self-report migraine questionnaire revealed that compared to diagnoses derived from the telephone interview, the measure showed both high sensitivity (92.3%) and high specificity (93.3%) for diagnosis of strictly-defined migraine. However, for the diagnosis of probable migraine, the questionnaire was found to be much less sensitive (75%) and specific (77.8%). Lowered sensitivity and specificity of the questionnaire for detecting probable migraine may be explained through the large proportion (64.4%) of subjects with probable migraine that were reclassified as migraine cases following telephone interview. Thus, it could be proposed that compared to the questionnaire measure, the telephone interview is more adept at classifying borderline cases, given its potential to allow further scope for interaction and clarification of questions and answers. Moreover, as previously discussed, the fact that over half of the probable migraine cases are found to be true migraine cases following the telephone interview supports the notion of acknowledging a broader definition of migraine.

A strength of this study is the large, clinically well-defined sample. Previous studies measuring migraine prevalence in BD have generally been conducted with much smaller sample sizes, making this study a valuable contribution to current literature. Furthermore, subjects were sampled from a community population, recruited through both systematic and non-systematic methods, thereby increasing its representative nature and generalizability. Moreover, studying comorbidities within a community-based sample means that they are less likely to be subjected Berkson's bias, where individuals reporting a diagnosis of one disorder are more likely to report a diagnosis of (or be diagnosed with) other disorders because of their more frequent contact with health professionals in the context of a clinical population (Berkson, 1946). This study also benefits from the use of International Headache Society (IHS) criteria and so is in line with current standardised criteria for migraine diagnosis.

It is important to interpret the findings in the context of certain limitations. Firstly, the cross-sectional nature of the study methodology does not allow for the determination of causality in the relationship between BD and migraine. In order to gain a better understanding of the temporal relationship between BD and migraine, a prospective study is necessary. Moreover, the retrospective assessment of migraine introduces the possibility of recall bias, limited by the subject's ability to clearly recall detailed aspects of their headaches, particularly relating to aura symptoms. Secondly, the lifetime history of migraine was ascertained through self-report measures, and so any under or over reporting of migraine cannot be ruled out. Migraine is often underdiagnosed in the first instance, as many sufferers do not seek medical attention (Lipton and Goadsby, 1999). However, an advantage of this study is that the self-report questionnaire asked symptom-based questions, from which a diagnosis was made based on IHS criteria, rather than simply asking about a lifetime diagnosis of migraine. Moreover, although an acceptable response rate of 40% was achieved, it is possible that a response bias exists, whereby those who experienced migraine may have been more likely to complete the questionnaire. This was considered less likely to be the case as the migraine questionnaire was part of a larger pack of 8 additional questionnaires, with the migraine being the last questionnaire in the pack. Examination of questionnaire pack completion rates revealed that of those who completed the migraine questionnaire (n=1569), 99.9% completed at least 6 of the remaining 8 questionnaires included in the pack. There were only 8 individuals (0.6%) who completed either part or all of the additional questionnaires but did not complete the migraine questionnaire; where 75% completed at least 6 of the remaining 8 questionnaires. Given the 40% response rate of the questionnaire packs, it is also important to be cautious in any claims regarding overall migraine rates within the BD cohort. Finally, analysis did not consider medication use. As noted in the introduction of this thesis, some pharmacological treatments are successful within both disorders, in particular valproate, which could have acted to dampen migraine symptomatology and therefore influence disease prevalence.

In summary, the nearly two-fold increased prevalence of migraine suggests that individuals with BD are at a higher risk of migraine than those without the disorder. As discussed within the background section of this thesis, there are

many possible reasons for this increased prevalence, including potential shared underlying pathophysiological mechanisms. Findings indicate that the presence of migraine may be used to delineate a more homogeneous subgroup of BD, which could prove useful for future studies assessing the aetiology of both disorders. In order to further evaluate the relationship of these comorbid phenomena, the next chapter of this thesis will focus on examining the impact of comorbid migraine on the course of the affective illness, to determine whether those with comorbid migraine experience different clinical characteristics to those without comorbid migraine. The next chapter will also look to explore the migraine phenotype in more detail by assessing the specific association of bipolar clinical variables with migraine subtypes, with and without aura.

Chapter 4

Clinical characteristics of bipolar disorder according to migraine status

4.1 Introduction

The introduction chapter of this thesis outlined evidence to suggest that migraine comorbidity may be associated with a distinct clinical course of the bipolar illness. Such studies have indicated that presence of migraine within bipolar disorder (BD) is associated with an earlier age of BD onset (Mahmood et al., 1999; McIntyre et al., 2006b), increased rate of attempted suicide (Ortiz et al., 2010), a higher prevalence of bipolar II disorder subtype (Fasmer, 2001; Ortiz et al., 2010), and an increased rate of a rapid cycling illness course (Gordon-Smith et al., 2015).

Moreover, there is some evidence to suggest that the relationship between affective disorders and migraine may differ depending on the type of migraine that is studied. For example, previous studies have identified differences in the psychiatric comorbidity of the migraine subtypes, migraine with aura (MA) and migraine without aura (MoA), where it has been suggested that MA may have a stronger association with psychiatric disorders than MoA. For example, Breslau et al. (1991) observed significantly increased rates of BD and panic disorder in patients with MA when compared to migraine free individuals. However this was not the case for the MoA group. More recently, Oedegaard et al. (2005a) reported that depression alone, and depression with comorbid anxiety, were more likely in women having MA than MoA, however this difference between MA and MoA was not observed in male subjects. An association has also been reported between MA and suicide attempt. For example, Breslau et al. (1991) observed an association of both MA and MoA with suicide attempt, however after controlling for the presence of psychiatric and substance use disorders, an

independent association remained for MA only. Despite these findings, much of the research exploring the clinical characteristics of BD associated with migraine comorbidity to date has not distinguished between the subtypes of migraine.

The present chapter looks to evaluate the relationship of migraine with the clinical course of the bipolar illness. Firstly, the chapter describes the clinical features of migraine experienced within the bipolar cohort. The chapter will then explore the impact of a migraine diagnosis on the lifetime clinical characteristics of the bipolar illness, by identifying characteristics that differentiate individuals with BD, according to the presence or absence of migraine. The final part of this chapter looks to examine whether the migraine subtypes, migraine with (MA) and without aura (MoA), are associated with specific lifetime bipolar clinical characteristics, in order to identify whether MA within individuals with BD represents a clinically useful subgroup that is characterised by specific clinical features or course of illness.

4.2 Methods

4.2.1 Subjects

Data were utilised from the Bipolar Disorder Research Network (BDRN). Further detail on the sample is provided in Chapter 2.

As detailed in Chapter 3 of this thesis, 1569 BDRN participants completed and returned a self-report questionnaire assessing lifetime history of migraine. Of these, 1428 met DSM diagnostic criteria for bipolar disorder type I (BDI), bipolar disorder type II (BDII) and schizoaffective, bipolar type (SABP), and so were included in the present study.

4.2.2 Assessments

Ascertainment of migraine symptomology, from which a migraine diagnosis was determined, was made via a self-report questionnaire assessing lifetime history of migraine. Further detail on this questionnaire measure is given in Chapter 2. Using this measure, a diagnosis of migraine was assigned in line with IHS criteria (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004) for a diagnosis of migraine with (MA) and without aura (MoA), hemiplegic migraine (HM) and probable migraine (PM).

4.2.3 Statistical analysis

Data were analysed using the statistical package SPSS version 20. Normality of the data was assessed using the Kolmogorov-Smirnov test. The majority of the data analysed were not normally distributed and so non-parametric tests were employed. Statistical tests were considered significant at the $p<0.05$ level (two tailed) unless stated otherwise.

4.2.3.1 Impact of migraine on the course of the bipolar illness:

<u>Univariate analysis</u>

Initially, data were explored with univariate tests in order to gain a better understanding of the data and to highlight potentially important variables to be included within multivariate analysis. Specifically, demographic and lifetime clinical characteristics of BD patients, with and without migraine, were

compared using Mann Whitney-U tests for continuous variables and categorical variables were assessed using 2x2 and 2x3 chi square tests. In instances where 20% or more of the cells in a chi-square table had an expected count of less than five, Fisher's exact tests (2x2 tables) and exact significance tests for Pearson's chi-square (2x3 tables and greater) were used. For 2x3 chi-square tables, a statistically significant finding was followed-up with *post hoc* comparisons on each pair using 2x2 chi-square tests.

Multivariate analysis

Variables found to be significant within univariate analysis at the $p<.05$ level were entered into a binary logistic regression model as explanatory variables (using the enter method), with presence or absence of migraine as the outcome/dependent variable. The presence of collinearity within the logistic regression model was assessed with the variance inflation factor (VIF) diagnostic (Hamilton, 2006). If necessary to drop a variable due to collinearity, the decision would be made based on order of clinical importance.

A second logistic regression was then performed, changing the criteria by which variables were selected from univariate analysis for inclusion into the logistic regression model. For this analysis, only those variables withstanding correction for multiple testing, using the conservative Bonferroni correction, were entered into the regression model. The Bonferroni procedure to control for multiple testing divides the test-wise significance level by the number of tests being performed. This method reduces the probability of making a type I error (inappropriately rejecting the null hypothesis), however is often criticised for being overly conservative, and is particularly troublesome if the number of comparisons is large (Bland and Altman, 1995). As 22 independent univariate tests were performed, a p-value threshold indicating significance was set at $p<0.00227$.

4.2.3.2 Analysis of migraine subtypes and bipolar disorder:

Demographic and lifetime clinical characteristics of BD patients were compared between i) migraine with aura (MA) vs. no migraine and ii) migraine without aura (MoA) vs. no migraine groups, in order to explore the relationship of each migraine subtype, separately, with the clinical features and course of the bipolar

illness. Comparisons were made using Mann Whitney-U tests for continuous variables and categorical variables were assessed using 2x2 chi square tests. Within each group comparison (MA vs. no migraine; and MoA vs. no migraine), variables significant within univariate analyses at the $p<.05$ level were entered into a binary logistic regression model as explanatory variables, with migraine group status as the dependent variable.

To examine potential clinical differences between BD subjects with migraine, with (MA) and without aura (MoA), demographic and lifetime bipolar clinical characteristics were compared between the two groups. Characteristics of migraine were also compared between MA and MoA groups. Continuous variables were assessed with Mann Whitney-U tests and 2x2 chi square tests for categorical variables. Demographic, lifetime bipolar clinical characteristics and migraine characteristics found to significantly differentiate MA and MoA groups (at the $p<.05$ level) were included as exploratory variables within a binary logistic regression model, with presence of aura (MA vs. MoA) as the dependent variable.

4.3 Results

4.3.1 Clinical features of migraine

As detailed within Chapter 3, 19.4% (N=277) of the bipolar sample were classed as having migraine according to the self-report questionnaire, diagnosed according to International Headache Society criteria (ICHD-II; Headache Classification Subcommittee of the International Headache Society 2004). As previously described, 153 (55.2%) met criteria for migraine with aura (MA); 45 (16.2%) of which met criteria for hemiplegic migraine, and 124 (44.8%) received a diagnosis of migraine without aura (MO). The current section details the clinical features of migraine within the bipolar sample.

4.3.1.1 Migraine symptomology

Frequency of migraine symptomology experienced by individuals with migraine is summarised in **Table 4.1**. One-hundred and fifteen (41.5%) individuals meeting criteria for migraine experienced nausea and/or vomiting; 139 (50.2%) reported hypersensitivity to light or sound; 179 (64.6%) experienced pulsating headaches; 204 (73.6%) had unilateral headaches; 119 (43.1%) described the pain intensity of their headaches as moderate; 152 (55.1%) described this pain as severe; and 93 (33.6%) individuals reported that their headaches were made worse by physical activity.

Table 4.1 Frequency of symptoms experienced by bipolar subjects with migraine

Migraine symptom	Frequency (%)
Moderate or severe pain intensity	271 (98%)
One-sided headache	204 (73.6%)
Pulsating headache	179 (64.6%)
Hypersensitivity to light or sound	139 (50.2%)
Nausea and/or vomiting	115 (41.5%)
Aggravated by physical activity	93 (33.6%)

4.3.1.2 Age of onset of migraine

Age of onset of migraine was known for n=195 individuals (70.4%). The median age of onset of migraine was 17 years, which was found to be younger than the median age of onset for BD illness impairment (19 years). The distribution of age of migraine and BD onset is displayed in **Figure 4.1**. For 110 (56.4%) individuals with migraine, onset of migraine preceded onset of BD illness impairment, whereas onset of BD impairment preceded migraine onset in 72 (36.9%) subjects. For 13 (6.7%) individuals, onset of migraine and BD impairment occurred within the same year.

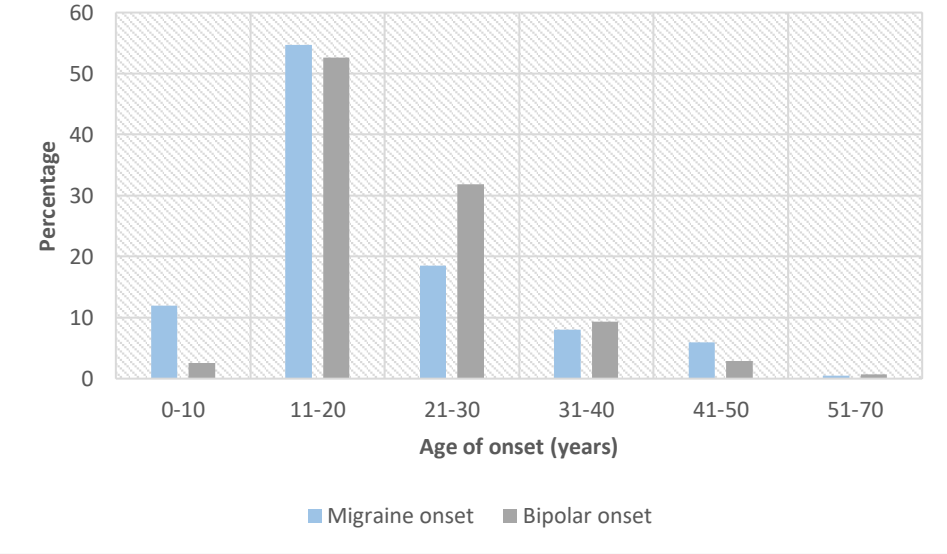


Figure 4.1 Distribution of age of onset of migraine, and age of onset of impairment of bipolar disorder.

4.3.1.3 Medication and other methods of headache relief

Figure 4.2 summarises the methods used by bipolar subjects with migraine to relieve their headache. One-hundred and ninety-four (70%) individuals stated that they had taken migraine medication to relieve their headache. One hundred and ninety-four (70%) individuals also reported taking non-migraine specific painkillers; with 136 of these being the same individuals who utilised migraine medication. One-hundred and sixty-two (58.5%) individuals used rest as a means of relieving their headache; 183 (66.1%) lay in a dark room; and 136 (49%) stated that they used sleep as a means of relieving their headache.

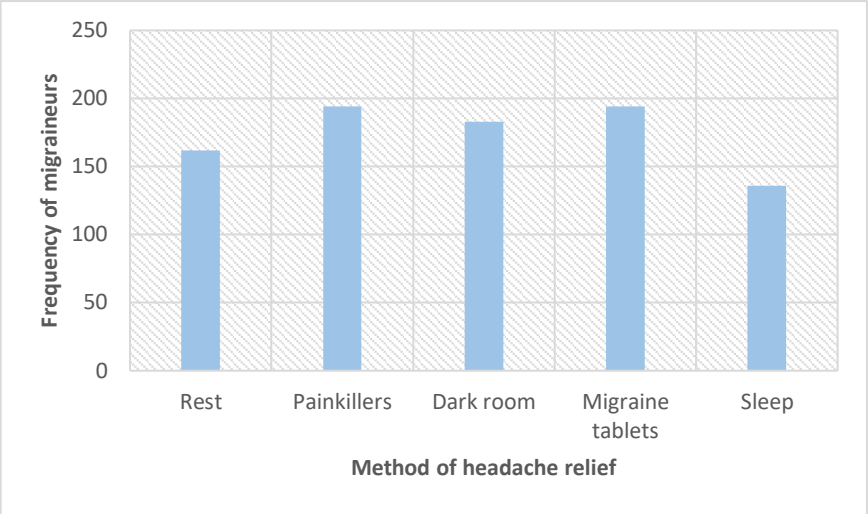


Figure 4.2 Methods of headache relief utilised by bipolar subjects with migraine

Forty-four (15.9%) individuals utilised all five methods of headache relief; 74 (26.7%) utilised four of the above methods; 77 (27.8%) utilised three methods; 40 (14.4%) utilised two methods; and 42 (15.2%) individuals utilised only one of the above methods for headache relief.

4.3.1.4 Frequency of recurrent headache

The frequency at which individuals with migraine experienced their recurrent headache was known for 260 individuals (94%) and is summarised in **Figure 4.3**. One-hundred (36.1%) individuals with migraine reported suffering daily headache at a time when their headaches were at their most frequent. A further 76 (27.4%) suffered with weekly headaches; 51 individuals (18.4%) suffered with monthly headaches; 27 individuals suffered (9.7%) with headaches every 1-3 months; 4 individuals (1.4%) suffered with headaches every 3-6 months; 1 individual (0.5%) suffered annually; and 1 (0.5%) individual suffered with headaches less than once a year.

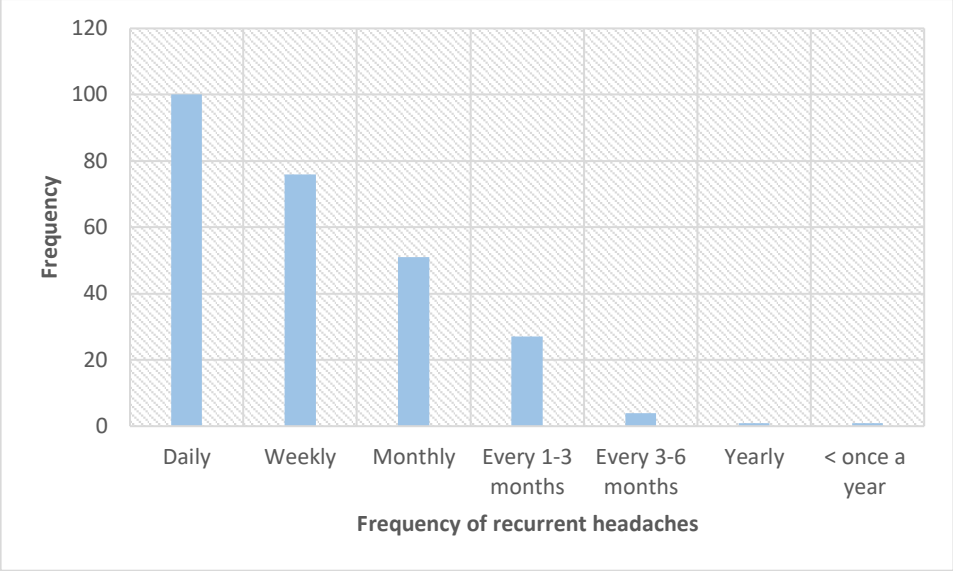


Figure 4.3 Frequency of recurrent headache of bipolar subjects with migraine

Although the self-report questionnaire assessed the occurrence of daily headache, the time period for which daily suffering was experienced was not assessed and so I was unable to identify and differentiate chronic migraine from episodic migraine. According to the ICHD-II, chronic migraine is defined as headache on least 15 days per month for a minimum of three months, either meeting criteria for migraine without aura or responding to migraine-specific medication (Headache Classification Subcommittee of the International Headache Society 2004).

4.3.1.5 Family history of migraine

Within the migraine group, 163 (76.2%) individuals had a family history of migraine (at least one biological first or second degree relative with a history of migraine headaches) and this was found to be significantly higher compared to the no migraine group (76.2% vs. 43.6%, p=.000001). There were, however, no significant differences found in the rate of family history of affective disorders between BD subjects with and without migraine when using both a broad definition of affective disorder (including bipolar II disorder, schizoaffective disorder and major depressive disorder); 89.7% vs. 85.2%, p=.089, or a narrow definition including only those with a diagnosis of bipolar I disorder; 45.5% vs.

40.1%, p=.524. Hence, there was no significant association found between migraine in bipolar probands and affective disorders in their relatives.

4.3.1.6 Migraine with aura (MA)

A summary of the frequency of MA individuals experiencing each aura type and the number of aura types experienced by individuals are outlined in **Tables 4.2-4.3**. 121 (79.1%) individuals with MA experienced visual disturbances (e.g. flickering lights, spots or lines, blurred vision or loss of vision), 68 (44.4%) had experienced sensory symptoms (such as pins and needles or numbness) and 29 (19%) reported speech disturbance. 104 (68%) individuals with MA had experienced one aura type, 34 (22.2%) experienced two aura types and 15 (9.8%) had experienced all three (visual, sensory and speech) aura types.

Table 4.2 Frequency of each aura type experienced by individuals with migraine with aura (MA)

Aura type	Frequency (%)
Visual aura	121 (79.1%)
Sensory aura	68 (44.4%)
Speech disturbance	29 (19%)

Table 4.3 Number of aura types experienced by individuals with migraine with aura (MA)

Number of aura types experienced	Frequency (%)
1	104 (68%)
2	34 (22.2%)
3	15 (9.8%)

Presence of aura was associated with a younger age of migraine onset (median: 15 vs 18.5 years, p=.004) and a significantly lower proportion of the MA group had taken migraine medication to relieve their headache compared to the migraine without aura (MO) group (62.7% vs. 79%, p=.003). Compared to those without aura (MoA), the MA group did not significantly differ in their rate of family history of migraine (MA: 70.8% vs. MoA: 80.5%, p=.098), however the MA group did have a significantly higher rate of family history of migraine with aura (92.1% vs. 68.4%, p=.002).

4.3.1.7 Hemiplegic migraine

Forty-five individuals from the migraine with aura (MA) group (29.4%; 3.2% of total sample) experienced motor weakness that met further development and duration criteria outlined by the IHS, and so were defined as having hemiplegic migraine. There was no significant difference in the age of onset of migraine between individuals with HM and MA (median: 14.5 vs. 15, p=.511), nor in the rate of migraine medication use (71.1% vs. 59.3%, p=.167). There was however, a significantly higher rate of family history of migraine with aura and additional motor weakness in the HM group compared to MA (72.7% vs. 21.2%, p=.003).

4.3.1.8 Probable migraine

As detailed within Chapter 3, 304 (21.3%) individuals met criteria for probable migraine (PM), according to the self-report questionnaire. The International Headache Society (IHS) define PM as an attack or headache missing one of the features needed to fulfil all IHS criteria for a migraine disorder. The migraine diagnostic criterion most frequently not fulfilled by these subjects was the duration criteria of between 4-72 hours, which was not met by 75.3% (n=229) subjects meeting criteria for PM.

4.3.1.9 Summary

This section has described the clinical features of individuals with migraine within the bipolar sample. The following section of this chapter will explore the impact of a migraine diagnosis on the lifetime clinical characteristics of the bipolar illness, by identifying characteristics that differentiate individuals with bipolar disorder, according to the presence or absence of migraine.

4.3.2 Characteristics associated with migraine in the bipolar sample: Univariate analysis

4.3.2.1 Demographic characteristics

A comparison of demographic variables between bipolar subjects with and without migraine is outlined in **Table 4.4**. Analysis revealed the migraine group to be significantly younger at interview than the no migraine group (45 vs. 50

years, p=.000001). There was also a significantly greater proportion of females in the migraine group (82.3% vs. 69%, p=.000021).

Table 4.4 Demographic characteristics of the bipolar sample according to migraine status

	BD + migraine (n=277)	BD - migraine (n=778)	P-value
Age at interview (years)			
Median	45	50	**.000001**
IQR	16	18	
Range	20-74	18-83	
Sex, n (%)			
Female	228 (82.3%)	537 (69%)	**.000021**
Recruitment, n (%)			
Systematic	58 (21.7%)	166 (22.3%)	.842
Family history of affective disorder, n (%)	209 (89.7%)	561 (85.3%)	.089

*BD=bipolar disorder; IQR= inter-quartile range. Figures in **bold** indicate variables significant at the p<.05 level.*

4.3.2.2 Bipolar clinical characteristics

A comparison of lifetime bipolar clinical characteristics between individuals with and without migraine is displayed in **Table 4.5**. Examination of such characteristics revealed that when compared to those with no history of migraine, bipolar individuals with migraine: were significantly younger at the onset of their bipolar illness (defined as the age at which symptoms of their affective disorder first caused significant impairment) (19 vs. 22 years, p=.000028); experienced more depressive episodes (10.1 vs. 6.1, p=.000001) and more episodes of mania (7 vs. 5.1, p=.002); had a lower rate of psychiatric admission (71.3 vs. 81.6%, p=.003); had higher rates of rapid cycling (28.4% vs. 18.3%, p=.000421); had higher rates of panic disorder (21.1% vs. 13%, p=.005) and anxiety disorder (67.6% vs. 52.8%, p=.000195); and a higher rate of suicide attempt (60.7% vs. 45.6%, p=.000024). Higher rates of regular cannabinoid use (23.3% vs. 15%, p=.002225) and regular use of other unspecified drugs (15.7% vs. 8.7%, p=.001547) were also found in the migraine group. Finally, migraine was found to be significantly associated with BD diagnostic subtype (p=.00004). 2x2 *post hoc* comparisons revealed a statistically significant difference between BDI

and BDII groups in migraine prevalence, with migraine found to be positively associated with a BDII diagnosis (p = .000004).

Table 4.5 Clinical characteristics of the bipolar sample according to migraine status

	BD + migraine (N=277)	BD - migraine (N=778)	P-value
DSM-IV diagnosis **BDI** **BDII** **SABP**	 168 (22.1%) 95 (37.7%) 14 (33.3%)	 593 (77.9%) 157 (62.3%) 28 (66.7%)	**.000004**
Age at illness onset (years) Median IQR Range	 19 11 6-51	 22 12 5-68	**.000028**
Lifetime number episodes of depression Median IQR Range	 10.1 15.1 0-100.1	 6.1 12 0-100.1	**.000001**
Lifetime number episodes of mania Median IQR Range	 7 16 1-100.1	 5.1 7.1 1-100.1	**.002348**
History of psychotic features, n (%)	158 (57%)	459 (59.2%)	.947
History of psychiatric admission, n (%)	191 (71.3%)	614 (81.6%)	**.000347**
History of suicide attempt, n (%)	162 (60.7%)	336 (45.6%)	**.000024**
History of rapid cycling, n (%)	78 (28.4%)	140 (18.3%)	**.000421**
History of panic disorder, n (%)	45 (21.1%)	71 (13%)	**.005**
History of anxiety disorder, n (%)	148 (67.6%)	289 (52.8%)	**.000195**
Ever been a regular smoker, n (%)	126 (54.3%)	371 (51.3%)	.377
Alcohol dependence, n (%)	47 (18.4%)	139 (19.7%)	.663
Lifetime regular use of cannabinoids, n (%)	61 (23.3%)	109 (15%)	**.002225**
Lifetime regular use of other unspecified drugs, n (%)	41 (15.7%)	63 (8.7%)	**.001547**

*IQR= inter-quartile range; BDI= bipolar I disorder; BDII= bipolar II disorder; SABP= schizoaffective-bipolar type. Figures in **bold** indicate variables significant at the p<.05 level.*

4.3.3 Multivariate model – Predictors of migraine within bipolar disorder

4.3.3.1 Model a) including variables significant at the p<.05 level:

Variables that were significant within univariate analysis at the p<.05 level (**Tables 4.4 and 4.5**), were entered into a binary logistic regression as explanatory variables. Logistic regression analysis indicated the characteristics that best predicted the presence of migraine within BD were: a younger age at interview (OR .976, 95% CI: .958-.994, p=.008); being female (OR 1.751, 95% CI: 1.074-2.855, p=.025); history of suicide attempt (OR 1.651, 95% CI: 1.092-2.497, p=.017); and a history of anxiety (OR 1.564, 95% CI: 1.036-2.359, p=.033). A summary of the significant predictors of BD and comorbid migraine is displayed in **Table 4.6.**

Table 4.6 Summary of significant predictors of migraine in the bipolar sample

	Wald X^2	**df**	**P-value**	**OR (95% CI)**
Age at interview	7.051	1	.008	.976 (.958-.994)
Sex (female)	5.046	1	.025	1.751 (1.074-2.855)
History of suicide attempt	5.648	1	.017	1.651 (1.092-2.497)
History of anxiety	4.536	1	.033	1.564 (1.036-2.359)
OR= odds ratio; 95% CI= 95% confidence interval; df= degrees of freedom.				

Model validation

Power

Logistic regression uses the maximum likelihood estimation (ML) to derive its parameters. Such a method relies on large-sample asymptotic normality, and so as the number of cases for each independent variable declines, so does the reliability of parameter estimates. A useful rule of thumb suggests at least ten cases per independent variable for the smaller classes of the dependent variable (Peduzzi et al., 1996). The model reported above includes 587 cases, with 168 of these belonging to the (smaller) migraine group. A total of 13 variables were entered into the model; therefore surpassing the minimum requirement of ten cases per predictor variable for the smaller outcome group.

Goodness-of-fit

Cases correctly classified

The accuracy of the model in predicting whether or not an individual has a diagnosis of migraine, is calculated by comparing predicted scores (individual having migraine or not) based on the independent variables within the model, with actual group. Within this model, 72.1% of individuals were correctly classified as having comorbid migraine or not.

Hosmer-Lemeshow

Indication of how well the model fits the data was evaluated using the Hosmer-Lemeshow goodness-of-fit measure. This measure indicates the extent to which the model provides a better fit than the null model. The H-L goodness-of-fit test statistic computed for the model was greater than p=.05 (χ^2 (8) =4.612, p =.798), indicating the model predicts values not significantly different from what we observed, signifying a good fit of the model to the data. A limitation of this goodness of fit measure is that it is simply a significance test and thus is only able to inform us of whether the model fits the data or not, rather than providing information on the extent of the fit.

Pseudo R^2

Within logistic regression analyses, there is no analogous statistic to the coefficient of determination R^2 that acts as an indicator of the percentage of variance in the dependent variable explained by the model. However, there are a number of approximations, known as Pseudo R^2 measures. Two of the main Pseudo R-square measures reported are Cox and Snell's, and Nagelkerke. A major limitation of Cox and Snell's R-square is that its maximum can be less than 1, thus making it difficult to interpret. Nagelkerke's modification divides Cox and Snell's R-square by its maximum, allowing it to vary from 0 to 1, providing a more reliable measure of the relationship. In the case of the model reported above, the Nagelkerke R^2 is 0.133, indicating that the model explains 13.3% of the variance within the dependent variable; presence of migraine.

Diagnostic analyses: Multicollinearity

Logistic regression is sensitive to high correlations between predictor variables, resulting in multicollinearity. To identify potential multicollinearity among the

13 predictor variables, a multiple linear regression was conducted with collinearity diagnostics requested. Tolerance is an indication of the percent of variance in the predictor that cannot be accounted for by the other predictors, and values less than .10 may merit further investigation. The VIF *(variance inflation factor)*, is denoted as; *1 / tolerance*, and as a rule of thumb a VIF value greater than 10 may merit further investigation. None of the predictor variables had a tolerance value below .10, or a VIF value greater than 10, thus indicating that multicollinearity is not apparent within the model.

Presence of multicollinearity among predictor variables was also examined by considering the standard errors for the b coefficient, with a standard error larger than 2.0 indicative of numerical problems, such as multicollinearity. None of the independent variables in this analysis had standard errors larger than 2, reinforcing that multicollinearity is not apparent within the model.

4.3.3.2 Model b) including variables surpassing Bonferroni correction:

A second logistic regression was computed, including only those variables surviving correction for multiple testing using the Bonferroni method. The total number of independent univariate tests performed was 22. This included the 21 comparisons displayed in **Tables 4.4 and 4.5** (including post-hoc tests) and an earlier comparison made between migraine and no migraine groups regarding the family history of migraine. Thus, the p-value threshold indicating significance was set at $p<0.00227$. Employing this more conservative criterion for variable selection meant the removal of two clinical variables; 'number of episodes of mania', and 'history of panic disorder', from entry in to the regression model. A summary of significant predictors of migraine using this method of variable entry is displayed in **Table 4.7**.

Table 4.7 Summary of significant predictors of migraine - Model b

	Wald X^2	df	P-value	OR (95% CI)
Age at interview	8.363	1	.004	.974 (.957-.992)
Sex (female)	5.935	1	.015	1.807 (1.124-2.908)
Episodes of depression	4.615	1	.032	1.014 (1.001-1.028)
History of suicide attempt	5.543	1	.019	1.619 (1.084-2.419)
History of anxiety	4.788	1	.029	1.538 (1.046-2.262)

OR=odds ratio; 95% CI=95% confidence interval; df=degrees of freedom.

As can be seen from the above summary, all variables that were found to best predict migraine within the bipolar sample using a more conservative criterion for determining entry into the model are the same as those found when using a threshold of p<.05. An additional variable found to independently predict migraine within model b was an increased number of episodes of depression. This model correctly classified 71.6% of individuals as having comorbid migraine or not. The H-L goodness-of-fit test statistic computed for the model was greater than .05 (χ^2 (8) =4.483, p =.811), signifying a good fit of the model to the data. According to the Nagelkerke pseudo R^2 measure, the model explained 13.2% of the variance in the dependent variable.

4.3.3.3 Summary

This section has made comparisons between bipolar subjects with and without a diagnosis of migraine on a number of demographic and bipolar clinical variables, as a means of exploring the impact of migraine on the bipolar illness. The next section will explore the migraine phenotype in more detail by assessing the specific association of bipolar clinical variables with migraine subtypes, migraine with and without aura.

4.3.4 Characteristics of bipolar disorder according to migraine subtypes compared to migraine-free subjects

Univariate comparisons of demographic and bipolar clinical characteristics between individuals with i) migraine with aura (MA) vs. no migraine and ii) migraine without aura (MoA) vs. no migraine are displayed in **Table 4.8**.

Table 4.8 Comparison of demographic and lifetime bipolar clinical variables in the migraine groups (migraine with aura and migraine without aura) and the no migraine group.

	MA (1) (n=153)	**MoA (2) (n=124)**	**No migraine (3) (n=778)**	**P-value 1 vs 3**	**P-value 2 vs 3**
Age at interview (years) Median (IQR) Range	46 (16) 20-70	44.5 (17) 23-74	50 (18) 18-83	**.000290**	**.000043**
Sex, n (%) Female	130 (85%)	98 (79%)	537 (69%)	**.000063**	**.023**
Systematic recruitment, n (%)	39 (26.4%)	19 (16%)	166 (22.3%)	.286	.117
Family history of affective disorders, n (%)	122 (90.4%)	87 (88.8%)	561 (85.3%)	.118	.353
DSM-IV diagnosis, n (%) BDI BDII SABP	89 (68.2%) 55 (35.9%) 9 (5.9%)	79 (63.7%) 40 (32.3%) 5 (4%)	593 (88.2%) 157 (20.2%) 28 (3.6%)	**.000023**	**.009**
Age at illness onset (years) Median (IQR) Range	19 (11) 6-51	20 (10) 6-51	22 (12) 5-68	**.000071**	**.023**
No. episodes of depression Median (IQR) Range	12.1 (14) 0-100.1	9.5 (16) 0-100.1	6.1 (12) 0-100.1	**.000001**	**.009**
No. episodes of mania Median (IQR) Range	7.5 (16.1) 1-100.1	5.1 (12) 1-100.1	5.1 (7.1) 1-100.1	**.000090**	.598
History of psychotic features, n (%)	85 (55.6%)	73 (58.9%)	459 (59.2%)	.400	.940

History of psychiatric admission, n (%)	102 (69.9%)	89 (73%)	614 (81.6%)	**.001**	**.025**
History of suicide attempt, n (%)	98 (66.7%)	64 (53.3%)	336 (45.6%)	**.000003**	.115
History of rapid cycling, n (%)	53 (34.6%)	25 (20.5%)	140 (18.3%)	**.000006**	.559
History of panic disorder, n (%)	33 (26.8%)	17 (13.3%)	71 (13%)	**.000132**	.931
History of anxiety disorder, n (%)	86 (68.8%)	62 (66%)	289 (52.8%)	**.001**	**.018**
Alcohol dependence, n (%)	26 (18.7%)	21 (18.1%)	139 (19.7%)	.789	.689
Lifetime history regular use of cannabinoids, n (%)	35 (24.5%)	26 (21.8%)	109 (15%)	**.005**	.057
Lifetime history regular use of other unspecified drugs, n (%)	22 (15.4%)	19 (16.1%)	63 (8.7%)	**.014**	**.012**

*MA=migraine with aura; MoA=migraine without aura; BDI=bipolar I disorder; BDI=bipolar II disorder; SABP=schizoaffective bipolar type. Figures in **bold** indicate variables significant at the p<.05 level.*

Examination of demographic and clinical characteristics between the migraine with aura (MA) and no migraine groups revealed statistically significant differences (p<0.05) between the two groups, in that the MA group: were younger at interview (46 vs. 50 years, p=.000043); were more likely to be female (85% vs. 69%, p=.000063); had a younger age of BD onset (19 vs. 22 years, p=.000071), experienced more episodes of both depression (12.1 vs. 6.1, p=.000001) and mania (7.5 vs.5.1, p=.000090); had a lower rate of psychiatric admission (69.9% vs. 81.6%, p=.001); had higher rates of suicide attempt (66.7% vs. 45.6%, p=.000003) and rapid cycling of illness (34.5% vs. 18.3%, p=.000006); had a higher rate of panic (26.8% vs. 13%, p=.000132) and anxiety disorder (68.8% vs. 52.8%, p=.001). Lifetime-ever regular use of cannabinoids (24.5% vs. 15%, p=.005), and other unspecified drugs (15.4% vs. 8.7%, p=.014) were also found to be significantly associated with MA compared to BD subjects with no migraine. MA was significantly associated with BD diagnostic subtype

(p=.000023). 2x2 *post hoc* comparisons revealed a statistically significant difference between BDI and BDII groups, with MA being positively associated with a BDII diagnosis (p=.000008).

Variables that were significant within univariate analysis at the p<.05 level between MA and no migraine groups (**Table 4.8**) were entered into a binary logistic regression as explanatory variables. Logistic regression analysis indicated the characteristics associated with migraine with aura (MA) compared to no migraine within BD subjects were: being female (OR: 2.424; 95% CI: 1.209-4.859); being younger (OR: .975; 95% CI: .952-.999); having a bipolar II diagnosis (OR: 1.772; 95% CI: 1.003-3.132); and a history of suicide attempt (OR: 2.017; 95% CI: 1.184-3.435). A summary of the significant predictors of BD with comorbid migraine with aura (MA) is displayed in **Table 4.9**.

Table 4.9 Summary of significant predictors of migraine with aura (MA) compared with bipolar subjects with no migraine

	Wald X^2	df	P value	OR (95% CI)
Female	6.225	1	.013	2.424 (1.209-4.859)
Age at interview	4.338	1	.037	.975 (.952-.999)
Bipolar II disorder diagnosis	3.876	1	.049	1.772 (1.003-3.132)
History of suicide attempt	6.672	1	.010	2.017 (1.184-3.435)

BDII=bipolar II disorder; df=degrees of freedom; OR=odds ratio; 95% CI=95% confidence interval.

This model correctly classified 82.3% of individuals as having comorbid migraine or not and according to the Nagelkerke pseudo R^2 measure, the model explained 19.2% of the variance in the dependent variable. A Hosmer-Lemeshow (H-L) fit statistic indicated a good fit of the model to the data (p=.05: χ^2 (8) = 7.794, p =.426). The clinical variables that best predicted migraine with aura, when compared to migraine-free individuals did not differ when only variables that surpassed Bonferroni correction for multiple comparisons (p-value threshold of (0.05/20) p<.0025) were entered into the logistic model as predictor variables (see **Appendix E**).

Univariate analysis (**Table 4.8**) revealed statistically significant differences (p<0.05) between the BD subjects with no history of migraine and individuals with migraine without aura (MoA), in that the MoA group: were younger (44.5 vs. 50 years, p=.000043); more likely to be female (79% vs. 69%, p=.023); had a higher rate of BDII (32.3% vs. 20.2%, p=.009); had an earlier onset of the bipolar illness (20 vs. 22 years, p=.023); experienced more episodes of depression (9.5 vs. 6.1, p=.009); had a lower rate of psychiatric admission (73% vs. 81.6%, p=.025); had a higher rate of anxiety disorders (66% vs. 52.8%, p=.018); and had a higher rate of lifetime-ever regular drug use (16.1% vs. 8.7%, p=.012). A logistic regression model entering variables that were significant within univariate analysis at the p<.05 level as explanatory variables, revealed that the only variable associated with MoA was age at interview (OR: .974, 95% CI: .952-.997, p=.024, Wald = 5.071). No clinical bipolar variables were found to be associated with MoA when compared to those with no history of migraine.

4.3.5 Comparison of bipolar clinical features and migraine characteristics between bipolar subjects with migraine with and without aura

A comparison of demographic and bipolar clinical characteristics between individuals with migraine with aura (MA) and migraine without aura (MoA) (**Table 4.10**) indicated that the MA group: were more likely to have been recruited systematically (p=.041); had more episodes of depression (p=.009), and mania (p=.018); and experienced higher rates of rapid cycling illness (p=.010), and panic disorder (p=.017).

Table 4.10 Comparison of demographic and bipolar clinical characteristics between bipolar patients with comorbid migraine, with and without aura.

	MA (n=153)	MoA (n=124)	P-Value
Age at interview (years) Median (IQR) Range	 46 (16) 20-70	 44.5 (17) 23-74	 .357
Sex, n (%) Female	 130 (85%)	 98 (79%)	 .198
Recruitment, n (%) Systematic	 39 (26.4%)	 19 (16%)	 **.041**
Family history of affective disorders, n (%)	122 (90.4%)	87 (88.8%)	.693
DSM-IV diagnosis, n (%) BDI BDII SABP	 89 (53%) 55 (57.9%) 9 (64.3%)	 79 (47%) 40 (42.1%) 5 (35.7%)	 .582
Age at illness onset (years) Median (IQR) Range	 19 (11) 6-51	 20 (10) 6-51	 .221
Number of episodes of depression Median (IQR) Range	 12.1 (14) 0-100.1	 9.5 (16) 0-100.1	 **.009**
Number of episodes of mania Median (IQR) Range	 7.5 (16.1) 1-100.1	 5.1 (12) 1-100.1	 **.018**
History of psychotic features, N (%)	85 (55.6%)	73 (58.9%)	.579
History of psychiatric admission, n (%)	102 (69.9%)	89 (73%)	.578
History of suicide attempt, n (%)	98 (66.7%)	64 (53.3%)	.027
History of rapid cycling, n (%)	53 (34.6%)	25 (20.5%)	**.010**
History of panic disorder, n (%)	33 (26.8%)	17 (13.3%)	**.017**
History of anxiety disorder, n (%)	86 (68.8%)	62 (66%)	.656
Alcohol dependence, n (%)	26 (18.7%)	12 (18.1%)	.990
Lifetime history regular use of cannabinoids, n (%)	35 (24.5%)	26 (21.8%)	.616
Lifetime history regular use of other unspecified drugs, n (%)	22 (15.4%)	19 (16.1%)	.874

*MA=Migraine with aura; MoA=migraine without aura; BDI=bipolar I disorder; BDI= bipolar II disorder; SABP=schizoaffective bipolar type. Figures in **bold** indicate variables significant at the p<.05 level.*

The characteristics of migraine across MA and MoA groups are displayed in **Table 4.11**. Presence of aura was associated with a younger age of migraine onset (median: 15 vs. 18.5 years; p=.004). Within the MA group, age of onset for migraine and BD was known for 116 individuals (76%). The median age of onset of migraine (15 years) was found to be younger than the median age of onset of BD within this group (19 years). For 69 (59.5%) individuals onset of migraine preceded onset of BD illness impairment, whereas onset of BD impairment preceded migraine onset in 38 (32.8%) individuals. For 9 (7.7%) individuals onset of migraine and BD impairment occurred within the same year. For the MoA group, age of onset of both migraine and BD illness impairment was known for 79 (64%) individuals. Within this group, median age of migraine onset (18.5 years) was also younger than the median age of onset of BD illness impairment (20 years). Thirty-nine individuals (49.4%) experienced migraine prior to onset of BD illness impairment, whereas BD impairment preceded migraine onset for 37 (46.8%) individuals. Lastly, within the MoA group, migraine and BD impairment onset occurred within the same year for 3 individuals (3.8%).

A significantly lower proportion of the MA group had taken migraine medication to relieve their headache compared to the MoA group (p=.003) and this was not related to the younger age of onset of migraine of the MA group. The distribution of migraine frequency was significantly different between MA and MoA groups (p=.004), with post hoc analysis revealing more frequent migraine among those with MA. The MA group had a higher rate of family history of migraine, however this was not found to be statistically significant (p=.098). Interestingly, there were no significant differences found in the rate of family history of affective disorders between BD subjects with MA and MoA (**Table 4.10**) (90.4% vs. 88.8%, p=.693).

Table 4.11 Comparison of migraine characteristics between bipolar patients with migraine subtypes, with and without aura.

	MA (n=153)	**MoA (n=124)**	**P-value**
Age of migraine onset (years) **Median** **IQR** **Range**	 15 9 1-70	 18.5 17 6-50	**.004**
Migraine frequency, n (%) **More than once a week** **More than once a month** **Less than once a month**	 69 (47.3%) 40 (27.4%) 37 (25.3%)	 31 (27.2%) 36 (31.6%) 47 (41.2%)	**.002** 1 vs 2, p=.002 1 vs 3, p=.015 2 vs 3, p=.730
Migraine medication, n (%)	96 (62.7%)	98 (79%)	**.003**
Family history of migraine, n (%)	95 (80.5%)	68 (70.8%)	.098
*MA=Migraine with aura; MoA=migraine without aura. Figures in **bold** indicate variables significant at the p<.05 level.*			

A logistic regression was computed entering demographic, bipolar clinical characteristics, and migraine characteristics that were found to significantly differentiate MA and MoA groups (at the p<.05 level) as explanatory variables, with presence of aura (MA vs. MoA) as the dependent variable. The regression model revealed that a history of panic disorder (OR: 8.481, 95% CI: 1.665-43.196, p=.010) and a younger age of migraine onset (OR: .955, 95% CI: .922-.988, p=.009) were predictive of aura status. However, with a total of 134 cases included in the model, and only 55 cases belonging to the smaller migraine without aura (MoA) group, this violates our earlier requirement of at least ten cases per independent variable for the smaller classes of the dependent variable (Peduzzi et al., 1996). We should therefore be very cautious in our interpretation of the above results.

4.4 Discussion

Analysis revealed that when compared to bipolar subjects with no history of migraine, those with comorbid migraine experienced a different clinical course of the bipolar illness. Moreover, the comorbid expression of the relationship between bipolar disorder (BD) and migraine was dependent on migraine subtype. Specifically, the observed differences in the clinical presentation of BD associated with migraine comorbidity were largely driven by the migraine with aura subtype.

When other significant differences were controlled for, subjects with comorbid migraine were more likely to; be younger, be female, have an increased rate of anxiety disorder and an increased rate of suicide attempt. Migraine prevalence is found to vary with age, increasing throughout adolescence and early adult life, peaking in the fourth and fifth decades and declining thereafter. Therefore, the significantly younger age of the migraine group (45 vs. 50 years) is compatible with this peak age distribution. The higher percentage of women in the migraine group is in line with the gender distribution of migraine in the general population, in which a female preponderance is observed (Breslau et al., 1991; Jette et al., 2008), and is in agreement with previous studies conducted within bipolar samples (Baptista et al., 2012; Saunders et al., 2014). The observed female preponderance of migraine has previously been explained, by hormonal changes, and more specifically, with falling levels or withdrawal of oestrogen (Lichten et al., 1996; Whitty et al., 1966).

Consistent with a number of studies, migraine was associated with a lifetime history of anxiety disorder in individuals with BD (McIntyre et al., 2006b; Ortiz et al., 2010). The association between migraine and anxiety disorder is well established. For example, a large, population-based study in the US reported that 9.1% of subjects with migraine, had comorbid generalised anxiety disorder, compared with 2.5% of those without migraine (OR 3.9, 95% CI 2.5 to 6.0). This association remained significant even after adjusting for demographic variables including other common pain conditions (arthritis and back pain) (McWilliams et al., 2004). Moreover, a prospective study by Merikangas et al. (1990) revealed that the association between migraine and anxiety disorders was even stronger than that for the affective disorders. Merkingas and colleagues reported

generalised anxiety disorder (OR 5.3, 95%CI 1.8 to 15.8) and social phobia (OR 3.4, 95% CI 1.1 to 10.9) as being the types of anxiety disorder exhibiting the strongest association with migraine. The combined effects of depression and anxiety in migraine have also been reported on. Breslau et al. (1991) revealed that the comorbidity of migraine and major depression occurred frequently in the presence of coexisting anxiety. They also reported that migraine onset was often preceded by onset of anxiety disorder and was followed by the onset of major depression. In the same paper, Breslau et al. (1991) revealed that whilst the presence of migraine alone increased the odds of major depression nearly threefold (odds ratio: 2.7), migraine together with co-occurring anxiety (vs. those with neither disorder) increased the odds of major depression by 22.8 times. This increase in odds exceeded what would have been expected by summing the individual effects of migraine and anxiety on the likelihood of major depression. In this analysis the category of major depression included all of those with such a history, including those with mania or hypomania.

Research suggests that anxiety disorders may be the most prevalent psychiatric comorbidity among BD. Epidemiological studies show that as many as 74.9% of individuals with BD have at least one anxiety disorder at some point in their life (Merikangas and Kalaydjian, 2007). Findings from the current chapter indicate that this relationship may be even higher among bipolar patients with migraine. Psychiatric comorbidity can further complicate the bipolar illness and may influence the course of illness leading to poorer outcomes and prognosis. Therefore, identifying, and treating comorbid psychiatric disorders is very important in the clinical management of the disorder. In particular, comorbid anxiety disorders have been associated with more affective relapses, increased suicidality, decreased social functioning, and sleep disturbances (Freeman et al., 2002; Hawke et al., 2013). They have also been shown to complicate the pharmacologic treatment of BD, by reducing the effectiveness of mood stabilisers (Keller, 2006), and increasing non-adherence to pharmacotherapy (Perlis et al., 2010).

Comorbid migraine was also found to be independently associated with a past history of suicide attempt. Such a finding is in line with Ortiz et al. (2010) who found that almost 40% of bipolar subjects with migraine had a history of suicide attempt, which was significantly greater than that seen within bipolar subjects

without migraine (27%). Moreover, Nguyen and Low (2012) reported that migraine comorbidity with mood episodes was associated with both suicidal ideation and suicidal attempt within their large Canadian nationally representative (n=26,984) population-based study. It is important to note the particularly high rate (60%) of suicide attempt observed within bipolar subjects with comorbid migraine within the current study. This figure surpasses that reported by Ortiz et al. (2010) and exceeds the commonly reported statistic that 25-50% of bipolar patients will attempt suicide at least once in their lifetime (Goodwin and Jamison, 1990; Hawton et al., 2005; Jamison, 2000; Valtonen et al., 2006). The link between migraine and suicidality is not fully understood. Whilst suicidal thinking and behaviour in migraine is often attributed to psychiatric disorders that can accompany migraine, evidence suggests that this association may be independent of psychiatric comorbidity, particularly for migraine with aura (Breslau et al., 1991). I will discuss this proposal in more detail when summarising the main findings of the migraine subtype analysis.

Within univariate analysis, bipolar subjects with migraine reported a greater number of episodes of depression compared to those without migraine. An increased number of episodes of depression was also found to be an independent predictor of migraine in the second multivariate model, entering variables that survived adjustment for multiple testing. This finding is in line with Brietzke et al. (2012b), who noted that migraine comorbidity within BD was associated with more mood episodes, especially those of depressive polarity. Such a finding has important clinical implications given the potential for an individual being inappropriately treated with anti-depressant monotherapy, increasing the risk of a pharmacologically-induced manic episode.

In addition to exploring the impact migraine comorbidity has on the bipolar illness, it is also important to determine whether migraine experienced within bipolar disorder is similar to that experienced within the general population. Within the current study, of those individuals for whom age of onset of migraine was known (n=195, 70.4%), 67% reported onset before the age of 20 years. This is in accordance with a number of studies stating that at least half of all migraine onsets begin before the age of 20 (Lipton et al., 2001; Silberstein and Lipton, 1993; Stewart et al., 1991). Regarding the characteristics of migraine, the most frequent migraine symptoms were: moderate or severe pain intensity (98%),

unilateral pain (73.6%), pulsatile pain (64.6%), hypersensitivity to light or sound (50.2%), nausea/vomiting (41.5%), with aggravation by physical activity being the least frequently endorsed symptom (33.6%). The only study to detail symptom frequencies of migraine within the general population, was Lipton et al. (2001) in their large US population-based American Migraine Study II. However, differences between the studies in the assessment of symptoms make them difficult to compare. Specifically, Lipton et al. (2001) did not assess the International Headache Society (IHS) criterion of 'aggravation by physical activity', and chose to report the symptoms of 'nausea' and 'vomiting' separately. In the current study and in line with IHS criteria, I report a combined figure assessing the presence of nausea and/or vomiting. Moreover, as discussed within the methods chapter of this thesis, the current study asked subjects about hypersensitivity to sound 'or' light, in contrast to Lipton et al. (2001) who asked about hypersensitivity to light 'and' sound, separately. Lipton et al. (2001) did report the frequencies for pulsatile and unilateral pain, of which pulsatile pain was found to be more prevalent; 85% vs. 59% for unilateral pain. This is in contrast to the current study where bipolar subjects more frequently endorsed unilateral pain.

Within the bipolar cohort of migraine sufferers, I identified a greater number of patients with migraine with aura (MA) than without aura (MoA). One-hundred and fifty-three individuals with migraine (55.2%; 10.7% of total sample) had experienced MA, compared to the 124 (44.8%; 8.7% of total sample) subjects that had suffered with MoA. This becomes even more prominent if the 69 subjects identified as having typical aura with non-migraine headache (n=65) and typical aura with no headache (n=4) are included within the former group. As discussed in Chapter 3, this finding is in contrast to the third of migraine patients reported to experience aura symptoms within the general population (Silberstein and Lipton, 1993). Fasmer (2001) also observed a greater number of patients with MA (n=12, 43% of migraine group; 19% of total sample) compared to MoA (n=10, 35.7% of migraine group; 16% of total sample) within their sample of inpatients with major affective disorders. Similarly, Ortiz et al. (2010) reported a two-fold prevalence of MA in a sample of subjects with bipolar spectrum disorders, compared to that reported in the general population (Russell and Olesen, 1996). Such a finding is in line with previous research

indicating a stronger association between affective disorders and MA, compared to MoA (Breslau et al., 1991; Oedegaard et al., 2005a; Ball et al., 2009).

Of the 153 individuals identified as having migraine with aura, visual aura was found to be the most frequent of aura symptoms (79.1%), followed by sensory (44.4%) and aphasic (19%). A similar pattern is observed within the general population (Russell and Olesen, 1996), although with a higher proportion of individuals experiencing visual aura (99%) and a lower proportion reporting sensory aura (31%), than observed within our BD sample of MA individuals. In line with existing literature, we revealed an earlier age of migraine onset for the MA group compared with MoA (15 vs. 18.5, p=.004). Age of onset of both MA and MoA were younger than the onset of BD in either group (19 and 22 years, respectively), suggesting that migraine may precede BD. Specifically, for the MA group, onset of migraine preceded BD onset in nearly 60% of individuals, whereas in the MoA group, migraine preceded BD in approximately equal proportions to those where BD onset preceded migraine onset (49.4% vs. 46.8%, respectively). Thus, MA may constitute a first hallmark of BD for some patients and raise clinicians' suspicion for the presence of affective pathology.

To our knowledge, this is the first study to differentiate between the subtypes of MA and MoA when exploring the relationship of migraine with the clinical features and course of BD. Multivariate analysis revealed that when compared to BD subjects with no history of migraine, those with migraine with aura (MA): were more likely to; be younger, be female, have a diagnosis of bipolar II disorder (BDII) and have a higher lifetime rate of attempted suicide. In Chapter 3, I observed a higher prevalence of both migraine with (MA) and without aura (MoA) among individuals with BDII compared to bipolar I disorder (BDI). When compared with bipolar subjects without migraine, there was a significant negative association with BDI and a significant positive association with BDII with both subtypes of migraine. Moreover, the strength of the association with BDII was observed to be larger for MA than that for MoA. In the current study, BDII was found to be an independent predictor of MA when compared with bipolar subjects without migraine, however was not found to be associated with

MoA within multivariate analysis, suggesting the association of BDII with migraine is perhaps driven by the MA subtype.

Given this independent association of MA with BDII, together with the proposal that a rapid cycling illness course is associated with the BDII subtype (Kupka et al., 2003), it could be suggested that association between MA and BDII may be explained by the association of a rapid cycling course of illness with BDII. Interestingly, a rapid cycling illness course was not found to be associated with MoA when compared to bipolar subjects without migraine. A significantly increased rate of rapid cycling illness was found in bipolar subjects with MA when compared to those with MoA, suggesting that the association with rapid cycling may be specific to migraine with aura.

MA was also associated with past history of suicide attempt. When focusing on all forms of migraine, evidence has suggested an increased rate of suicide attempt within BD patients. In addition, as outlined within the introduction of this thesis, an association has also been noted between suicide attempt and MA, even after adjusting for presence of major depressive disorder (MDD) and other psychiatric comorbid conditions (Breslau, 1992; Breslau et al., 1991). Within the current study, a history of suicide attempt was not found to differentiate BD subjects with MoA compared to those with no migraine. A comparison between bipolar subjects with MA and MoA revealed an increased rate of suicide attempt in the MA group, suggesting that the relationship between suicide attempt and any migraine within BD is specific to the MA subtype. Thus, identifying the presence of MA in bipolar patients may help clinicians to identify those at increased risk for suicide, therefore enabling appropriate management and intervention.

No bipolar clinical characteristics were found to be associated with MoA when compared to bipolar subjects without migraine in the multivariate model, suggesting that the migraine-BD comorbidity may have more serious implications for those with MA and that the relationship between BD and migraine is perhaps driven by the MA subtype. When differentiating MA from MoA, significant differences were found in the clinical characteristics of BD and

migraine. A multivariate model revealed history of panic disorder and a younger age of migraine onset to be associated with aura status. Our group previously reported an independent association of panic attacks with comorbid migraine (not distinguishing between subtypes) in BD, even after controlling for other significant differences (Gordon-Smith et al., 2015). Results of the current study suggest that a history of panic attacks and an early onset of migraine in bipolar patients with MA may be indicative of a subgroup of individuals at increased risk for a number of important clinical outcomes, including suicidality.

This study benefits from a large, clinically well-defined, sample of subjects with bipolar disorder. Furthermore, subjects were sampled from a UK community population, recruited through both systematic and non-systematic methods. This representative sample therefore increases the generalisability of the study findings. A further strength of this study is the use of IHS criteria (Headache Classification Subcommittee of the International Headache Society, 2004) for determining migraine diagnosis. It is, however, important to interpret findings in the context of certain limitations. Firstly, as mentioned within the previous chapter, the cross-sectional nature of the study methodology does not allow for the determination of causality in the relationship between BD and migraine and therefore future prospective studies would be useful. Secondly, lifetime history of migraine was ascertained through retrospective self-report measures and is therefore subject to recall bias and may have resulted in either an under or over reporting of migraine. Moreover, although an acceptable questionnaire response rate of 40% was achieved, it is possible that a response bias may exist. However, as described in Chapter 3, the migraine questionnaire was part of a larger pack of 13 questionnaires and so it is unlikely that individuals completed this questionnaire based on their migraine status. Finally, analysis did not consider medication use, which will inevitably modify the bipolar illness. Moreover, some pharmacological treatments are successful within both disorders, most notably valproate, and so it is unknown to what extent such treatment options influenced the prevalence and course of both disorders.

The results in this chapter suggest that comorbid migraine may represent a subtype of BD that is associated with a distinct set of lifetime clinical characteristics. Moreover, differences identified in the comorbid expression of this relationship suggest that the relationship between migraine and BD may be

driven by the migraine with aura subtype. This finding emphasizes the importance of not only recognising migraine within individuals with bipolar disorder, but also the value of identifying subtypes of migraine among this patient group. This could help to predict the course of the bipolar illness and identify those at increased risk for important illness outcomes and hence, offer appropriate management sooner. Further research aimed at unravelling the complex relationship between migraine subtypes and BD will help us to better understand and characterise the clinical features of the migraine-BD comorbidity and identify sub-populations of individuals with BD that could benefit clinically from more effective, targeted diagnostic and treatment strategies, and may provide a useful focus for future aetiological studies, potentially revealing common pathophysiology underlying both disorders.

Chapter 5

Exploring the genetic susceptibility of bipolar disorder and comorbid migraine: a genome-wide association study

5.1 Introduction

As has already been discussed in earlier chapters of this thesis, migraine is a common comorbid condition within bipolar disorder (BD), with studies consistently showing an increased prevalence of migraine among those with BD (Mahmood et al., 1999; McIntyre et al., 2006b; Ortiz et al., 2010; Gordon-Smith et al., 2015). Moreover, studies have suggested that migraine comorbidity may influence course of illness in BD. For example, presence of migraine has been associated with: an earlier age of onset of BD (Mahmood et al., 1999; McIntyre et al., 2006b); attempted suicide (Ortiz et al., 2010); a rapid cycling course of illness (Gordon-Smith et al., 2015); and a bipolar II diagnosis (Fasmer, 2001; Ortiz et al., 2010). Such findings suggest that recognition of migraine may be a meaningful way of refining the bipolar phenotype to identify more homogeneous patient populations.

As outlined within the introduction of this thesis, a number of possible shared underlying mechanisms influencing susceptibility to migraine and BD have been suggested. For example, both migraine and BD have been linked to disturbances in the serotonergic (Hamel, 2007; Mahmood and Silverstone, 2001; Silberstein, 1994), dopaminergic (Emilien et al., 1999; Peroutka, 1997), and glutamatergic systems (Vaccaro et al., 2007). Disturbances in inflammatory cytokines (Brietzke et al., 2012a) and alterations in ion channels (Di Lorenzo et al., 2012; Fasmer et al., 2009) have also been implicated in the pathophysiology of both disorders. In addition, some pharmacological treatments are common to migraine and BD. For example, valproate is a treatment for BD but can also

be used in the prophylactic treatment of migraine, reducing the number of attacks, duration of headache and intensity of pain (Silberstein, 1996).

As discussed within the introduction of this thesis, previous studies have suggested that migraine may provide a useful tool for stratifying individuals with BD, potentially identifying subgroups of patients for which there may be shared genetic variation. For example, using the migraine-bipolar phenotype, a genome-wide linkage study on 31 families (n=202) identified an overlapping locus on chromosome 20p11 for both BD and migraine (Oedegaard et al. 2010b). Regions of genetic susceptibility have also been identified for the migraine-bipolar phenotype through genome-wide association studies (GWAS). Based on a sample of 56 bipolar cases with comorbid migraine compared with 699 controls (bipolar subjects without any headache), Oedegaard et al., (2010a) found evidence of association for several single-nucleotide polymorphisms (SNPs) approaching genome-wide significance (5×10^{-8}) on chromosome 13q14.1 (e.g. rs9566845, $p=7.7 \times 10^{-8}$; and rs9566867, $p=8.2 \times 10^{-8}$), in a region containing the uncharacterised gene KIAA0564. Whilst little is known about the gene, a Dutch genome-wide linkage study supported the involvement of this genomic region in migraine by reporting linkage to a region in close proximity to that harbouring KIAA0564 (Ligthart et al., 2008).

In a second GWAS involving 460 bipolar subjects with self-reported migraine (cases) and 914 bipolar subjects without migraine (controls), Jacobsen et al., (2015) identified a genome-wide significant association for rs1160720 in the *NBEA* gene (chromosome 13q13). The *NBEA* gene encodes neurobeachin, a scaffolding protein primarily expressed in the brain (Lauks et al., 2012). *NBEA* has also been shown to be involved in trafficking vesicles containing GABA and glutamate receptors (Lauks et al., 2012; Nair et al., 2013), thus implicating the glutamatergic system as a potential pathway leading to the development of the combined migraine-bipolar phenotype (Cherlyn et al., 2010; Ligthart et al., 2011). Interestingly, this variant failed to show association with migraine or BD individually, leading the authors to speculate the etiological specificity of this gene to the combined phenotype and to hypothesize that BD with comorbid migraine may be a distinct syndrome with different genetic risk factors than for either migraine, or BD alone.

The above studies support the proposal that the BD-migraine combined phenotype has the potential to reclassify individuals into a more homogeneous genetic subgroup. However, neither of the above published GWAS of migraine and BD used standardised, International Headache Society (IHS) criteria, which may have resulted in phenotypic heterogeneity, potentially limiting the power of these studies to identify susceptibility genes for the combined BD-migraine phenotype.

So far, the current thesis has identified a group of bipolar subjects with comorbid migraine as defined by IHS criteria (Chapter 3) and has revealed differences in the clinical course of the bipolar illness according to the presence of migraine (Chapter 4). These findings add support to the proposal that migraine comorbidity may be used to delineate subgroups among individuals with BD for which there may be common genetic variation. The current study looked to extend previous work by examining genetic susceptibility to BD with comorbid migraine (defined according to IHS criteria), through a genome-wide association study.

5.2 Methods

5.2.1 Subjects

Chapter 3 of this thesis identified 277 bipolar subjects meeting International Headache Society (Headache Classification Subcommittee of the International Headache Society, 2004) criteria for migraine, according to a self-report questionnaire based on The Structured Migraine Interview (SMI; Samaan et al., 2009). 778 bipolar subjects were identified as being free from migraine comorbidity. Out of the combined total of 1,055 subjects, genotype data was available for 712 subjects (of which n=526, 74% were female). Thus, the case-control study reported here included 210 bipolar subjects with migraine and 502 bipolar subjects without migraine. Of the 210 bipolar subjects identified as having migraine, 119 (57%) met IHS criteria for migraine with aura (MA).

All subjects were derived from the Bipolar Disorder Research Network (BDRN). Please see Chapter 2 for a description of the sample and assessment information. Of the 712 subjects included in the current study; 486 (68.3%) subjects met criteria for bipolar I disorder (BPI), 199 (27.9%) met criteria for bipolar II disorder (BPII), and the remaining 27 (3.8%) subjects met criteria for schizoaffective, bipolar type (SABP). All participants were: above 18 years of age; unrelated; and of white European descent (according to both self-report and principal component analysis of GWAS data – see Section 5.2.3).

5.2.2 Genotyping and quality control

Genotype data for the current study was provided by Professor Elaine Green (Professor of Genomics, Plymouth University), via the Broad Institute. DNA extraction was performed by Kbiosciencs (now known as LGC; http://www.lgcgroup.com/our-science/genomics-solutions/#.V17Cm_krK70). Samples were genotyped at the Broad Institute on either the Illumina HumanOmniExpress-12v1, or the Illumina HumanOmniExpressExome-8v1. Specifically, of the 712 subjects included in the current study, 217 individuals were genotyped on the HumanOmniExpressExome-8v1, and 495 on the HumanOmniExpress-12v1. The proportion of cases (bipolar subjects with migraine) genotyped on each array was comparable, with 28.9% of those

genotyped on HumanOmniExpressExome-12v1, and 30.9% of those genotyped on HumanOmniExpressExome-8v1, being cases (bipolar subjects with migraine).

Data was provided by EG in the following binary files; a '.bed' file (containing genotype data for individuals), a '.bim' file (a mapping file, providing information on each genetic marker), and a '.fam' file (providing participant identification information). As part of the data pre-processing stage, I created a new binary data file (using the '--make-bed' command in PLINK) to keep only those individuals to be used within the analysis (i.e. bipolar cases with migraine, and bipolar cases without migraine). This was performed using the '--keep' command in PLINK followed by a '.txt' file listing the individual identifier of the 712 individuals to be included in the study. In order to allocate disease status to included participants (1=unaffected-no migraine; 2=affected- migraine), I read in information from an alternative phenotype file using the '--pheno' command. This phenotype file included the family identifier, individual identify and phenotype for each individual. As above, I then created a new binary data file including updated disease status using the '--make-bed' command, which, by default created a '.bed', '.bim' and '.fam' file. Once the genotype and phenotype information had been read into PLINK, it was possible to conduct the next stage of data pre-processing; sample-level and single nucleotide polymorphism (SNP)-level filtering. This is explained in more detail below.

Initial quality control (QC) was performed at the Broad Institute. I checked QC parameters within the current analysis and all passed the thresholds in line with those followed by the Psychiatric Genetics Consortium (see Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Within the current analysis, QC thresholds for the dataset were set so that single nucleotide polymorphisms (SNPs) were excluded if: they had a minor allele frequency (MAF) below 5%; had less than 97% genotyping call rate; and if they significantly deviated from Hardy-Weinberg Equilibrium (*P*-value < 0.0001). In addition, thresholds were set so that samples with more than 3% failed genotypes were excluded. I also tested for relatedness using IBD estimation (-- genome –0.2), and autosomal heterozygosity deviation (| Fhet | < 0.2), in PLINK, which did not identify any individuals to be excluded.

5.2.3 Genome-wide association analysis

Principal component estimation was performed by Dr Sophie Legge using EIGENSTRAT (Price et al. 2006) to identify potential outliers and explore potential effects of population stratification (differences in allele frequency between cases and controls due to systematic ancestry differences) in the sample. Using EIGENSTRAT, principal components analysis is used to infer continuous axes of genetic variation (eigenvectors) that reduce the data to a small number of dimensions, whilst describing as much variability between individuals as possible. Next, genotypes and phenotypes are continuously adjusted by amounts attributable to ancestry along each axis, creating a virtual set of matched cases and controls. Finally, association statistics are computed using ancestry-adjusted genotypes and phenotypes (Price et al., 2006).

I included the first three principal components as covariates to account for population structure. Association analysis was performed using logistic regression in PLINK (Purcell et al. 2007), using the '--logistic' command. In addition, I used the '--ci 95' command to output the standard error and 95% confidence intervals of the odds ratio. Manhattan and quantile-quantile (QQ) plots were generated in R (http://www.R-project.org). SNPs were functionally annotated using the UCSC Genome Browser (Kent et al., 2002; https://www.genome.ucsc.edu/), and Ensembl Genome Browser (Flicek et al., 2014; http://www.ensembl.org/index.html). Following the association analysis, PLINK was used to identify independent (in relative linkage disequilibrium) SNPs (--clump-p1 0.0001 --clump-p2 0.0001 --clump-r2 0.1 --clump-kb 3000), where the SNP with the highest association was selected as the index SNP. I employed a genome-wide significance level of $P < 5 \times 10^{-8}$, which is commonly used in GWAS and corresponds to a Bonferroni multiple testing correction of a 0.05 Type 1 error level for 1 million independent tests (Johnson et al., 2010).

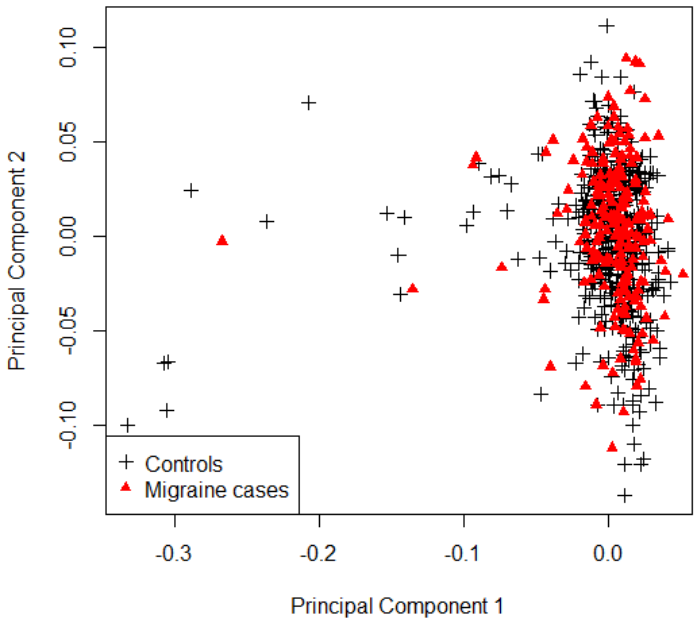


Figure 5.1 Principal component analysis plot displaying principal component 1 and 2. Points represent individual samples; black points represent bipolar subjects without migraine (controls) and red points represent bipolar subjects with migraine (cases). Cases and controls appear to overlap considerably, therefore it can be presumed that they originate from similar populations.

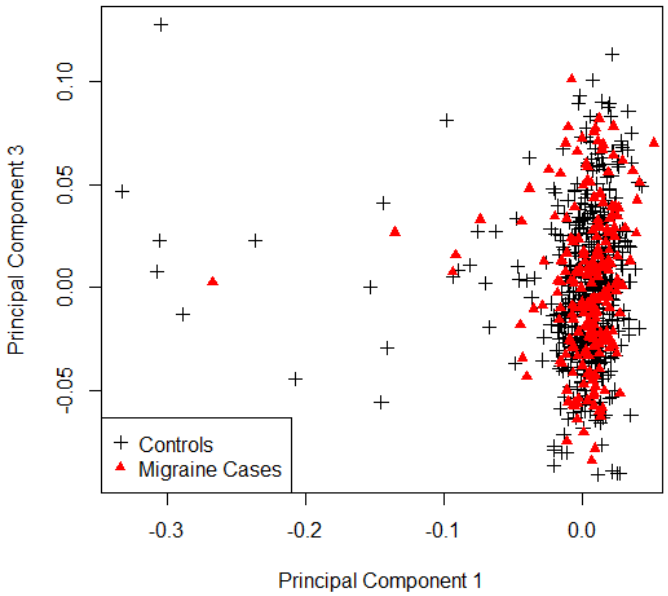


Figure 5.2 Principal component analysis plot displaying principal components 1 and 3. Points represent individual samples; black points represent bipolar subjects without migraine (controls) and red points represent bipolar subjects with migraine (cases). Cases and controls appear to overlap considerably, therefore it can be presumed that they originate from similar populations.

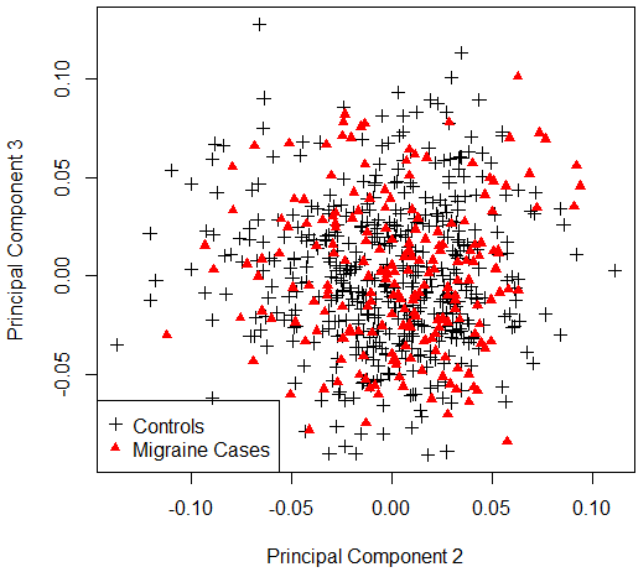


Figure 5.3 Principal component analysis plot displaying principal component 2 and 3. Points represent individual samples; black points represent bipolar subjects without migraine (controls) and red points represent bipolar subjects with migraine (cases). Cases and controls appear to overlap considerably, therefore it can be presumed that they originate from similar populations.

5.3 Results

Association was tested in a total of 210 bipolar subjects with migraine (cases) and 502 bipolar subjects without migraine (controls). 1,325 SNPs were excluded due to a MAF below 5%, and 1 SNP was excluded for failing HWE, leaving 377,465 SNPs available for analysis. **Figure 5.4** shows a quantile-quantile (QQ) plot displaying the relationship between observed p-values (y axis) and expected p-values (x axis). Both the QQ plot (**Figure 5.4**) and estimated genomic inflation factor show no evidence of inflation (λ=1) and so this was not corrected for in the association analysis. **Figure 5.5** shows a Manhattan plot of all SNPs in the analyses, displaying the p-values of the comparisons between the bipolar subjects with migraine (cases), and without migraine (controls).

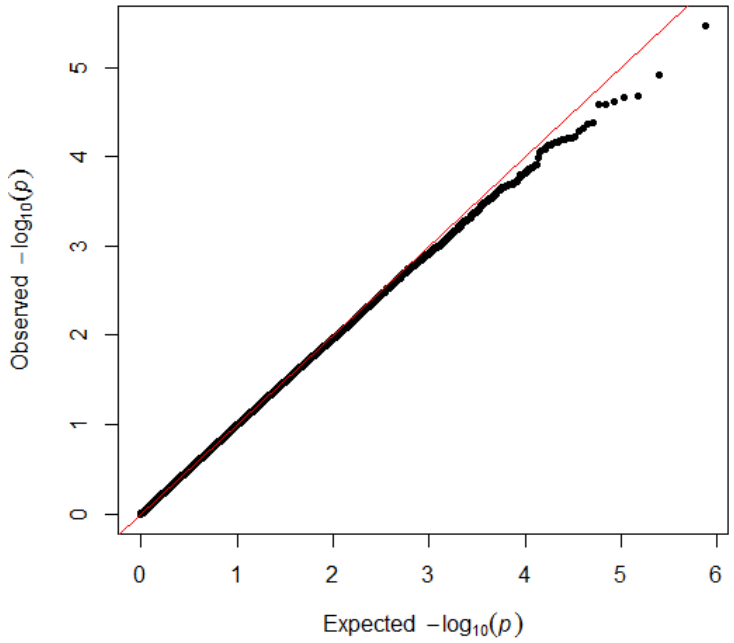


Figure 5.4 QQ plot of –log10 observed logistic regression p-values (y-axis) against expected p-values (x-axis). $\lambda_{GC} = 1$.

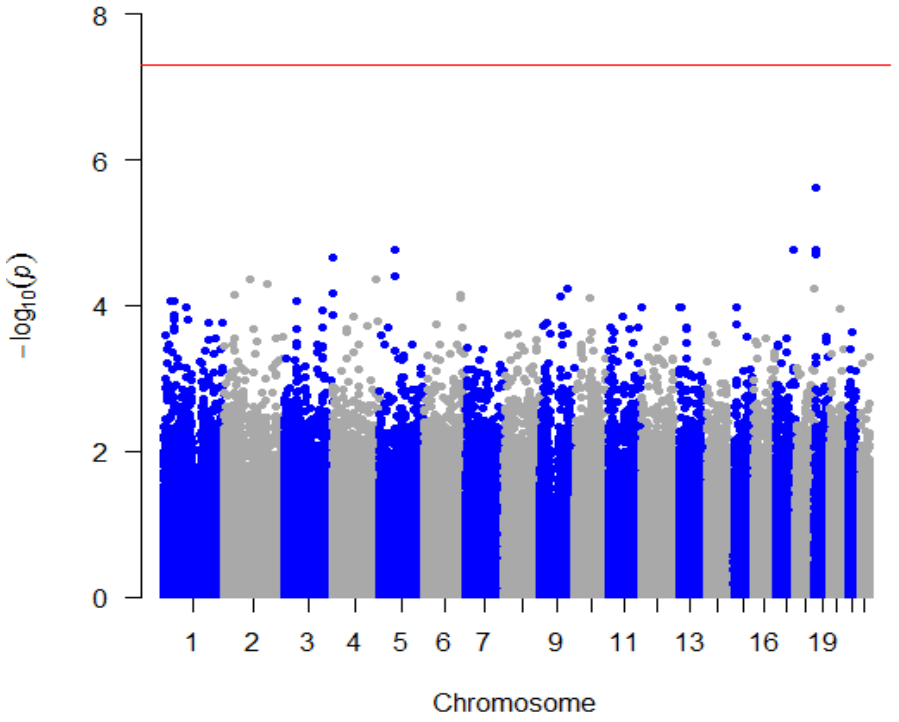


Figure 5.5 Manhattan plot of -log10 p-values for each SNP (y-axis), plotted by chromosomal position (x axis). Red line represents genome wide significance level ($P < 5 \times 10^{-8}$).

As seen within **Figure 5.5,** no SNP surpassed the genome wide significance level of $p < 5 \times 10^{-8}$. **Table 5.1** lists the ten most strongly associated SNPs in relative linkage equilibrium. The strongest signal associated with comorbid migraine within bipolar disorder (BD) was found for a locus on chromosome 19p13.3, marked by rs4375794 and located within the Protease Serine 57 (*PRSS57*) gene. The minor allele of rs4375794 (T) was more frequent in bipolar subjects with migraine compared to those migraine-free controls (OR = 1.921, 95% CI = 1.454-2.537, $p=3.45 \times 10^{-6}$) (**Table 5.1; Figure 5.5**). A further 6 of the top independent SNPs were significant at the $p< 5 \times 10^{-5}$ level (**Table 5.1**) with three of these being located in known genes; IQ Motif Containing G (IQCG), Long Intergenic Non-Protein Coding RNA 683 (*LINC00683*); and SP3 Transcription Factor (*SP3*).

SNP	CHR	Position	A1/A2	MAF A	MAF U	OR	95% CI	P-value	Gene	Location	Predicted function
rs4375794	19	691909	T/C	0.2571	0.1527	1.921	1.454- 2.537	$3.45x10^{-6}$	*PRSS57*	Exonic	Synonymous
rs13175238	5	68058660	A/G	0.1476	0.07186	2.237	1.559-3.209	$1.22x10^{-5}$		Intergenic	
rs3898584	17	68800128	C/T	0.1024	0.2006	0.4545	0.3199-0.6459	$2.08x10^{-5}$		Intergenic	
rs9880989	3	197665599	T/G	0.2238	0.1347	1.852	1.382- 2.481	$2.17x10^{-5}$	*IQCG*	Exonic	Missense
rs17059667	18	74337641	T/C	0.1357	0.06786	2.157	1.486- 3.13	$4.20x10^{-5}$	*LINC00683*	Downstream gene variant	
rs2376070	2	104646414	T/C	0.2619	0.164	1.809	1.375- 2.38	$3.49x10^{-5}$		Intergenic	
rs4972618	2	174769344	T/C	0.3714	0.479	0.6426	0.5088- 0.8117	$4.75x10^{-5}$	*SP3*	Downstream gene variant	
rs7583046	2	42468471	G/A	0.3952	0.506	0.6381	0.5062-0.8043	$5.93x10^{-5}$	*EML4*	Intronic	
rs870713	9	84227158	C/A	0.3881	0.508	0.6143	0.4871- 0.7748	$6.14x10^{-5}$	*TLE1*	Intronic	
rs4978770	9	111887219	T/G	0.1627	0.08982	1.969	1.404- 2.761	$6.33x10^{-5}$	*TMEM245*	Upstream gene variant	

Columns are: variant ID (SNP); chromosome (CHR); chromosomal position (Position); minor reference allele (A1); major allele (A2); minor allele frequency in cases (MAF A); and minor allele frequency in controls (MAF U); odds ratio (OR); 95% confidence interval (95% CI); p-value; gene; location to/in gene; and predicted function.

Table 5.1 Top 10 independent single nucleotide polymorphisms (SNPs) from GWAS analysis.

5.4 Discussion

The current chapter describes a genome-wide association study (GWAS) in which 210 bipolar subjects with comorbid migraine (cases) and 502 bipolar subjects without migraine (controls) were analysed. No single SNP met the threshold for genome-wide association with migraine in bipolar disorder (BD). The strongest evidence for association was for rs4375794, an exonic SNP found within Protease Serine 57 (*PRSS57)* on chromosome 19p13.3 (OR = 1.921, 95% CI = 1.454-2.537, p=3.45 x 10^{-6}). In addition, a further 6 of the top 10 independent SNPs showed moderate significance at the p< 5 x 10^{-5} level: rs13175238 (chromosome 5), rs3898584 (chromosome 17), rs9880989 (chromosome 3), rs17059667 (chromosome 18), rs2376070 (chromosome 2), and rs4972618 (chromosome 2). Three of these SNPs were located in known genes; IQ Motif Containing G (IQCG) (rs9880989), Long Intergenic Non-protein Coding RNA 683 (LINC00683) (rs17059667); and SP3 Transcription Factor (*SP3*) (rs4972618).

A description of the possible candidate genes in regions implicated by the top 10 independent SNPs is included in **Appendix F.** Review of gene ontology databases for these genes did not reveal any obvious implications for current theories of BD or migraine pathophysiology. Moreover, variants within these genes have not been previously implicated in BD, migraine, nor with the combined migraine-BD phenotype. Below, I briefly summarise any known function of the genes associated with the migraine-BD phenotype in this study up to a significance level of p< 5 x 10^{-5} (*PRSS57, IQCG, LINC00683*, *SP3*):

PRSS57 (Protease, Serine, 57)

PRSS57 is involved in serine-type endopeptidase activity. Serine proteases are proteolytic enzymes that break the peptide bond that joins amino acids together in proteins. In mammals, serine proteases are involved in a number of biological processes, such as; digestion, blood clotting, reproduction and the complement system.

IQCG (IQ Motif containing G)

IQCG is one of several IQ motif–containing genes of unknown function. IQ motifs are present in several hundred proteins, most notably myosins, but also in a variety of nonmyosin proteins such as neuronal growth proteins, voltage-

gated channels, phosphatases, spindle-associated proteins, and sperm surface proteins (Bähler and Rhoads, 2002). Harris et al. (2014) recently reported a male-specific infertility mutant in which the genetic lesion was traced to IQCG. These mice exhibited spermiogenesis defects.

LINC00683 (Long Intergenic Non-Protein Coding RNA 683)

LINC00683 is a non-annotated RNA gene, affiliated with the non-coding RNA class.

SP3 (Sp3 Transcription Factor)

SP3 is a protein coding gene, belonging to a family of Sp1 related genes that encode transcription factors that regulate transcription. This protein contains a zinc finger DNA-binding domain and several transactivation domains, and functions as a bifunctional transcription factor, both activating and repressing transcription (Suske, 1999).

Whilst it is possible to identify risk variants for complex disease in a small sample (Klein et al., 2005), it is generally accepted that the GWAS approach requires very large samples, with numbers typically reaching the tens of thousands (Craddock et al., 2008). Therefore, a lack of statistical power, given the limited number of cases and controls may be a potential explanation for the current study not finding any genome-wide significant effects. GWAS rely on the 'common disease-common variant' (CDCV) model, in which several common variants are thought to confer a small risk and interact to give rise to the disorder (Barnett and Smoller, 2009). Therefore, GWAS require large numbers of cases and controls in order to detect such small effects with statistical confidence. Moreover, considering the stringent significance threshold enforced by GWAS (because of the requirement to adjust for the large number of statistical tests performed), power is likely to be inadequate to detect small effect sizes unless large numbers of cases and controls are studied. One way of increasing the number of samples in the current study could be to include cases identified as having probable migraine. In Chapter 3, an additional 304 subjects were identified to have probable migraine, defined as an attack or headache missing one of the features needed to fulfil all International Headache Society (IHS) criteria for a migraine disorder (ICHD, 2004). Chapter 3 demonstrated that of the

45 probable migraine cases selected for a follow-up telephone interview, 64.4% were in fact found to meet full criteria for migraine, thus supporting the proposal of including probable migraine cases within a replication of the current study.

An alternative to the 'common disease-common variant' model is the 'common disease-multiple rare variants' model in which a proportion of disease is said to be caused by highly penetrant rare genetic variants, each with large effect (Pritchard, 2001). GWAS are not designed to detect the effects of such variants that are often suggested to account for much of the 'missing heritability' problem associated with GWAS (Maher, 2008). It is therefore possible that susceptibility to the migraine-BD phenotype may be explained by rare variants that could not be detected by the current GWAS approach.

Moreover, there has been much debate concerning whether the migraine subtypes, migraine with (MA) and without aura (MoA) are distinct subtypes or whether they are part of the same disease spectrum (Ligthart et al., 2006; Nyholt et al., 2004; Russell et al., 2002, 1996). The observation that both types of attack can occur within the same individual (Launer et al., 1999), and that MA and MoA are frequently found within the same family (Carlsson et al., 2002) is often cited as evidence of a shared aetiology between the subtypes. In contrast, MA has been identified as having a higher genetic component than MoA, with Russell and Olesen (1995) revealing a considerably higher heritability estimate and sibling recurrence risk compared to MoA (3.8 vs. 1.9). Such a finding suggests that MA and MoA may have different aetiologies and therefore different modes of inheritance. Furthermore, results from a recent meta-analysis of 23,285 migraine cases and 95, 425 controls of European ancestry identifying 142 SNPs surpassing genome-wide significance at 12 loci, revealed important differences between subjects with MA and MoA (Anttila et al., 2013). When analyzing MoA and MA separately, Antilla et al. (2013) revealed a larger number of significant loci associated with MoA compared to MA (despite similar sample sizes). In addition, subgroup comparisons for the 12 implicated loci indicated that the effect sizes were larger in MoA compared to MA cases. Whilst this was unexpected given the suggested higher heritability of MA compared to MoA, one possible explanation for the observed difference is that MA may be less influenced by common variants than MoA, and mediated more by rare

variants with larger effect. Given that over half (57%) of the migraine subjects within the current study were identified as having MA, this provides further support for the possibility that causal variants of large effect, not picked up by GWAS, may be contributing to the migraine and BD phenotype.

In addition, future research investigating the potential shared aetiological underpinnings between migraine and BD, may benefit from focusing on the rare subtype of MA, hemiplegic migraine (HM). As described in the introduction of this thesis, the familial subtype of HM (FHM) is genetically heterogeneous, with polymorphisms in at least three genes being implicated; C*ACNA1A* (Ophoff et al., 1996), *ATP1A2* (DeFusco et al., 2003), and *SCN1A* (Dichgans et al., 2005). All three FHM genes either encode ion channels or are involved in ion transportation, thus implicating ion channels within the molecular pathophysiology of both migraine and BD. Chapter 3 of this thesis identified 45 individuals meeting criteria for hemiplegic migraine (HM) (3.1% of total sample). This greatly exceeds the 0.01% rate of HM reported by Thomsen et al. (2002) in a Danish population-based epidemiological survey. Whilst the number of individuals identified within the current thesis would likely be underpowered to conduct a GWAS, it is important that future research focus on this migraine subtype when searching for potential shared susceptibility genes for the migraine-BD phenotype.

Whilst there have been two previously published GWAS using the bipolar disorder (BD)-migraine combined phenotype (Oedegaard et al., 2010a; Jacobsen et al., 2015), neither employed the gold-standard criteria for the diagnosis for migraine established by the International Headache Society (Headache Classification Subcommittee of the International Headache Society, 2004). It is therefore possible that these studies were subject to phenotypic heterogeneity, and that the methods used to identify cases may have resulted in false positive migraine identification. Therefore, the associations observed in these studies, may not be replicated in samples employing these criteria. Introduction and adoption of IHS classification for migraine has helped to clarify our understanding of the scope of the public health problem posed by migraine. For example, a meta-analysis of 24 studies, only five of which employed IHS

classification criteria (ICHD-I; Headache Classification Committee of the International Headache Society, 1988), revealed that case definition accounted for the largest portion of variation in migraine prevalence among studies (36%) (Stewart et al., 1995). A second meta-analysis including 18 population-based studies, all of which had utilised IHS criteria, revealed that following standardisation of case definition, a substantial proportion of variation in prevalence was explained for by very few factors, such as age and geographic location of the study population (Scher et al., 1999). Therefore, in searching for genes predisposing individuals to migraine and BD, studies should endeavor to reduce the degree of genetic heterogeneity by reducing the clinical heterogeneity in study samples.

Identifying risk variants associated with the combined migraine-BD phenotype, and understanding the mechanisms through which they confer susceptibility, could improve our knowledge of the pathogenesis of both disorders, potentially leading to novel approaches to treat and prevent these disorders. Given the lack of statistical power of the current study, it is essential for future studies to ensure large samples, to increase the likelihood of identifying shared genetic variation. Moreover, given the proposed differences between the migraine subtypes, migraine with (MA) and without aura (MoA), it is important for future studies examining the genetic susceptibility to migraine and BD to differentiate between these subtypes. This is particularly important given the findings of the current thesis suggesting that the clinical expression of the migraine-BD phenotype may be particularly associated with the MA subtype (Chapter 4). Finally, it is possible that the shared genetic component between migraine and BD is explained by rare variation that is not detected through the GWAS approach. Therefore, future studies would benefit from adopting more powerful methods able to detect such variation, such as next generation sequencing.

Chapter 6

Epilepsy in bipolar disorder: impact on clinical features, course and outcome

6.1 Introduction

It is well recognized that mood disorders and epilepsy commonly co-occur. The psychiatric comorbidity of epilepsy has been well described, with mood disorders reported to occur at much greater rates than the background prevalence; estimates vary due to sampling strategies, between 20-50% (Kanner, 2003). However, to date, much of the neuropsychiatric literature has focused on the study of unipolar depression with investigation into bipolar disorder (BD) remaining limited.

In addition, there has been a distinct lack of studies exploring the systematic assessment of well-characterized epilepsy within a bipolar population. Rather, much of the research to date has focused on the assessment of multiple physical health disorders concurrently, with studies often grouping disorders together by organ system (i.e. neurologic disorders). Such studies have identified an increased prevalence of neurologic disorders within BD, compared to controls subjects (Carney and Jones, 2006; Evans-Lacko et al., 2009). However, whilst this has acted to increase our knowledge of medical burden, and broadly defined neurologic disorders within BD, it has not allowed for comprehensive investigation of epilepsy within BD.

Several converging lines of research suggest a relationship between bipolar disorder and epilepsy. Both conditions are substantially heritable, follow an episodic course (for which a kindling paradigm has been suggested), can be associated with a brain that has a superficially normal structure, and respond to anticonvulsant medications. Such shared features between the two disorders

are often cited as evidence of possible shared underlying pathophysiology and ignite interest in the mechanisms surrounding this relationship.

The current chapter looks to explore the comorbid relationship between BD and epilepsy. Firstly, the chapter will assess the rate of self-reported epilepsy within a large, well-characterised sample of UK participants with a DSM-IV (American Psychiatric Association, 2000) diagnosis of BD. The chapter will then describe the process for identifying a cohort of bipolar individuals with well-defined, expert-confirmed epilepsy. Using these two definitions of epilepsy (self-report and expert-confirmed), the chapter will then explore lifetime clinical characteristics of illness in individuals with bipolar disorder according to their lifetime history of epilepsy, in order to explore whether the co-occurrence of epilepsy within individuals with BD alters the clinical course of the bipolar illness.

6.2 Methods

6.2.1 Participants

Participants were drawn from the Bipolar Disorder Research Network (BDRN), a clinical and genetic study of individuals across the United Kingdom with mood disorders, described in detail within Chapter 2. Individuals with a lifetime DSM-IV diagnosis of bipolar I disorder (BDI), bipolar II disorder (BDII) or schizoaffective, bipolar type (SABP), were included in the current study.

6.2.2 Assessment of epilepsy

As described in Chapter 2 of this thesis, lifetime history of epilepsy and seizures within the BDRN bipolar cohort was identified through the use of a staged screening strategy.

6.2.2.1 Screening stage 1: Self-report questionnaire assessment of epilepsy/seizures

Participants were initially screened for a lifetime history of epilepsy/seizure disorder via a self-report questionnaire. The self-report questionnaire was a modified version of a brief screening instrument to identify individuals with epilepsy, designed by (Ottman et al., 2010) (**Appendix C**). The original instrument and revision employed by BDRN are both described in detail within Chapter 2. For the purposes of the current study, self-reported epilepsy/seizures was defined as anyone who screened positively (answering either 'yes' or 'possible') to the main seizure disorder/epilepsy question:

'Other than the seizure[s] you had because of a high fever (so other than febrile seizures), have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?'

The self-report epilepsy questionnaire was included as part of a larger questionnaire pack and sent to 5216 individuals who had originally taken part in BDRN, in June 2013. Of these, 2169 individuals completed and returned the questionnaire pack (response rate of 42%) and of these, 2082 (96%, 40% of the total sample) had completed the epilepsy questionnaire. Given that the self-report epilepsy questionnaire was disseminated to BDRN participants as part of

a larger questionnaire pack, it was possible that those participants with a history of epilepsy may have been more likely to complete the epilepsy questionnaire, potentially biasing the sample. To further explore this, I examined completion rates of the additional 6 questionnaires included in the questionnaire pack, by those who completed the epilepsy questionnaire. This is summarised in **Table 6.1**.

Table 6.1 Completion rates of additional questionnaires by participants completing the epilepsy questionnaire

Number of additional questionnaires completed by participants completing the epilepsy questionnaire	**N (%)**
All 6 additional questionnaires	1955 (93.9%)
5 additional questionnaires	111 (5.3%)
4 additional questionnaires	15 (0.7%)
3 additional questionnaires	1 (0.1%)
2 additional questionnaires	0 (0%)
1 additional questionnaire	0 (0%)
0 additional questionnaires	0 (0%)

Of the 2082 subjects who completed the epilepsy questionnaire: 1955 individuals (93.9%) completed the additional 6 questionnaires included within the pack; and a further 111 individuals (5.3%) completed 5 questionnaires. No individuals completed the epilepsy questionnaire only.

As mentioned above, 96% of the 2169 BDRN subjects who returned the questionnaire pack completed the epilepsy questionnaire. Examination of the 87 subjects (4%) who returned their questionnaire pack but did not complete the epilepsy questionnaire revealed that: 42 (48.3%%) completed all of the further 6 questionnaires included in the pack; 22 (25.3%) completed 5 other questionnaires; 11 (12.6%) completed 4 other questionnaires; 6 (7%) completed 3 other questionnaires; 5 (5.7%) completed 2 other questionnaires; and finally 1 (1.1%) completed only 1 other questionnaire included in the pack.

A total of 486 individuals were excluded from the study. The reasons for exclusion are summarised in **Table 6.2**. A number of individuals were excluded as they did not meet original BDRN study criteria (reasons 1-3 in **Table 6.2**) and so clinical data was not available for these individuals (described within Chapter 2). The current study aimed to examine epilepsy within individuals with bipolar

spectrum disorders, which included bipolar I disorder (BDI), bipolar II disorder (BDII), and schizoaffective, bipolar type (SABP). Therefore, individuals not meeting DSM-IV diagnostic criteria for these disorders were excluded from the study (n=169). Finally, a large number of individuals (n=270) could not be included in the current study as their original BDRN study data (interview, case-notes and questionnaires) were yet to be reviewed by the research team and therefore diagnostic and clinical ratings were not available for these individuals. Following these exclusions, 1596 participants remained in the current study.

Table 6.2 Reasons for exclusion from the study

Reason for exclusion	**N**
1. Relative in the study	6
2. Age of onset of bipolar disorder was after 65 years	1
3. Ethnicity other than Caucasian	40
4. Excluded for diagnosis	169
5. Interview awaiting rating	270
Total	486

6.2.2.2 Screening stage 2: Identifying individuals for telephone interview

Individuals who screened positively for epilepsy/seizures via the main screening question underwent a second stage of screening, in an attempt to separate true from false positives and identify individuals to be contacted for a more detailed assessment via a telephone interview. During this process, individuals had the remainder of their questionnaire responses (questions 3-5; **Appendix C**) reviewed by a Research Psychologist (Sarah Knott: SK) and Consultant Epileptologist (Professor Mike Kerr: MK), separately. Additionally, individuals who had answered 'don't know' to the main screening question also underwent this second stage of screening. This was to allow for any potential confusion or misinterpretation by the participants between the symptomatology of BD and epilepsy and was considered an important group to further explore.

During stage two of the screening process individuals were classified in to one of three groups based on their questionnaire responses: 'definite epilepsy', 'possible epilepsy' and 'no epilepsy'. An individual was categorised as having: 'definite epilepsy' if within the rest of the individual's questionnaire responses, there was clear evidence of well-described seizures; 'possible epilepsy' if the

responses were suggestive of a story in-keeping with epilepsy but further information was not available to confirm; and 'no epilepsy' if the further information provided in the questionnaire responses was not supportive of an epilepsy diagnosis. This stage of screening was considered necessary as time constraints meant that it was not possible to follow up all of those who had initially screened positive for self-reported epilepsy/seizures (i.e. all those who answered either 'yes' or 'possible' to the main screening question) with a more detailed assessment in the form of a telephone interview (screening stage 3). Caveats of this method are discussed at the end of this chapter.

6.2.2.3 Screening Stage 3: Telephone interview

Individuals identified as 'definite' or 'possible' epilepsy cases from the second stage of screening were selected for the follow-up telephone interview. In addition, a random sample of 20 individuals from those identified as 'no epilepsy' from the second stage of screening were also selected for telephone interview. A diagram to illustrate the staged screening process to identify lifetime history of epilepsy within the bipolar sample is shown in **Figure 6.1**. The telephone interview utilised within this study was an adaptation of a standardised, structured diagnostic inventory employed by the Epilepsy Phenome Genome Project (EPGP) and is described in detail within Chapter 2. All completed interviews were assessed together by MK and SK, in order to determine epilepsy status.

Those BDRN participants chosen for a follow-up telephone interview were sent an initial contact letter providing brief details about the research. The letter informed individuals that a BDRN researcher would contact them, by telephone, over the next few weeks to answer any questions they may have regarding the research and to discuss whether they would be interested in taking part. Individuals were also given the opportunity to refuse any further contact regarding this research, by contacting the study team by telephone or email.

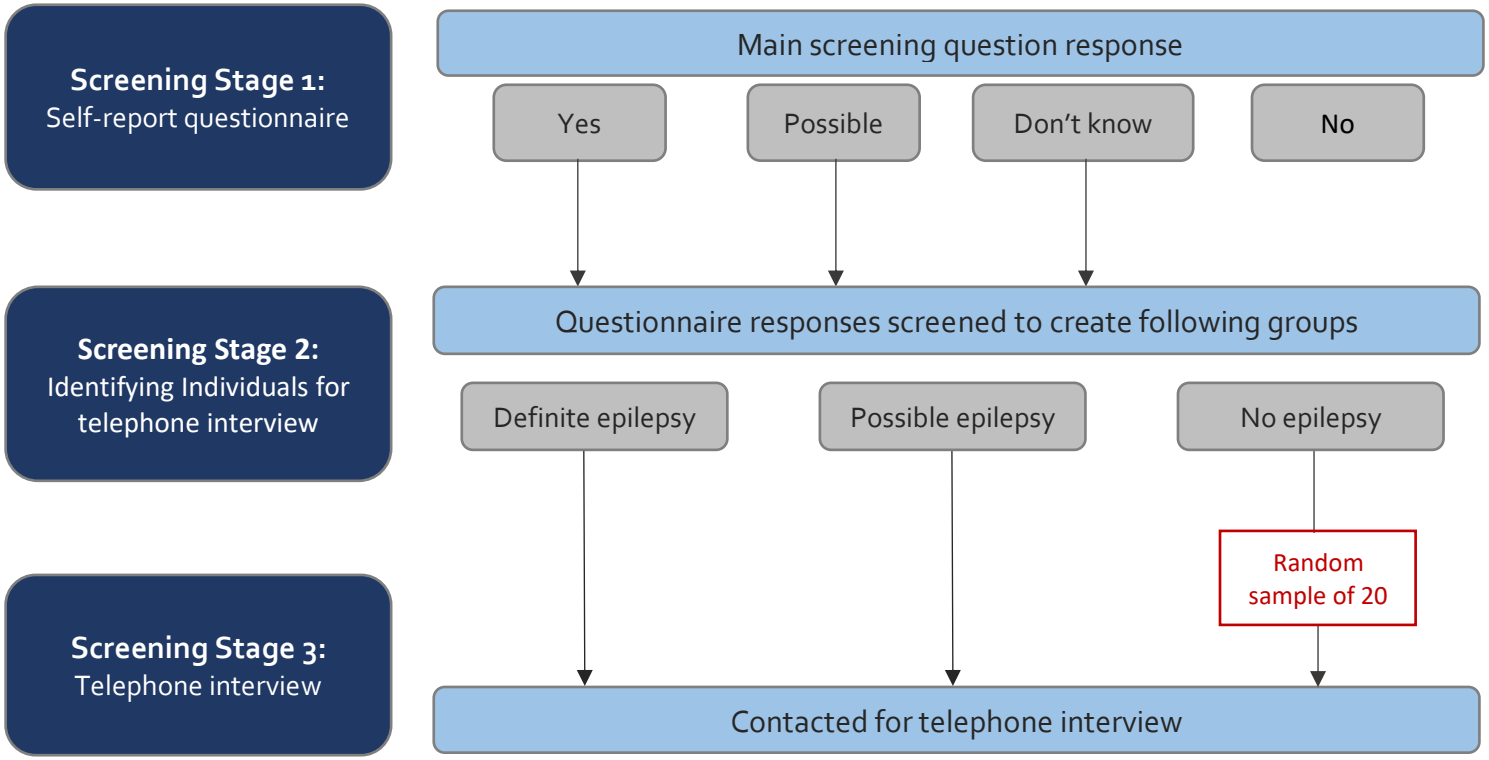


Figure 6.1 Three stage screening process for identifying lifetime history of epilepsy within the Bipolar Disorder Research Network (BDRN) sample

6.2.3 Statistical analysis

Data were analysed using the statistical package SPSS version 20. Normality of the data was assessed using the Kolmogorov-Smirnov test. The majority of the data analysed were not normally distributed and so non-parametric tests were employed. Statistical tests were considered significant at the $p<0.05$ level (two tailed) unless stated otherwise.

6.2.3.1 Comparison of clinical characteristics according to the presence of comorbid epilepsy - univariate analysis

Demographic and lifetime clinical characteristics of bipolar subjects were compared between: i) self-reported epilepsy vs. no epilepsy; and ii) expert-confirmed epilepsy vs. no epilepsy, in order to explore the relationship between epilepsy and the clinical features and course of the bipolar illness, using both a broad and narrow definition of epilepsy. Comparisons were made using Mann Whitney-U tests for continuous variables and categorical variables were assessed using 2x2 and 2x3 chi square tests. In instances where 20% or more of the cells in a chi-square table had an expected count of less than five, Fisher's exact tests (2x2 tables) and exact significance tests for Pearson's chi-square (2x3 tables and greater) were used.

6.2.3.2 Comparison of clinical characteristics according to the presence of comorbid epilepsy - multivariate analysis

To identify independent predictors of comorbid epilepsy within individuals with bipolar disorder, variables significant at the 5% level in univariate analyses were included as explanatory variables in a logistic regression model (using the enter method) with presence or absence of epilepsy as the dependent variable.

6.3 Results

6.3.1 Identifying lifetime history of epilepsy within a sample of individuals with bipolar disorder

6.3.1.1 Screening stage 1: Self-reported epilepsy/seizures

One-hundred and twenty-seven individuals (8%) screened positively (i.e. answered either 'yes' or 'possible') to the main screening question; '*Other than the seizure(s) you had because of a high fever, described above, have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?'* hence were identified as having self-reported epilepsy/seizure disorder. A breakdown of responses to the main screening question is shown in **Table 6.3**.

Table 6.3 Participant responses to the initial screening question on the self-report epilepsy questionnaire in the bipolar sample.

Response to the initial screening question "Have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy'	**N (%)**
Yes	82 (5.1%)
Possible	45 (2.8%)
No	1386 (87.0%)
Don't know	64 (4.0%)
Missing/did not respond	19 (1.1%)
Total	1596 (100.0%)

6.3.1.2 Screening stage 2: Identifying individuals for telephone interview

As described in the methods section, the 127 individuals who screened positively for self-reported epilepsy underwent a second stage of screening, whereby the remainder of their questionnaire responses were reviewed. In addition, those who answered 'don't know' (n=64) to this question also went through the second screening process in order to allow for any potential confusion in the symptomatology of bipolar disorder (BD) and epilepsy. Thus, in total 191 individuals had their questionnaire responses further reviewed within the second stage of screening. Stage two of the screening process was completed by both SK and MK, separately. A kappa statistic (Cohen, 1960) of 0.8 revealed an excellent level of agreement (Fleiss, 1981). In instances where there was disagreement between raters, the case was further discussed and a consensus was reached.

Following this screening process, individuals were classified into one of three diagnostic groups; 'definite epilepsy', 'possible epilepsy' and 'no epilepsy'. **Table 6.4** displays a summary of the diagnostic groups following stage two of screening, as well as a breakdown of how each diagnostic group responded to the main seizure question during the first stage of screening.

Table 6.4 Breakdown of responses to the main seizure question (screening stage 1) for each stage 2 diagnostic group

Diagnostic group following screening stage 2 (n)	**Response to the main screening question in screening stage 1**
Definite epilepsy (n=13)	Yes, n=13 (100%)
Possible epilepsy (n=66)	Yes, n=38 (57.6%) Possible, n=21 (32%) Unsure, n=7 (10.4%)
No epilepsy (n=112)	Yes, n=31 (27.7%) Possible, n=24 (21.4%) No, n=57 (50.9%)

6.3.1.3 Screening stage 3: Telephone interview

As described previously, all those identified as 'definite' (n=13) and 'possible' (n=66) epilepsy cases within the second stage of screening were selected for the third stage follow-up telephone interview in order to more definitely define

epilepsy within the cohort. A random sub-sample of 20 'no epilepsy' cases identified within stage two of screening were also selected to be contacted for the third stage telephone interview. Thus, in total, 99 individuals were selected to complete the detailed telephone interview within the third and final stage of the screening process.

I conducted all telephone interviews over an eight-month period, between April-November 2014. As described within the methods section of this chapter, individuals were sent an initial contact letter briefly detailing the research before first contact by telephone was made. This was the case for 83 individuals, however there was no contact number available for 15 individuals. For these cases an initial letter was sent requesting that interested individuals complete an attached contact form updating the study team of their contact details and return it to the study team in an enclosed stamped addressed envelope. If there was no response to this letter after a period of one month, a reminder letter was sent. Finally, one individual had an invalid address and contact number and so contact could not be made by either letter or telephone. Individuals were contacted a maximum of 5 times by telephone, on different days and at different times of the day if successful contact had not been made on the previous attempts.

The process from initial contact letter to completed interviews is summarised in **Figure 6.2**.

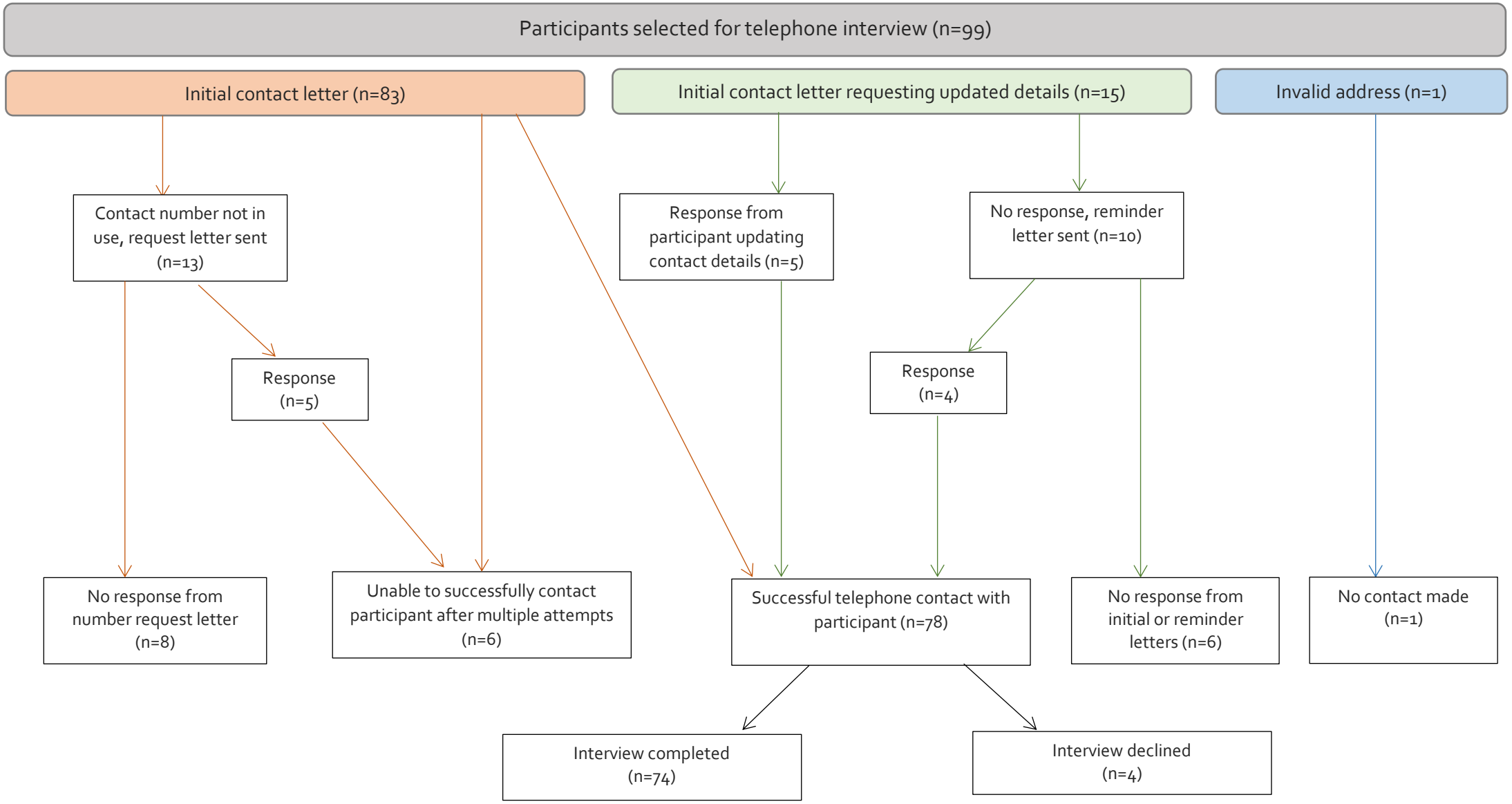


Figure 6.2 Screening stage 3 process from initial contact letter to completed telephone interview

Of the maximum 99 possible interviews, I successfully completed 74 (75%) within the eight-month period. A breakdown of the number of interviews completed within each of the screening stage 2 epilepsy diagnostic group is shown in **Table 6.5.**

Table 6.5 Number of interviews completed within stage 2 epilepsy diagnostic groups

Number of interviews conducted within….	**N (%)**
Definite epilepsy (n=13)	11 (84.6%)
Possible epilepsy (n=66)	48 (72.7%)
No epilepsy (n=20 randomly selected cases)	15 (75%)
Total (n=99)	74 (75%)

The largest proportion of completed interviews were conducted within the 'definite epilepsy' group (84.6%), with similar rates within both the 'possible' and 'no epilepsy' groups (72.7% and 75%, respectively). Only four individuals declined the interview, two from those classified as 'possible epilepsy' cases and two classified as 'no epilepsy'. I was unable to contact the remaining 21 individuals despite multiple attempts. There were two cases that could not be contacted for interview within the 'definite epilepsy' group. The first did not have a contact number available and did not respond to letters requesting updated contact details. The second could not be reached despite multiple attempts. Within the 'possible epilepsy' group, 16 individuals could not be reached following multiple attempts and two declined the interview. Of the 20 randomly selected 'no epilepsy' cases, three were unable to be contacted and two declined the telephone interview.

For those individuals who could not be contacted for telephone interview (n=25), I attempted to gather information to help establish the presence of epilepsy through the use of medical records. As part of the initial BDRN consent process, all participants had consented for their medical records to be requested and reviewed in strict confidence by members of the research group. However, as 88% of the 25 individuals who could not be successfully contacted for telephone interview were originally interviewed for BDRN three or more years (range 2-7 years) prior to the time telephone interviews were conducted in 2014, it was deemed inappropriate to request general practice medical records for

these individuals. Alternatively, for these individuals, existing psychiatric case notes (obtained at the time of original BDRN interview) were reviewed. Psychiatric case notes were available for 15 (60%) of the individuals that I was unable to contact for telephone interview. For this group, there was no mention of epilepsy or seizures for 11 individuals. For two individuals, seizures/fits were discussed; one individual was noted as having a seizure following a high temperature, and another was noted as having several fits in 2010, with inconclusive MRI and EEG results and an entry from a neurologist in 2010 documenting that they were optimistic there would be no further events. For a further two individuals, a 'possible epilepsy' diagnosis had been recorded within their medical records. The first of these had a brief mention of 'absences/concentration lapses', with no further information available, and the second had a reference to a possible diagnosis of temporal lobe epilepsy (TLE). This individual was described as having a seizure in 2001 following a drug overdose. There was no further mention of seizures until 2009 when TLE was raised as a possibility, however it was noted that this was complicated by heavy alcohol use. There was no further mention of seizures or investigations for TLE. When the above four cases were reviewed by myself and Professor Mike Kerr, we concluded that there was not enough information to robustly establish the presence of epilepsy, and so without a supplementary telephone interview, these cases could not be included in the 'expert-confirmed epilepsy' group.

As described in the methods section of this thesis (Chapter 2) the telephone interview employed within this study was an adaptation of a standardised, structured diagnostic inventory employed by the Epilepsy Phenome Genome Project (EPGP). Within the interview, participants provided a detailed description of each of their seizure 'types', a description of seizure triggers, information regarding any investigations and medication the participant had undertaken, and finally information regarding alcohol intake and any potential relationship with seizures. All interviews were reviewed by SK and MK, in order to determine a diagnosis of epilepsy.

Of the 74 completed telephone interviews, 19 cases were identified as having a lifetime diagnosis of epilepsy and 40 cases were not considered to have a lifetime diagnosis of epilepsy, following expert review. Ten cases were identified as being either borderland or complex cases and were blind reviewed by a

second Consultant Epileptologist, Dr Rhys Thomas (RT), and a consensus diagnosis was reached. Following this process, a further 7 cases were confirmed to have a lifetime diagnosis of epilepsy. General practice case notes were requested for all 26 expert-confirmed epilepsy cases. If no response was made to this request, a second letter was sent to the participant's GP surgery. In instances where there was no response to the requests for medical records, existing psychiatric case notes (obtained at the time of original BDRN interview) were reviewed. General practice medical records were obtained for 8 of 26 cases; 7 of which documented a history of seizures and/or epilepsy. For the remaining 18 cases, psychiatric case notes were reviewed and evidence suggestive of a history of seizures and/or epilepsy was noted for 10 cases. Thus, a history of seizures and/or epilepsy was corroborated by medical records for 17 of 26 cases (65%).

For the remaining 5 completed interviews, there was not enough information to confidently confirm or refute a diagnosis of epilepsy until further evidence had been sought. Medical case notes were available for all 5 cases; either following a request from the participant's GP (n=3) or from existing case notes requested following original BDRN interview (n=2). Subsequent re-review of these cases identified a further 3 cases as having a lifetime diagnosis of epilepsy. And so, within the sample of 1596 individuals with bipolar disorder, 29 were identified as having expert-confirmed epilepsy (1.8%), of which 20 (70%) cases were found to have evidence corroborating a history of seizures and/or epilepsy within their medical records. **Tables 6.6** summarises the breakdown of expert-confirmed epilepsy cases (n=29) within each diagnostic group identified within the second stage of screening.

Table 6.6 Breakdown of cases identified as having expert confirmed epilepsy within screening stage 2 diagnostic groups

Intermediate diagnosis following screening stage 2	**Number of expert-confirmed epilepsy cases identified following telephone interview (%)**
Definite epilepsy (of n=11 interviewed)	n=10 (91%)
Possible Epilepsy (of n=48 interviewed)	n=18 (37.5%)
No epilepsy (of n=15 interviewed)	n=1 (6.7%)

As can be seen from **Table 6.6,** one individual identified as having 'definite epilepsy' within the second stage of screening was not confirmed by an expert as having epilepsy following review of their telephone interview. Within their self-report questionnaire, this individual noted having convulsions in their early childhood for which they received medication, thus was considered to have a past history of epilepsy and was placed within the 'definite epilepsy' group. Following a description of these events at telephone interview, an epilepsy diagnosis was not confirmed, but rather the individual was believed to have had a history of febrile convulsions, for which they had received rectal diazepam administered as an emergency treatment.

Interestingly, an individual who was initially placed within the 'no epilepsy' group within the second stage of screening, was in fact deemed as having an expert-confirmed diagnosis of epilepsy following telephone interview. This individual screened positively for self-reported epilepsy within the screening questionnaire stating that they had experienced three seizures (aged 50) 'due to alcoholism'. This was considered not to be epilepsy but an alcohol-related seizure and so the individual was subsequently placed within the 'no epilepsy' group. Following description of these events, a clinical decision was made in agreement by two epilepsy experts (MK and RT) to reclassify the individual as having epilepsy that was 'possibly exacerbated by alcohol'. In this instance, there did not appear to be a compelling relationship between the use of alcohol and the seizures experienced. In fact it has been suggested that an individual is more likely to experience a seizure due to compensatory physiologic changes in the context of abrupt cessation of alcohol (rather than from the consumption of

alcohol itself), a condition that does not require a diagnosis of epilepsy (Engel, 2001).

A diagram to illustrate the number of individuals in each screening stage is shown in **Figure 6.3**.

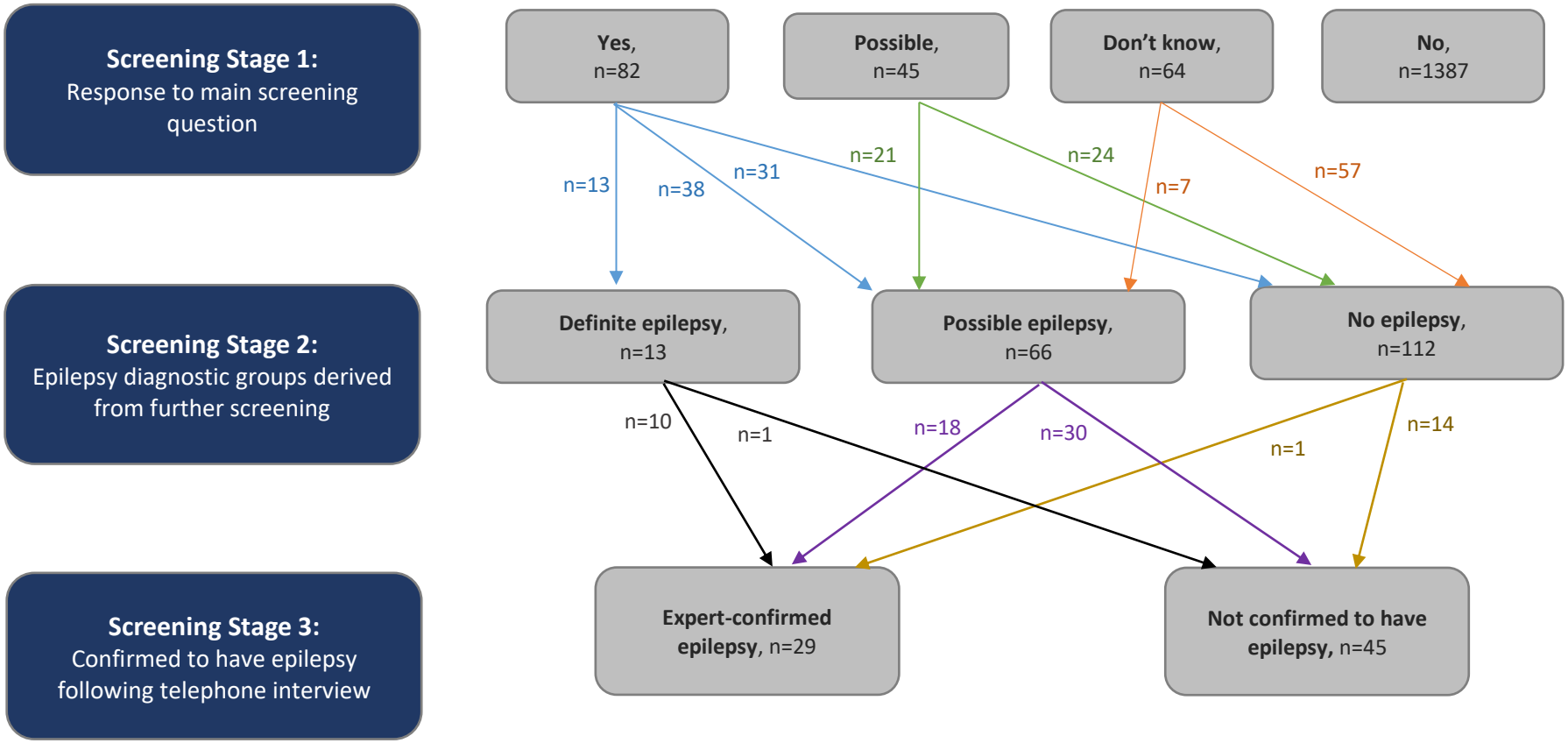


Figure 6.3 A summary of the number of individuals involved in each stage of screening for epilepsy within the bipolar sample

This section has described the process of identifying a lifetime history of epilepsy within the bipolar cohort. Firstly, the section presented the rate of individuals with self-reported epilepsy (n=127, 8%), before outlining the methods employed to more definitely define epilepsy within the cohort and to identify a group of individuals with 'expert-confirmed-epilepsy' (n=29, 1.8%). The following section of this chapter will utilise these two definitions of epilepsy to examine clinical differences in the course of illness for bipolar individuals with and without coexisting epilepsy.

6.3.2 Clinical characteristics according to presence of comorbid epilepsy – univariate analysis

6.3.2.1 Demographic Characteristics

A comparison of demographic characteristics between bipolar subjects with no lifetime history of epilepsy and i) self-reported epilepsy, and ii) expert-confirmed epilepsy is presented in **Table 6.7**. There were no significant differences between bipolar subjects with and without a lifetime history of epilepsy, using either definition. There was, however, a trend towards those with expert-confirmed epilepsy being older than bipolar subjects with no history of epilepsy, and this difference was approaching statistical significance at the $p<.05$ level.

Table 6.7 Demographic variables according to the presence of comorbid epilepsy

	No epilepsy (1) N=1386	**Self-reported epilepsy (2) N=127**	**Expert-confirmed epilepsy (3) N=29**	**P-value 1 vs 2**	**P-value 1 vs 3**
Age at interview Median (IQR) Range	49 (17) 20-84	47.50 (15) 22-69	53 (14) 31-68	.632	.058
Female, n (%)	974 (70.3%)	86 (68.3%)	22 (75.9%)	.635	.514
Marital history – ever married, n (%)	1146 (85.4%)	112 (89.6%)	26 (89.7%)	.198	.789 (F)
Post-secondary education, n (%)	969 (74.6%)	78 (67.8)	19 (70.4%)	.112	.618
Systematic recruitment, n (%)	360 (26.8%)	35 (28.1%)	6 (20.7%)	.770	.463
Family history of affective disorders, n (%)	991 (86.2%)	92 (83.6%)	19 (79.2%)	.464	.365 (F)
IQR= inter quartile range; F=Fishers exact test.					

6.3.2.2 Bipolar Disorder Clinical Characteristics

A comparison of lifetime bipolar clinical characteristics between individuals with and without epilepsy (self-report and expert-confirmed) is displayed in **Table 6.8**. Examination of illness characteristics revealed that when compared to bipolar subjects with no history of epilepsy, those with self-reported epilepsy were significantly more likely to have attempted suicide in their lifetime (64.2% vs. 47.4%, p=.000367). There was also a trend for bipolar subjects with self-reported epilepsy to experience more lifetime episodes of depression (10 vs. 8, p=.068), however the median number of lifetime manic episodes experienced was identical between groups. Bipolar subjects with and without self-reported epilepsy were also similar in terms of their: level of functioning in their lifetime worst depressive episode (indicated by their identical scores on the GAS

depression dimension); rate of rapid cycling of episodes (defined as four or more episodes in a one year period); and age of onset of their bipolar illness.

Focusing on analysis comparing the group of bipolar subjects with better defined, expert-confirmed epilepsy to those with no history of epilepsy, the epilepsy group was found to experience a significantly greater number of lifetime episodes of depression (13.55 vs. 8, p=.043). The expert-confirmed epilepsy group also scored significantly higher on the BADDS depression dimension, reflecting increased occurrence and severity of depressive episodes (83.5 vs. 69.5, p=.007), meeting criteria for 'incapacitating depression' (referring to severe major depression that includes presence of one or more of the following features: stupor; mutism; loss of contact with reality, including psychotic features).

A trend was also observed for those with expert-confirmed epilepsy to experience a higher rate of suicide attempt compared to those with no history of epilepsy (65.5% vs. 47.4%, p=.054) and this was found to be bordering on statistical significance. Interestingly, the rate of suicide attempt in those with expert-confirmed epilepsy is nearly identical to that observed within those with self-reported epilepsy, suggesting that there may be an issue of limited power to detect a statistically significant effect, given the small sample size of the group. There were also trends for the expert-confirmed epilepsy group to experience a better level of functioning in their lifetime worst manic episode, reflected in a higher GAS (Global Assessment of Functioning) mania subscale score (48 vs. 35, p=.058); and for their manic episodes to be less severe and frequent, evidenced by their lower score on the BADDS mania dimension (80.5 vs. 83, p=.066). Interestingly, these trends were not observed for the broader definition, self-report epilepsy group.

Table 6.8 Bipolar disorder illness variables according to the presence of comorbid epilepsy

	No epilepsy (1) N=1386	Self-reported epilepsy (2) N=127	Expert-confirmed epilepsy (3) N=29	P-value 1 vs 2	P-value 1 vs 3
DSM-IV diagnosis, n (%) BDI BDII SABP	940 (67.8%) 400 (28.9%) 46 (3.3%)	85 (67.7%) 36 (28.3%) 5 (3.9%)	16 (55.2%) 13 (44.8%) 0 (0%)	.928	.128
Age of BD onset Median (IQR) Range	21 (12) 5-64	20 (15) 9-51	19.50 (17) 9-63	.528	.834
No. episodes of mania Median (IQR) Range	5.1 (8) 1-300	5.1 (7.1) 1-100.1	6 (17.6) 1-30	.884	.825
No. episodes of depression Median (IQR) Range	8 (16) 0-150.1	10 (15.1) 0-100.1	13.55 (13.1) 20-40.1	.068	**.043**
Psychotic features, n (%)	733 (61.1%)	60 (64.4%)	14 (58.3%)	.471	.784
Rapid cycling, n (%)	291 (21.1%)	30 (23.8%)	6 (20.7%)	.475	.959
Suicide attempt, n (%)	631 (47.4%)	79 (64.2%)	19 (65.5%)	**.000367**	.054
History of psychiatric section, n (%)	498 (37.6%)	41 (33.9%)	7 (25%)	.417	.172
GAS Mania Median (IQR) Range	35 (30) 5-65	39.50 (30) 10-60	48 (27) 20-60	.652	.058
GAS Depression Median (IQR) Range	40 (15) 10-81	40 (14) 3-80	40 (13) 20-53	.155	.138
BADDS Mania Median (IQR) Range	83 (5) 20-100	83 (5.03) 40-99	80.5 (42.5) 40-90	.500	.066
BADDS Depression Median (IQR) Range	69.5 (22) 0-100	76 (22.6) 0-99	83.5 (14.1) 53-90	.194	**.007**
BADDS Psychosis					

Median (IQR) Range	22 (19) 1-100	21 (18.25) 10-99	21 (4.75) 20-75	.876	.498

*BDI= bipolar I disorder; BDII= bipolar II disorder; SABP= schizoaffective bipolar type; IQR= inter quartile range. GAS= Global Assessment Scale; BADDS= Bipolar Affective Disorder Dimensional rating Scale. Figures in **bold** indicate statistically significant differences between groups at the p<.05 level.*

6.3.2.3 Psychiatric Comorbidity

Table 6.9 shows a comparison of co-existing self-reported psychiatric disorders between bipolar subjects with and without epilepsy (self-report and expert-confirmed definitions). When compared to bipolar subjects with no history of epilepsy, those with self-reported epilepsy experienced a higher rate of anxiety spectrum disorders including; phobias (13.6% vs. 5.7%, .004), in particular agoraphobia (10.1% vs. 4.6%, p=.017) and panic disorder (29.6% vs. 16.1%, p=.001). The epilepsy group also experienced a greater rate of generalised anxiety disorder, however this failed to reach statistical significance (67.7% vs. 59.1%, p=.096). In addition, a significantly higher rate of alcohol (18.6% vs. 10.6%, p=.017) and other substance abuse (10.2% vs. 4%, p=.009) was observed within the self-reported epilepsy group.

Similar to those with self-reported epilepsy, when compared to bipolar subjects with no history of epilepsy, those with expert-confirmed epilepsy experienced higher rates of panic disorder (35% vs. 16.1%, p=.034) and other substance abuse (15% vs. 4%, p=.048). Although the associations of increased rates of phobias (particularly agoraphobia) and alcohol abuse are no longer observed, the reported rates of these conditions within the expert-confirmed group are very similar to those seen within the more broadly-defined, self-report group, suggesting that this is likely explained by the lack of statistical power given the small sample size of the expert-confirmed epilepsy group. Unlike the analysis focusing on self-reported epilepsy, there was a significantly higher rate of generalised anxiety disorder in those with expert-confirmed epilepsy when compared to bipolar subject with no history of epilepsy (81% vs. 59.1%, p=.044).

Table 6.9 Psychiatric comorbidity according to the presence of comorbid epilepsy

	No epilepsy (1) N=1386	Self-reported epilepsy (2) N=127	Expert-confirmed epilepsy (3) N=29	P-value 1 vs 2	P-value 1 vs 3
Affective and psychotic disorders					
Depression, n (%)	983 (88.2%)	84 (84%)	20 (95.2%)	.213	.499 (F)
Schizophrenia, n (%)	77 (6.9%)	3 (3.1%)	0 (0%)	.154	.392 (F)
Anxiety spectrum disorders					
Agoraphobia, n (%)	51 (4.6%)	10 (10.1%)	2 (9.5%)	**.017**	.259 (F)
Panic disorder, n (%)	175 (16.1%)	29 (29.6%)	7 (35%)	**.001**	**.034 (F)**
Phobias, n (%)	63 (5.7%)	13 (13.6%)	3 (14.3%)	**.004**	.120 (F)
Generalised anxiety disorder, n (%)	648 (59.1%)	67 (67.7%)	17 (81%)	.096	**.044**
Substance abuse disorders					
Alcohol abuse, n (%)	119 (10.6%)	18 (18.6%)	4 (20%)	**.017**	.260 (F)
Other substance abuse, n (%)	45 (4%)	10 (10.2%)	3 (15%)	**.009 (F)**	**.048 (F)**

*F=Fishers exact test. Figures in **bold** indicate variables significant at the p<.05 level.*

6.3.3 Clinical characteristics according to presence of comorbid epilepsy – multivariate analysis

6.3.3.1 Self-reported epilepsy:

To identify independent predictors of self-reported epilepsy within individuals with bipolar disorder (BD), variables significant at the 5% level in univariate analyses were included as explanatory variables in a logistic regression model (using the enter method) with absence or presence of epilepsy as the dependent variable. Analysis revealed a history of suicide attempt to be a significant predictor of self-reported epilepsy (OR: 1.790, 95% CI: 1.130-2.836, p=.013, Wald: 6.162, df=1).

The model explained 5.1% of the variance (Nagelkerke R^2=0.51) within the dependent variable (presence of epilepsy) and a Hosmer and Lemeshow goodness of fit test statistic of χ^2 (3) =.912, *p* =.823, suggested a good fit of the model to the data (greater than p=.05). However, as described earlier within this thesis, a limitation of this test statistic is its ability to inform us only whether a model fits the data or not, rather than indicating the extent of the fit. The current model correctly classified 91.9% of individuals as having epilepsy or not. As described within Chapter 4, logistic regression analysis is sensitive to high correlations between predictor variables, resulting in multicollinearity. To identify potential multicollinearity among predictor variables, a multiple linear regression was conducted with collinearity diagnostics requested. As no Tolerance values (indication of the proportion of variance in the predictor that cannot be accounted for by the other predictors) were less than .10, and no VIF values (*Variance inflation factor)* were greater than 10, this suggests that multicollinearity was not apparent among predictor variables.

6.3.3.2 Expert-confirmed epilepsy:

The small number of cases within the expert-confirmed epilepsy group (n=29) creates problems with logistic regression analysis given that the method uses the maximum likelihood estimation (ML) to derive its parameters and as such, relies on large-sample asymptotic normality. A useful rule of thumb suggests at least 10 cases per independent variable for the smaller classes of the dependent variable (Peduzzi et al., 1996) (in this instance those with expert-confirmed epilepsy, n=29). As a total of five variables were found to be significantly associated with expert-confirmed epilepsy within univariate analysis at the p<.05 level, this would not meet the minimum requirement of 10 cases per predictor variable for the smaller outcome group required for a logistic regression model. Thus, the analysis would be underpowered and parameter estimates would be unreliable. For this reason, a logistic regression model to identify independent predictors of expert-confirmed epilepsy within individuals with bipolar disorder was not computed.

6.3.3.3 Multivariate model summary

Logistic regression analysis revealed a history of suicide attempt to be significantly associated with self-reported epilepsy within individuals with bipolar disorder. The following section of this chapter looks to further explore the relationship between epilepsy and suicide attempt within BD.

6.3.4 Explaining the increased rates of suicide attempt in bipolar subjects with self-reported epilepsy

6.3.4.1 Lithium use

A potential explanation for the increased rate of suicide attempt observed within our bipolar subjects with comorbid epilepsy, compared to those without comorbid epilepsy, may be related to the possible reduced use of lithium within people with epilepsy. Lithium is an effective treatment for reducing the risk of suicide in those with mood disorders (Cipriani et al., 2013). However, international consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy, suggest that lithium should not be considered in those with BD and epilepsy, as it has been associated with increased seizures and neurotoxicity (Kerr et al., 2011). It may also be the case that individuals with BD and epilepsy are less likely to be prescribed lithium if they are already being treated with alternative mood stabilizing anti-epileptic medication. Therefore, it is of interest to assess whether the increased rate of suicide attempt in those with BD and epilepsy may be related to a lowered rate of lithium use within this group. Comparison of lifetime rates of lithium use (**Figure 6.4**), revealed that bipolar subjects with self-reported epilepsy were less likely than those without epilepsy to have been treated with lithium, however this was not found to be statistically significant (62.7% vs. 68.6%, p=.175). Interestingly, the association of lifetime history of suicide attempt with self-reported epilepsy within BD remained when controlling for the use of lithium treatment (OR: 2.024; 95% CI: 1.376-2.978, p=.000346). Conversely, rate of lithium use was found to be higher in the expert-

confirmed epilepsy group compared to bipolar subjects without epilepsy, however, again this was found to be non-significant (75.9% vs. 68.6%, p=.403).

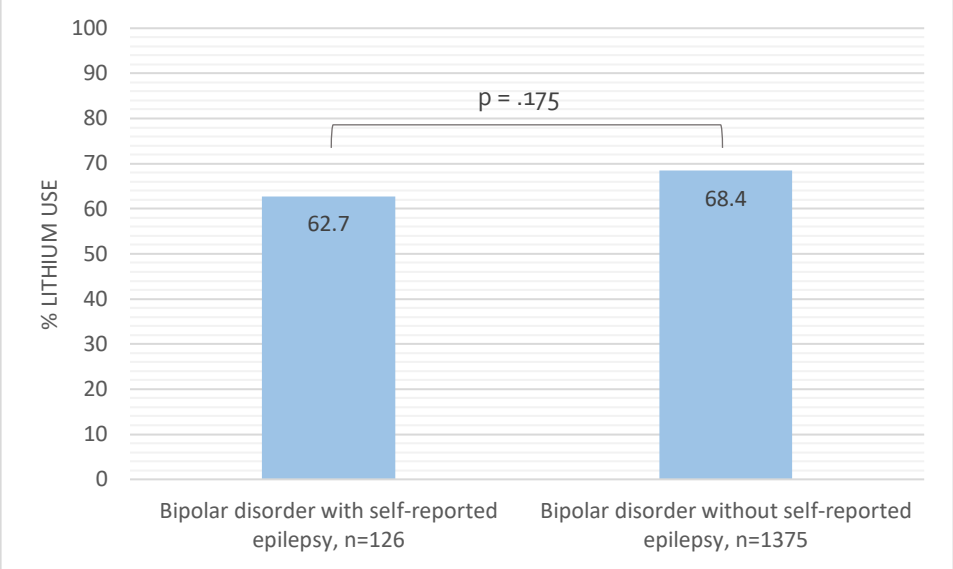


Figure 6.4 Rate of lithium use across bipolar subjects with and without self-reported epilepsy

6.3.4.2 Anti-depressant medication

The relationship between the use of anti-depressants and increased suicide risk is complex and often disputed. However, evidence from large meta-analyses of randomized controlled trials has indicated a trend towards a higher risk of suicidal behaviour for patients receiving anti-depressant medication than those receiving placebo (Khan et al., 2003; Whittington et al., 2004). Unipolar depression is often noted as the most frequent psychiatric disorder in people with epilepsy, with incidences ranging from 20-30% in community-based epilepsy samples, and 20-55% in specialist epilepsy clinics (Kanner and Balabanov, 2002; Blum et al., 2003; Robertson et al., 1994; Ottman et al., 2011). Moreover, within the above univariate analyses, bipolar subjects with comorbid epilepsy (both self-reported and expert-confirmed) experienced a greater number of lifetime episodes of depression. Such a finding suggests that bipolar subjects with comorbid epilepsy may experience an illness course predominated

by episodes of depression and therefore, may be more likely to be misdiagnosed with unipolar depression and treated with anti-depressant monotherapy, potentially contributing to their increased risk for suicidal behaviour. However, when a comparison between bipolar subjects with and without self-reported epilepsy was conducted within the current sample (**Figure 6.5**), the groups were found to be similar regarding their use of anti-depressant medication (90.7% vs. 92.4%, p=.509).

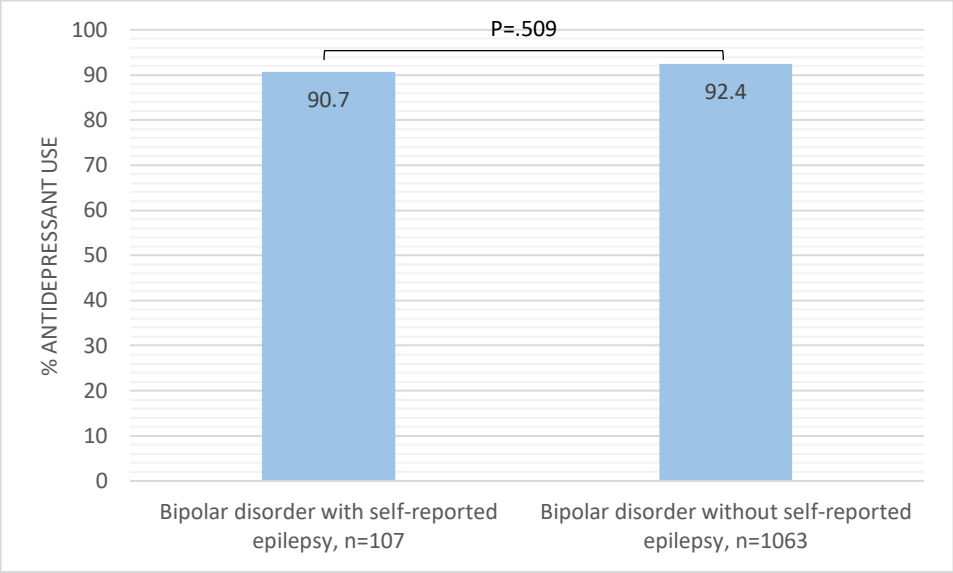


Figure 6.5 Rates of anti-depressant use across bipolar subjects with and without self-reported epilepsy

6.3.4.3 Anti-epileptic medication

It is also possible that the increased rate of suicide attempt observed in bipolar subjects with comorbid epilepsy may be related to the use of anti-epileptic medication. In 2008, the Food and Drug Administration (FDA) issued a controversial alert regarding a two-fold increased risk of suicidal thoughts and behaviour related to the use of anti-epileptic drugs (AEDs). This alert was based on a meta-analysis including data from 199 placebo-controlled trials of 11 anticonvulsant drugs for three indications, including epilepsy. Since its publication, the validity of the study and its methodology has been called into

question, with Hesdorffer and Kanner (2009) maintaining that; "*The relationship between suicidality and epilepsy is a complex, multifactorial problem, and AEDs probably have little impact.*" Within our cohort of bipolar subjects identified as having self-reported epilepsy, there was an increased rate of antiepileptic drug use in those with a history of suicide attempt against those without such history, however this was not found to be statistically significant (**Figure 6.6**) (46.3% vs. 34.2%, p=.229). Similarly, within those with expert-confirmed epilepsy, there was an increased rate of anti-epileptic drug use within those with a history of suicide attempt, however, again this was found to be non-significant (94.4% vs. 80%, p=.236). It is important to highlight, however, that these were within-group analyses of already modest sized groups, thus they are limited by their small sample size and as a result, statistical power.

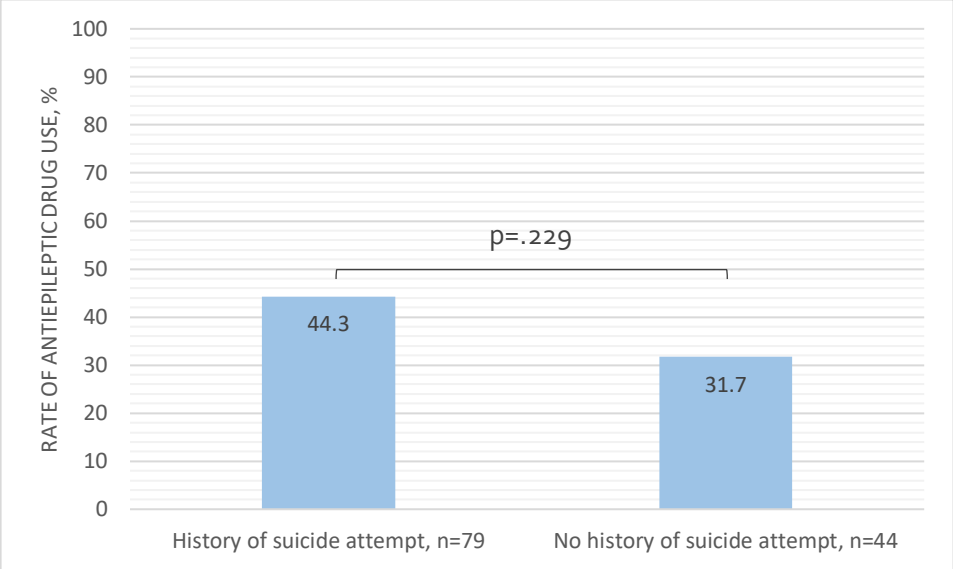


Figure 6.6 Rate of anti-epileptic drug use within bipolar subjects with self-reported epilepsy, with and without a history of suicide attempt

6.3.4.4 Summary

An association has been observed between a history of suicide attempt and self-reported epilepsy within individuals with bipolar disorder, and preliminary analysis suggests that this increased risk may not be explained through the

potential effects of medication. The following section will further explore this association by assessing whether comorbid epilepsy remains a risk factor for suicide attempt within bipolar disorder, in light of other coexisting disorders and known risk factors.

6.3.5 Suicide attempt in bipolar disorder: Epilepsy and other risk factors

It is known that the presence of secondary psychiatric disorders within bipolar disorder (BD) is associated with an increased risk of suicide attempt (Chen and Dilsaver, 1995; Frank et al., 2002; Goodwin and Hoven, 2002; Nemeroff, 2002). Earlier, this chapter identified increased rates of anxiety spectrum disorders as well as alcohol and substance abuse in both self-reported and expert-confirmed definitions of epilepsy and that these were significantly increased in the larger, self-reported epilepsy group. Therefore, in terms of clinical relevance, it is important to assess whether having epilepsy increases suicide risk within BD, over and above having another neuropsychiatric disorder.

Moreover, as discussed within the background section of this thesis, medical illness and psychiatric disorders are known to co-occur more often than would be expected by chance (Stenager and Stenager, 2000), both demonstrating an independent association with suicidal behaviour within clinical samples. Furthermore, data from community settings have repeatedly observed high rates of suicidal ideation among medical patients (Lin et al., 1989; Lish et al., 1996), particularly for chronic medical illness (Druss and Pincus, 2000). Given that epidemiologic studies confirm high rates of medical comorbidity within epilepsy (Seidenberg et al., 2009), it is important to assess the association of epilepsy with suicide in light of other coexisting chronic medical illness.

Table 6.10 displays the psychiatric and chronic medical comorbidity of subjects with BD, according to their history of suicide attempt. Bipolar subjects with a history of suicide attempt experienced a higher rate of: comorbid depression (92.3% vs. 84.5%, p=.000014); anxiety spectrum disorders (66% vs. 57.6%,

p=.002); alcohol abuse (15% vs. 8.6%, p=.001); migraine (27.4% vs. 22.1%, p=.030); asthma (24.8% vs. 19%, p=.014); and diabetes (6.2% vs. 2.6%, p=.002).

Table 6.10 Psychiatric and medical comorbidity within subjects with bipolar disorder according to their history of suicide attempt

	History of suicide attempt n=764	**No history of suicide attempt n=770**	**P-value**
Psychiatric comorbidity			
Depression, n (%)	591 (92.3%)	506 (84.5%)	**.000014**
Schizophrenia, n (%)	48 (7.6%)	31 (5.1%)	.082
Anxiety spectrum disorders, n (%)	426 (66%)	352 (57.6%)	**.002**
Alcohol abuse, n (%)	96 (15%)	52 (8.6%)	**.001**
Other substance abuse, n (%)	36 (5.6%)	21 (3.5%)	.067
Chronic medical comorbidity			
Epilepsy (self-reported measure), n (%)	79 (11.1%)	44 (5.9%)	**.000367**
Migraine, n (%)	175 (27.4%)	143 (22.1%)	**.030**
Asthma, n (%)	156 (24.8%)	113 (19%)	**.014**
Multiple sclerosis, n (%)	1 (0.2%)	1 (0.2%)	1.000 (F)
Arthritis, n (%)	105 (16.3%)	80 (13.1%)	.111
Diabetes, n (%)	40 (6.2%)	16 (2.6%)	**.002**
Heart disease, n (%)	23 (3.6%)	14 (2.3%)	.187
*Figures in **bold** indicate variables significant at the p<.05 level.*			

Within a logistic regression model, coexisting psychiatric and medical comorbid conditions found to differentiate bipolar subjects with and without a history of suicide at the p<.05 level (**Table 6.10**), were entered as predictor variables along with self-reported epilepsy, with presence of a history of suicide attempt as the dependent variable. The regression model revealed self-reported epilepsy to be an independent predictor of suicide attempt when controlling for other

significantly associated comorbid conditions. Multivariate analysis revealed that comorbid alcohol abuse, depression, and diabetes were also associated with a lifetime history of suicide attempt within BD (**Table 6.11**).

Table 6.11 Summary of significant comorbidities predicting suicide attempt within subjects with bipolar disorder

	Wald	Df	P-value	OR (95% CI)
Epilepsy (self-report)	9.521	1	.002	2.080 (1.306-3.311)
Alcohol abuse	5.294	1	.021	1.588 (1.071-2.354)
Depression	11.705	1	.001	2.034 (1.354-3.055)
Diabetes	6.712	1	.010	2.287 (1.223-4.276)
df=degrees of freedom; OR = odds ratio; 95% CI = 95% confidence interval				

It was considered important to further understand the relationship between epilepsy and suicide in bipolar patients, by considering other demographic, epilepsy-related and bipolar-related variables that may be relevant. **Table 6.12** shows a comparison of demographic, epilepsy-related and bipolar clinical characteristics between bipolar subjects with and without a history of suicide attempt.

Table 6.12 Demographic, epilepsy-related and bipolar illness variables within subjects with bipolar disorder according to their history of suicide attempt

	History of suicide attempt n=764	No history of suicide attempt n=770	P-value
Demographic variables			
Age Median (IQR) Range	 49 (16) 21-84	 49 (19) 20-86	.697
Female, n (%)	577 (75.5%)	509 (66.1%)	**.000050**
Married/lived as married, n (%)	649 (87%)	635 (85.2%)	.325
Epilepsy-related variables			
Age of epilepsy onset Median (IQR) Range	 18.5 (23) 1-67	 13 (29) 0-58	.853
Epilepsy illness duration Median (IQR) Range	 28 (20) 0-67	 27.5 (42) 3-71	1.000
Lifetime AED use (specifically for epilepsy/seizures), n (%)	44 (10.1%)	30 (6.8%)	.085
Bipolar illness variables			
Age of onset Median (IQR) Range	 19 (10) 7-63	 22 (13) 5-64	**.000001**
BD illness duration Median (IQR) Range	 27 (17) 1-59	 23 (20) 0-67	**.000001**
History of mixed episodes, n (%)	156 (37.3%)	122 (28.4%)	**.006**
No. episodes of depression Median (IQR) Range	 6.1 (11) 0-150.1	 10.1 (14.1) 0-100.1	**.000001**
*IQR= inter quartile range; BD = bipolar disorder; AED=anti-epileptic drugs. Figures in **bold** indicate variables significant at the p<.05 level.*			

Within a second logistic regression model; sex, age of bipolar onset, bipolar disorder illness duration, history of mixed episodes, and the lifetime number of episodes of depression were included as predictor variables, along with self-reported epilepsy and other significantly associated comorbid conditions (alcohol abuse, depression and diabetes), with history of suicide attempt as the

dependent variable. Multivariate analysis revealed self-reported epilepsy to be an independent predictor of suicide attempt after controlling for significantly associated demographic, bipolar illness variables and comorbid conditions. Analysis also revealed that bipolar subjects with a history of suicide attempt were more likely to have: comorbid depression; diabetes; a younger age of bipolar onset; longer bipolar illness duration; more lifetime episodes of depression; and a history of mixed episodes (**Table 6.13**).

Table 6.13 Summary of significant predictors of history of suicide attempt within subjects with bipolar disorder

	Wald	df	P-value	OR (95% CI)
Epilepsy (self-reported)	5.019	1	.025	2.149 (1.100-4.196)
Comorbid depression	6.186	1	.013	1.929 (1.149-3.237)
Comorbid diabetes	4.731	1	.030	2.171 (1.104-6.688)
Age of BD onset	4.769	1	.029	.978 (.958-.998)
BD illness duration	8.127	1	.004	1.022 (1.007-1.038)
Number of episodes of depression	9.632	1	.002	1.017 (1.006-1.027)
Presence of mixed episodes	4.364	1	.037	1.47 (1.023-2.047)

6.4 Discussion

6.4.1 Identifying lifetime history of epilepsy within bipolar disorder

Lifetime history of epilepsy and seizures within the bipolar sample was assessed using a staged screening strategy. The first stage involved a self-report questionnaire, where 127 individuals (8%) screened positively for a lifetime history of epilepsy, based on the following question; "*Have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?*" This is considerably higher than the 2% lifetime prevalence of epilepsy identified within (Ottman et al., 2011) US population-based study employing the same screening question. It is important to note, however, that the current study defined a positive screen for epilepsy as those answering either 'yes' or 'possible' to the above screening question (in line with Ottman et al., 2010), whilst Ottman et al. (2011) restricted the definition to a self-reported 'yes' to the same question. Using this restricted definition within the current study, we still see a more than two-fold increased rate of epilepsy within the sample of individuals with bipolar disorder compared to that reported by Ottman et al. (2011) (5.1 vs. 2%).

As previously outlined within the background section of this thesis, there exists a distinct lack of studies exploring rate of epilepsy within a bipolar population, with many instead focusing on the assessment of multiple physical health disorders concurrently, often grouping disorders together by organ system (i.e. neurological disorders). Moreira et al. (2011) is one of very few studies to separately assess epilepsy within their evaluation of general medical conditions in a Brazilian sample of outpatients with bipolar I disorder. Through the use of a self-report questionnaire, Moreira et al. (2011) revealed an epilepsy prevalence of 8.2%, consistent with findings reported in the current study. Moreover, the 8% rate of epilepsy reported within the current study is larger than the 3.4% identified by Forty et al. (2014), also based on a sample drawn from the Bipolar Disorder Research Network (BDRN). Within their study, Forty et al. (2014) examined rates of a number of medical illnesses, including epilepsy, by asking

subjects whether they had ever been told by a health professional that they have any of 20 listed health problems. The lowered rate of epilepsy observed by Forty et al. (2014), utilising subjects drawn from the same sample as that reported in the present thesis, may be explained by the requirement of health conditions to have been diagnosed by a health professional. It could be argued that the rate of epilepsy within the current study may be inflated or overestimated due to a potential response bias, with individuals with epilepsy being more likely to complete and return the self-report questionnaire. However, this is unlikely given that the epilepsy questionnaire was part of a larger pack and 96% of those who returned the pack had completed the epilepsy questionnaire. Moreover, validation of the original screening question within individuals with medical record-documented epilepsy, isolated unprovoked seizures and those who were seizure free on medical record review (Ottman et al., 2010), revealed a sensitivity of 76%, suggesting that the rate of self-reported epilepsy observed within the current study, may in fact be underestimated. However, as the screening question had not been validated within a psychiatric population, this can be speculated only.

The next stage was to identify a group of individuals with well-defined epilepsy for further analysis concerning clinical characteristics associated with BD and comorbid epilepsy. For this reason and because of time constraints, a decision was made not to follow up all those who screened positively for epilepsy within the first stage of screening with further assessment. Alternatively, I implemented a second stage of screening, whereby participants had the remainder of their questionnaire responses reviewed in an attempt to separate true from false positives and to identify those to be contacted for further assessment. A limitation of this method meant that the study is unable to comment on the prevalence of well-defined/expert-confirmed epilepsy within bipolar disorder, or to assess the sensitivity of the screening questionnaire within a bipolar sample. Throughout the study, an emphasis was placed on identifying a group of individuals for whom we were confident in their case definition of epilepsy, in order to undergo further clinical analysis and for comparison with the broader definition group of self-reported epilepsy.

In total, 191 subjects underwent the second stage of screening; 127 individuals who screened positively for epilepsy within stage 1 of screening, as well as 64 individuals who answered 'don't know' to the initial screening question. During this process, individuals were classified into one of three diagnostic groups; 'definite epilepsy' (n=13), 'possible epilepsy' (n=66), and 'no epilepsy' (n=112). Individuals classified as either 'definite' (n=13) or 'possible' (n=66) epilepsy within the second stage of screening were selected for further assessment in the form of a detailed telephone interview, along with a random sample of 20 individuals classified as 'no epilepsy'. Following telephone interview and review by an epilepsy expert, 29 individuals were confirmed to have a lifetime history of epilepsy (1.8% of total sample), of which 70%, were corroborated by a review of general practice/psychiatric case notes. As already expressed, the purpose of this stage was not to identify everybody within the bipolar sample that had a definite history of epilepsy, but rather to confidently identify a group of individuals with expert-confirmed epilepsy for further analysis. Nevertheless, it should be noted that this very conservative estimate already matches the 2% rate of more broadly-defined self-reported epilepsy from Ottman et al.'s (2011) survey conducted within the general population. Finally, it should be noted that whilst all interviews were interpreted by an epilepsy specialist and case notes were successfully sought for a large proportion of 'expert-confirmed' cases, these participants did not have their clinical history taken by a neurologist, nor did they undergo physical examination or further investigation, including EEG, MRI or telemetry, for example.

6.4.2 Clinical characteristics according to the presence of comorbid epilepsy

The current study is the first of its kind to assess bipolar illness characteristics associated with comorbid epilepsy. Specifically, the study looked to examine clinical differences in the course of the bipolar illness according to the presence or absence of epilepsy, for both broad 'self-report', and narrow 'expert-confirmed' definitions of epilepsy.

Multivariate analysis revealed an independent association of a history of suicide attempt with self-reported epilepsy within individuals with BD. It is important to emphasize that due to the exploratory nature of the analysis and modest size of the samples, variables were selected for entry into the logistic regression model predicting self-reported epilepsy, if they surpassed a significance threshold of $p<.05$ and many associations identified within univariate analysis would not stand up to corrections for multiple testing. It is therefore crucial to treat any significant findings with caution and also emphasizes the need for larger samples when examining the comorbid relationship between epilepsy and BD. However, it is also of note that of the variables found to be significantly associated with self-reported epilepsy within univariate analysis, a history of suicide attempt, as well as comorbid panic disorder would survive a more stringent significance threshold of $p<.01$ and even a very conservative Bonferroni correction ($.05/27=.002$).

Suicidal behaviour is a serious consequence of BD and it is known that between 25-50% of sufferers will attempt suicide at least once in their lifetime (Goodwin and Jamison, 1990; Hawton et al., 2005; Jamison, 2000; Valtonen et al., 2006). Findings of the current study suggest that these rates may be even higher in bipolar patients with comorbid epilepsy. Moreover, although multivariate analysis could not be conducted with expert-confirmed epilepsy as an outcome (due to the insufficient number of cases), a high rate of suicide attempt was observed within univariate analysis when the group was compared to those with no history of epilepsy (65.5% vs. 47.4%). Whilst this difference didn't quite reach statistical significance ($p=.054$), the rate of suicide attempt was nearly identical to that observed within those with self-reported epilepsy (64.2%), suggesting the lack of statistical significance is likely to result from the reduced sample size and reduced statistical power. In addition, when bipolar subjects with expert-confirmed epilepsy were compared to those with no history of epilepsy, they were found to experience a greater frequency and severity of lifetime episodes of depression. It has been reported that prolonged exposure to depressive episodes increases the risk of suicide attempt in bipolar patients (Valtonen et al., 2006). Thus, the finding of an increased number and severity of depressive

episodes within those with expert-confirmed epilepsy may help explain the increased risk of suicide seen within these subjects. Unfortunately, this can only be speculated as I was not able to explore this within multivariate analysis. Further research with a larger sample of individuals with well-characterised epilepsy is required to further elucidate this relationship.

Lithium is associated with reduced suicidality within individuals with mood disorders (Cipriani et al., 2013). However, given its previous association with increased seizures and neurotoxicity, the use of lithium is not advised within individuals with epilepsy. Exploratory work revealed no significant differences in the rates of lithium use in bipolar subjects with and without epilepsy. This suggests that the increased rate of suicide attempt observed within comorbid epilepsy may not be explained by the lowered rate of lithium use of this group. Moreover, although controversial, an increased risk of suicidal thoughts and behaviour has been associated with anti-epileptic medication (FDA et al., 2008). Within-group analysis of bipolar subjects with comorbid epilepsy (both self-report and expert-confirmed) revealed an increased rate of anti-epileptic drug use in those with a history of suicide attempt against those without such history, however these findings were not found to be statistically significant. However, it is important to keep in mind the small sample sizes involved in these analysis; increasing the chance of a Type II error.

Within univariate analysis, presence of epilepsy, using both a self-reported or expert-confirmed definition, did not appear to influence the age of bipolar illness onset, the lifetime number of manic episodes, nor the rate of rapid cycling of illness episodes. However, results did suggest differences in the rate of a number of coexisting psychiatric conditions. Both, self-report and expert-confirmed epilepsy groups reported significantly higher rates of panic disorder and substance abuse (not including alcohol abuse), when compared to bipolar subjects with no epilepsy. Moreover, higher rates of phobias (particularly agoraphobia) and alcohol abuse were observed in both epilepsy groups, but were only significantly increased in those with self-reported epilepsy. However, once again, the rates observed in those with expert-confirmed epilepsy were very similar to those reported by the broader self-report epilepsy group,

suggesting the lack of association is likely to result from the reduced sample size and reduced statistical power. The co-occurrence of anxiety disorders and substance abuse disorders is well-documented (Radat and Swendsen, 2005), and both are known to be highly comorbid with BD (Keller, 2006; Regier et al., 1990b). Furthermore, people with epilepsy have a higher prevalence of anxiety disorders than controls, in both community and specialist settings (Scicutella 2001; Tellez-Zenteno et al. 2007). Results suggest that the presence of epilepsy within BD may further increase the risk for comorbid anxiety spectrum disorders. For example, anxiety experienced by bipolar patients may be further exacerbated by individuals' psychological reactions to comorbid epilepsy that may stem from the unpredictable nature of the epileptic illness, restrictions on normal living, and stigmatization.

6.4.3 Suicide attempt in bipolar disorder: Epilepsy and other risk factors

Within the general population, people with epilepsy are at an increased risk for suicide, with an estimated lifetime prevalence of suicide and suicide attempts between 5-14% (Robertson, 1997). Moreover, rates have been reported as being 6-25 times higher in temporal lobe epilepsy compared with the general population and even higher in those who have undergone epilepsy surgery (Harris and Barraclough 1997). Psychiatric comorbidity within epilepsy is recognised as an important risk factor for suicide attempt (Nilsson et al., 2002). For example, Jones et al. (2003) observed that the highest risks for suicide attempt in people with epilepsy were associated with a lifetime history of major depressive disorder and lifetime manic episode (odds ratio of 5.9 and 12.6, respectively). Moreover, Christensen et al. (2007) found an almost 14-fold risk of suicide in people with epilepsy when psychiatric comorbidity (in particular mood and anxiety disorders) was taken in to account. However, it is important to note, that not all the increased risk of suicide associated with epilepsy could be explained by psychiatric history.

In addition, chronic medical conditions are known to often coexist in people with epilepsy (Boro and Haut, 2003; Gaitatzis et al., 2004), and a presence of general medical illness is associated with suicidality, with the presence of more than one illness conferring a particularly high risk (Druss and Pincus, 2000). Importantly, Druss and Pincus (2000) found that the relationship between medical illness and suicidality persisted even after adjustment for factors such as depression and heavy alcohol use. Within the current study, although a number of coexisting psychiatric and medical disorders were associated with suicide attempt within the bipolar sample, the relationship between epilepsy and suicide attempt persisted, after adjusting for these factors, suggesting that it is not fully mediated by these disorders. Moreover, within a multivariate model, having epilepsy was associated with a 2.08 times increase in the odds of suicide attempt, which was greater than for having comorbid depression or alcohol abuse disorder (2.03 and 1.58, respectively). Interestingly, among associated comorbidities, having diabetes showed the greatest increase in odds for suicide attempt within bipolar disorder (2.29). While diabetes has previously been associated with suicidality in youth (Goldston et al., 1997, 1994; Hayes, 1993), studies within an adult population have not shown a direct link (Goodwin et al., 2003; Kyvik et al., 1994).

When bipolar illness variables were compared between bipolar subjects with and without history of suicide attempt, as expected, a younger age of bipolar onset, longer illness duration, greater number of episodes of depression, and history of mixed episodes were all significantly associated with suicide attempt. Age of onset of epilepsy, duration of epileptic illness, and lifetime use of antiepileptic medication for epilepsy/seizures were also compared across the whole bipolar sample, however did not differ according to the presence of suicide attempt. In contrast, within an inpatient setting, Nilsson et al. (2002) identified a strong association between risk of suicide and onset of epilepsy at an early age (particularly during adolescence). Nilsson and colleagues (2002) did not find associations with risk of suicide for severity of epilepsy, as expressed by seizure frequency and anti-epileptic drug polytherapy, or with the localization or lateralization of epileptogenic focus. Unfortunately, the above epilepsy-

characteristics were not measured by the self-report questionnaire in the current study and so cannot be commented on here.

Multivariate analysis revealed an independent association of epilepsy with suicide attempt even when controlling for significantly associated bipolar-related variables and comorbid conditions (identified in earlier analysis and described above) (OR: 2.149, 95% CI: 1.100-4.196, p=.025). Analysis also revealed that having comorbid epilepsy was associated with a greater increase in the odds ratio for suicide attempt, than for the number of episodes of depression, history of mixed episodes, bipolar illness duration and comorbid depression.

The overall aim of the current study was to examine the relationship between epilepsy and BD and to present findings from the first systematic study of epilepsy within BD. Strengths of this study include its large, well-characterised sample of individuals with bipolar disorder and the staged screening process for the identification of epilepsy cases, including evaluation by an epilepsy expert and medical case note review. Moreover, to the best of my knowledge, this study is the first of its kind to examine clinical characteristics associated with comorbid epilepsy within BD. Nonetheless, a number of limitations need to be considered, in addition to those already mentioned above.

Firstly, self-reported epilepsy was defined by the response to a single question on a questionnaire used to screen for lifetime history of epilepsy within epidemiological studies (Ottman et al., 2010). Validation of the single screening question within the general population revealed a sensitivity of 76% for epilepsy. Within the validation study, sensitivity increased through the use of a broader positive screen definition of epilepsy, such that when all questions in the screening instrument were included, sensitivity rose to 96%. However, it is important to emphasize that the optimal choice for screening depends on both available resources and objectives of the study. If the purpose was to examine prevalence, maximum sensitivity would need to be ensured to avoid underestimation. However, consequently, a large number of false positives would need to be evaluated at further stages of screening. As the purpose of this

study was to identify individuals with epilepsy within BD for further analysis (as per Ottman et al., 2011), it was decided that the use of the main screening question alone would be appropriate. It is also worth reiterating that as not all of those identified as having comorbid epilepsy from the first stage of screening were followed up with a detailed telephone interview, the study is unable to comment on the rate of well-defined, expert-confirmed epilepsy within BD. In addition, due to exploratory nature of the analysis and the modest size of both the self-report and expert-confirmed epilepsy groups, corrections were not routinely made for multiple testing. Therefore, any significant findings must be treated with caution. In similar vein, due to the insufficient number of cases within the expert-confirmed epilepsy group, I was unable to conduct multivariate analysis to assess clinical characteristics associated with a narrower definition of epilepsy. However, reassuringly, the same direction of effects was observed for the majority of variables within univariate analysis for those with expert-confirmed epilepsy as the self-report group, when compared to bipolar subjects with no history of epilepsy.

In summary, the current study identified high rates of lifetime history of epilepsy within a sample of individuals of BD, and identified differences in the clinical characteristics of BD according to the presence or absence of epilepsy, including history of suicide attempt and coexisting psychiatric disorders. The study also revealed an independent association of suicide with self-reported epilepsy that did not appear to be explained by medication effects; however more work is needed within larger samples to fully explore these effects. Finally, the study revealed comorbid epilepsy to be an independent risk factor for suicide attempt within individuals with BD, after controlling for other associated risk factors, such as number of episodes of depression, bipolar illness duration and coexisting medical and psychiatric illness.

The results of this study highlight the importance of recognising and identifying comorbid epilepsy within individuals with BD, given the association with important illness outcomes, including increased suicidality. Further research exploring detailed characteristics of epilepsy within bipolar disorder, in terms of

determining the type of epilepsy, and its epileptogenic features are required to further unravel their complex comorbid relationship. Ultimately, it is crucial for clinicians to recognize the benefit of improved collaboration between the practice of neurology and psychiatry as a means of improving the evaluation and management of comorbid epilepsy and mood disorders. Equally, recognition of epilepsy within BD and further understanding of their comorbid relationship may reveal an attractive opportunity for subcategorising for future genetic studies, potentially identifying common pathophysiological mechanisms.

Chapter 7

General Discussion

The overall aim of this thesis was to examine the relationship between bipolar disorder (BD) and the neurological conditions of migraine, and epilepsy. This final chapter will summarise the findings from the four results chapters and discuss potential implications of the findings. Next, strengths and limitations of the thesis will be discussed, followed by suggestions for future work and final conclusions.

7.1 Summary of findings

7.1.1 Bipolar disorder and migraine

Evidence from clinical (Fasmer, 2001; Mahmood et al., 1999) and population-based (McIntyre et al. 2006b) studies suggest that migraine is frequently comorbid with bipolar disorder (BD). In addition, it has been reported that individuals with bipolar II disorder (BDII) may be disproportionately affected by migraine (Fornaro and Stubbs, 2015). Given the caveats of many existing studies regarding: small sample sizes; lack of standardised criteria for migraine; unrepresentative clinical samples; and inconsistency across studies in their definition of bipolar subtypes (in particular BDII), Chapter 3 of this thesis looked to examine the relationship between BD and migraine in a large, well-defined UK sample of individuals with a diagnosis of BD (Bipolar Disorder Research Network; BDRN).

The first aim of this chapter was to explore the rate of migraine (as defined by standardised International Headache Society criteria) within BD and to assess this rate across the bipolar diagnostic subtypes; bipolar I disorder (BDI), bipolar II disorder (BDII) and schizoaffective, bipolar type (SABP). Chapter 3 identified

a rate of migraine within BD of 19.4%. This is higher than the 12.8% rate of migraine reported by Breslau et al. (1991) using a similar questionnaire-based method for identifying migraine within the general population. Consistent with previous studies (Fasmer, 2001; Ortiz et al., 2010), Chapter 3 also found a significantly higher prevalence of migraine among subjects with BDII compared to those with BDI (25% vs. 16.9%, respectively). Findings from the first results chapter also extend previous literature by showing that individuals with BD also experience high rates of probable migraine (21.3%), which is defined by the International Headache Society (IHS) as a headache fulfilling all but one criterion for migraine with or without aura (Headache Classification Subcommittee of the International Headache Society 2004). If Chapter 3 was to incorporate a broader definition of migraine; including both strict and probable migraine, the observed rate of migraine within BD would increase to 40.7%. This is larger than the combined lifetime prevalence of probable and strictly-defined migraine (29.2%) within the general population reported by Lantéri-Minet et al. (2005) within their French population-based survey.

The category of 'probable migraine' was introduced within the second edition of the IHS criteria (ICHD-II; Headache Classification Subcommittee of the International Headache Society, 2004), replacing the previously termed 'migraneous disorder' of the first IHS criteria (ICHD; Headache Classification Committee of the International Headache Society, 1988). This was largely due to criticism from clinicians who believed such patients should be considered as genuine migraine sufferers. In addition, it appeared that a large proportion of likely migraine patients were falling into this category. For example, Rains et al. (2001) reported that of patients presenting to an outpatient headache clinic, 36% were given a diagnosis of 'migrainous disorder'. Moreover, Michel et al. (1993) revealed that whilst the IHS criteria for migraine had excellent specificity, sensitivity was low (<50%), suggesting that that the diagnostic criteria for migraine may perhaps be too restrictive. Therefore, in light of such criticism, the second edition of the International Classification of Headache Disorders (ICHD-II; Headache Classification Subcommittee of the International Headache Society 2004) acknowledged this category of headache sufferers as being an

integral part of migraine, introducing the new subtype of 'probable migraine'. The finding from the current thesis revealing that a large proportion (64.4%) of those identified as having probable migraine were reclassified as meeting criteria for strict migraine, following telephone interview, adds further support to the use of a broader or more inclusive definition of migraine that includes probable migraine cases. Research has revealed similarities between probable and strictly-defined migraine in terms of their epidemiologic features, associated disability, impact on health-related quality of life, and treatment profiles (Patel et al., 2004; Silberstein et al., 2007), further supporting the proposal that probable and strict migraine may be two phenotypic forms of the same entity. However, a population-based study conducted in the US has shown that probable migraine is dramatically underdiagnosed and undertreated. For example, among 1262 participants in a health plan identified as having probable migraine, only 2.7% had received a prescription for an acute migraine specific drug (Bigal et al., 2006). This suggests that improvements in the clinical recognition of probable migraine as an important migraine subtype are required, and that research studies (both within the general population and within BD) focusing solely on strictly-defined migraine may be underestimating both the prevalence and burden of migraine.

Previous research has noted that the psychiatric comorbidity of migraine is dependent on migraine subtype, with migraine with aura (MA) suggested to have a stronger association with psychiatric disorders than migraine without aura (MoA) (Breslau et al. 2000; Oedegaard et al. 2005a; Samaan et al. 2009). Therefore, the second aim of this chapter was to explore the association between the migraine subtypes; migraine with aura (MA) and migraine without aura (MoA), and BD. In this chapter, just over half of bipolar individuals with migraine were identified as having MA compared to MoA (153, 55.2% vs. 124, 44.8%), which is in contrast to the third of migraine patients reported to experience aura symptoms in the general population (Silberstein and Lipton, 1993). Moreover, rates of MA were higher than MoA in each of the bipolar diagnostic subtypes (BDI, BDII and SABP), and when controlling for sex and age, both MA and MoA, had a significant positive association with BDII, with the

strength of this association being stronger for the MA subtype. This is in line with the finding by Breslau et al. (1991) who revealed that rates of BDI and BDII were increased in individuals with MA compared to those with no migraine, a finding that was not observed for individuals with MoA.

The final aim of Chapter 3 was to assess concurrent validity of the differing methods used by BDRN for the assessment of migraine. When compared to diagnosis derived from the self-report questionnaire measure (the primary method used by BDRN to determine a diagnosis of migraine), the single-item checklist item asking individuals whether they had ever been told by a doctor that they had migraine, was found to have moderate sensitivity (56.6%) and high specificity (93.8%). This indicates that a 'doctor diagnosis' screen for migraine is likely to result in an underestimate of true migraine cases, in that whilst a positive screen is unlikely in a patient who does not truly have the disease, false negatives are highly likely in the event of a negative screen. A positive predictive value of 0.78 and negative predictive value to 0.85, indicate that the 'doctor diagnosis' screen is better at ruling out migraine than it is at ruling in migraine. This finding is consistent with a recent meta-analysis of the prevalence and moderators of migraine within BD (Fornaro and Stubbs, 2015) that found the prevalence of migraine was substantially higher in studies employing standardised IHS criteria, compared to those employing non-standardised criteria, such as self-report. In the current study, when compared to migraine status derived from the detailed telephone interview (based on criteria of the IHS), the self-report questionnaire was found to have high sensitivity (92.3%) and high specificity (93.3%). Measures of PPV (0.92) and NPV (0.93) indicated that the questionnaire was equally effective in ruling in migraine as it is ruling out migraine. The self-report questionnaire was found to be much less sensitive (75.0%) and specific (77.8%) for diagnosing probable migraine. This was explained by the large proportion of individuals with probable migraine (64.4%) that were found to meet full criteria for migraine diagnosis following telephone interview. Therefore, whilst questionnaire-based methods adhering to IHS criteria are sufficient for identifying those with strictly defined migraine,

identification of 'probable' cases may warrant further investigation to establish if these are indeed true migraine cases.

Identifying migraine as a common comorbid condition within BD is important to understand the additional burden faced by patients and adds support to the proposal that there may exist shared underlying pathophysiological mechanisms between the two disorders. It is possible that such pathophysiological homogeneity may reflect clinical homogeneity, and so Chapter 4 looked to establish whether the presence of migraine defined a clinical subtype of bipolar subjects who experience a distinct course of the bipolar illness. Findings from this chapter showed that when other significant differences were controlled for migraine comorbidity within BD was associated with a history of suicide attempt and anxiety disorder. Moreover, when the multivariate model was re-run entering only variables that survived correction for multiple testing, migraine comorbidity was also found to be associated with an increased number of episodes of depression. These findings build upon existing research suggesting that comorbid migraine may represent a clinically useful subgroup characterised by specific clinical features.

As reported above, previous research has noted that the psychiatric comorbidity of migraine is dependent on migraine subtype, with MA suggested to have a stronger relationship with BD than MoA (Breslau et al., 2000, 1991; Oedegaard et al., 2005a; Samaan et al., 2009). However, to date no studies exploring the relationship of migraine with the clinical features and course of BD have differentiated between these subtypes. Therefore, the second part of Chapter 4 looked to examine whether there exist differences in the lifetime bipolar clinical characteristics associated with MA and MoA. Findings from this chapter suggested that the comorbid expression of the relationship between BD and migraine was dependent on migraine subtype and that observed differences in the clinical presentation of BD associated with migraine comorbidity were largely associated the migraine with aura subtype. Multivariate analysis revealed that when compared to BD subjects with no history of migraine; those with migraine with aura (MA) were more likely to: be younger; be female; have a diagnosis of bipolar II disorder (BDII); and have a higher lifetime rate of

attempted suicide. The independent association of a BDII diagnosis with MA was unsurprising given the already mentioned finding that both migraine subtypes were found to be significantly associated with BDII and that this association was stronger for MA (Chapter 3). Conversely, no bipolar clinical characteristics were found to be associated with MoA when compared to bipolar subjects without migraine within a multivariate model. This suggests that the migraine-BD comorbidity may have more serious implications for those with migraine with aura and that the relationship between BD and migraine is perhaps explained by the association with the MA subtype.

A number of possible mechanisms may explain the increased comorbidity of migraine with mood disorder among bipolar patients. Firstly, the association of the two disorders may be a result of chance. For example, there may be spurious increased rates of migraine in BD due to Berkson's bias, whereby individuals reporting a diagnosis of one disorder are more likely to report a diagnosis of (or be diagnosed with) other disorders within clinical samples because of their increased contact with health professionals (Berkson, 1946). However, given that comorbidity has been demonstrated in population-based, and community studies, this is unlikely to be the complete explanation. Secondly, the relationship may be causal; with BD directly increasing the risk of migraine and/or vice versa. Finally, the association may be explained by potential shared environmental and/or biological risk factors that produce an underlying brain state that predisposes to both disorders. In the latter case, evidence has suggested that there may be shared genetic variation between migraine and BD (Oedegaard et al., 2010a; Oedegaard et al., 2010b; Jacobsen et al., 2015). Therefore, the aim of Chapter 5 was to examine genetic susceptibility to BD with comorbid migraine, through a genome-wide association study (GWAS). Whilst Chapter 5 did not identify genetic variation associated with the migraine-BD phenotype, this was not surprising, given the limited number of cases and controls involved, compared to what is generally required to detect common variation of small effect that is identified with the GWAS approach (Craddock et al., 2008).

7.1.2 Bipolar disorder and epilepsy

Mood disorders have long been considered frequent psychiatric comorbid conditions in people with epilepsy; however, to date much of the neuropsychiatric literature has focused on the study of unipolar depression, (Baker et al., 1996; Kanner and Balabanov, 2002; Blum et al., 2003; Eden and Toone, 1987; Robertson et al., 1994; Ottman et al., 2011; Hesdorffer et al., 2000). In addition, the majority of the research assessing the relationship between bipolar disorder (BD) and epilepsy has looked to establish the rate of BD and bipolar symptomatology in people with epilepsy, with findings suggesting higher rates within people with epilepsy compared to the general population (Ettinger et al., 2005), and with other chronic disorders (Ottman et al., 2011).

In contrast, there is a distinct lack of research exploring the occurrence of epilepsy within a bipolar population. However, there is some evidence to suggest that there may be an increased prevalence of epilepsy within BD subjects compared to that observed within the general population (Moreira et al., 2011; Weber et al., 2011; Forty et al., 2014). Given that very few studies have explicitly assessed epilepsy within a bipolar sample, the final results chapter looked to assess whether epilepsy is overrepresented in BD, by identifying the rate of self-reported epilepsy within a large, well-characterised sample of UK participants with a diagnosis of BD. Using a single screening question developed by Ottman et al. (2010), 127 (8%) individuals were identified as having self-reported epilepsy in the current study. This is higher than the 2% lifetime prevalence of epilepsy identified within Ottman et al's. (2011) US population-based study employing the same screening question, and higher than the 1.2% lifetime prevalence of epilepsy in the adult population of England, employing a similar 'doctor diagnosis' self-report definition of epilepsy (Rai et al., 2012). The rate of self-reported epilepsy described in Chapter 6 was consistent with Moreira et al. (2011) who reported an 8.2% prevalence of self-reported epilepsy in their Brazilian sample of outpatients with bipolar I disorder. Findings therefore indicate that epilepsy may be overrepresented in BD and may reflect a common comorbid condition of the bipolar illness that requires further exploration.

Next, Chapter 6 aimed to identify a group of bipolar individuals with well-defined, 'expert-confirmed' epilepsy from those who initially screened positive for epilepsy, for further analysis. This process identified 29 individuals as having a lifetime history of epilepsy, confirmed by a consultant epileptologist, of which 70% were corroborated by a review of general practice/psychiatric case notes. Using these two definitions of epilepsy (self-report and expert-confirmed), Chapter 6 then looked to explore the impact of epilepsy on the clinical course of the bipolar illness, to assess, whether comorbid epilepsy constituted a distinct subgroup of BD characterised by specific clinical features.

This was the first study of its kind to assess bipolar illness characteristics associated with comorbid epilepsy. Univariate analysis revealed self-reported epilepsy to be associated with: a higher rate of suicide attempt; and higher rates of additional psychiatric comorbidity including; agoraphobia, phobias, panic disorder, and alcohol and other substance abuse. When compared to bipolar subjects with no history of epilepsy, expert-confirmed epilepsy was associated with: more frequent and severe episodes of depression; and increased rates of panic disorder, generalised anxiety disorder and substance abuse. Moreover, there were trends for those with expert-confirmed epilepsy to: experience higher rates of suicide attempt; have better functioning in their worst episode of mania; and experience less frequent and severe manic episodes. Whilst a multivariate model could not be computed for the presence of expert-confirmed epilepsy due to the limited number of individuals within this group, multivariate analysis revealed an independent association of a history of suicide attempt with self-reported epilepsy within individuals with BD. Moreover, when bipolar subjects were compared on characteristics according to their lifetime history of suicide attempt, analysis revealed self-reported epilepsy to be an independent predictor of suicide attempt even after controlling for other significantly associated risk factors, including; bipolar-related illness characteristics, such as number of episodes of depression, history of mixed episodes, and bipolar illness duration; as well as coexisting psychiatric and chronic medical and illness. This finding is in line with reports in the general population suggesting that people with epilepsy are at an increased risk for suicide (Christensen et al., 2007;

Pompili et al., 2005; Robertson, 1997). Whilst psychiatric comorbidity (mood disorders in particular) within epilepsy is recognised as an important risk factor for suicide attempt (Nilsson et al., 2002), not all of the increased risk of suicide associated with epilepsy is explained by psychiatric history (Christensen et al., 2007).

Overall, the results of this thesis suggest that both migraine and epilepsy may disproportionately affect individuals with BD, and that when present they have the potential to modify or complicate the course of illness within BD. Individuals with bipolar II disorder (BPII) may be particularly likely to have comorbid migraine and this may be particularly relevant for the migraine with aura (MA) subtype. Comorbidity with both migraine, and epilepsy were associated with severe outcomes, characterised by increased psychiatric comorbidity and suicide attempt. In addition, expression of the migraine-BD comorbidity appears to be dependent on migraine subtype and may have more serious implications for those with migraine with aura compared to migraine without aura. Recognition and treatment of migraine and epilepsy within individuals with BD may therefore have a beneficial impact on the course of illness and outcome in people with BD. Further implications of these findings will be discussed in the next section (Section 7.2).

Migraine and epilepsy are often comorbid, and individuals with one of the disorders are more than twice as likely to have the other (Lipton et al., 1994; Ottman and Lipton, 1994). A review of 13 studies by Andermann and Andermann (1987) revealed that the prevalence of epilepsy in individuals with migraine ranged from 1-17%, with a median of 5.9%. In addition, the prevalence of migraine among individuals with epilepsy is estimated at 8-24% (Ottman and Lipton, 1994). Migraine and epilepsy are both chronic disorders characterised by recurrent neurologic attacks, and neither should be considered single clinical entities. Both disorders are thought to result from hyperexitability in the brain and there exist overlaps in the therapeutic agents used to treat each disorder (Bianchin et al., 2010). Moreover, there is also some evidence to suggest shared genetic effects on migraine and epilepsy (Bianchin et al., 2010; Deprez et al., 2007; Polvi et al., 2012; Winawer and Connors, 2013).

Whilst not an aim or central focus of the current thesis, it was of interest to consider whether migraine and epilepsy occurred at an increased rate with each other within BD. To explore this, I examined the number of bipolar subjects who reported having self-reported epilepsy and also met criteria for migraine according to the questionnaire measures. Of the 877 bipolar subjects who completed both the migraine and epilepsy questionnaires; n=175 (20%) had migraine, n=64 (7.3%) had epilepsy, and n=20 (2.2%) were found to have both migraine and epilepsy. If migraine and epilepsy occurred independently with BD and did not occur at an increased rate with each other, one would expect 1.46% to report both migraine and epilepsy (frequency[migraine] x frequency[epilepsy]=0.2x0.073=0.0146). Therefore, if migraine and epilepsy did not occur at an increased rate with each other, one would expect 12.8 bipolar subjects to have both disorders (1.46% of 877). The 20 individuals observed to have comorbid migraine, and epilepsy within the sample suggests an increased number to what would be expected. Moreover, a one-tailed chi square test would deem this increased rate to be statistically significant at the $p<.05$ level. However, this finding should be interpreted with caution and requires replication within larger samples.

7.2 Potential implications

The findings of this thesis suggest that migraine and epilepsy are common comorbid conditions of bipolar disorder (BD). Given that the presence of migraine, and epilepsy, were associated with a more severe course of illness, including increased suicidality, this highlights the need for effective screening and identification of these conditions within individuals with BD, so that they can be incorporated into individual risk assessment care plans. Ideally, screening for migraine and epilepsy should occur early on in the individual's psychiatric assessment as this may help clinicians to identify those at increased risk for important illness outcomes, such as suicidality and further psychiatric comorbidity. Whilst I am not suggesting that clinicians should or would not already assess for suicide risk as part of a formal risk assessment with the

patient, knowing the patient also suffers from migraine and/or epilepsy, should alert clinicians to those who are at especially increased risk for such adverse outcome and tailor management and treatment plans accordingly.

Specifically, screening for migraine may be particularly important in individuals with bipolar II disorder (BDII) since these individuals were shown to have significantly increased rates of migraine compared to those with bipolar I disorder (BDI). In addition, findings of this thesis indicate that it is important to differentiate between migraine subtypes, such that the presence of aura symptoms may alert the clinician to those who may be at increased risk for adverse outcome. Moreover, given the large proportion of 'probable migraine' cases described in this thesis, it may also be important to pay attention to cases that just miss the strict classification for full migraine. This may be particularly relevant given that probable migraine is known to be a frequent, undertreated and disabling condition with an epidemiologic profile similar to that of strict migraine (Silberstein et al., 2007). Finally, given that migraine was shown to precede BD illness impairment in 57% of cases, migraine may constitute a first-visit hallmark for some bipolar patients and warrant the screening of affective psychopathology.

The bipolar illness characteristics experienced by bipolar subjects with comorbid migraine and epilepsy suggest that these patients may benefit from a tailored treatment approach. Specifically, the increased rates of anxiety disorders experienced by these groups may benefit from targeted psychological therapy. Psychiatric comorbidity within BD can further complicate the bipolar illness and may influence the course of illness and lead to poorer outcomes and prognosis (Vieta et al., 2001) and in particular, comorbid anxiety itself has been associated with increased suicide risk (Simon et al., 2007).

Chapter 4 identified that presence of migraine within BD was associated with a greater number of episodes of depression. Moreover, a trend for an increased number of episodes of depression was observed in bipolar subjects with self-reported epilepsy compared to those with no history of epilepsy. Further support was provided from analysis of expert-confirmed epilepsy cases,

revealing significantly increased occurrence and severity of depressive episodes. Such findings suggest that BD patients with comorbid migraine or epilepsy may suffer more from the depressions of bipolarity. Such a finding has important clinical implications given the potential for an individual being inappropriately treated with anti-depressant monotherapy, increasing the risk of a pharmacologically-induced manic episode. Decisions concerning pharmacotherapy for an individual with BD should take into consideration comorbid conditions such as migraine and epilepsy, and where possible it would be advantageous to select such agents that act on both disorders. Once migraine and/or epilepsy has been identified within an individual with BD, it is essential for the clinician to firstly assess whether they are already being treated for the condition and to assess whether there exist any potential drug interactions between the agents used to treat these disorders. If we consider the long-lasting, chronic course of BD, and the impact of comorbidity on evaluation, diagnosis, illness course, and social and economic costs of psychiatric disorders (Merikangas and Kalaydjian, 2007), it is essential that the management of complex comorbid conditions constitutes an important and fundamental part of individualized treatment. Comorbidity within psychiatric disorders affects evaluation, diagnosis, illness course as well as social and economic costs of the disorder. Therefore, it is crucial for clinicians to recognize the benefit of improved collaboration between the practice of neurology and psychiatry as a means of improving the evaluation and management of individuals with BD, migraine, and epilepsy.

Aside from the potential clinical implications of recognizing migraine, and epilepsy within individuals with BD, the use of these disorders to define more clinically homogeneous patient populations may be useful for future aetiological investigations. For example, the differences observed regarding the clinical characteristics of the bipolar illness according to the presence of migraine, and epilepsy support the proposal that these comorbid conditions may represent a subtype of individuals with BD who are more biologically similar. Thus, a greater understanding of the pathophysiological mechanisms that underlie BD with migraine, and BD with epilepsy, and indeed BD with

migraine and epilepsy, may contribute to our understanding of the underlying aetiology of all three disorders, and have important implications for psychiatric nosology.

7.3 Strengths and limitations

Specific strengths and limitations relevant to the individual studies within this thesis are discussed within the appropriate chapters. The present section will discuss methodological strengths and limitations more generally.

One of the major strengths of this thesis is the large, clinically well-defined sample of subjects with bipolar disorder (BD) upon which the findings are based. All subjects were assessed using standardized and rigorous clinical assessment methods, which where possible were supported by psychiatric and general practice case notes. The rich clinical data available through Bipolar Disorder Research Network (BDRN) allowed for a thorough assessment of the relationship of migraine, and epilepsy with the clinical features and course of illness within BD. Moreover, the sample was recruited from throughout the UK using a variety of both systematic and non-systematic methods, thus relying on both volunteers and NHS services. Therefore, in relation to the assessment of comorbidity within BD, the sample is less likely to suffer from Berkson's bias whereby individuals reporting a diagnosis of one disorder are more likely to report a diagnosis of (or be diagnosed with) other disorders because of their more frequent contact with health professionals in the context of a clinical population (Berkson, 1946). The large sample recruited by BDRN over many years meant that the current thesis could extend previous small scale research evaluating the relationship between migraine and BD and permitted further detailed investigation of the migraine phenotype, by differentiating between the migraine subtypes, migraine with and without aura when exploring the association between migraine and the clinical features of BD. Moreover, the large sample involved in the current thesis also allowed for the exploratory

analysis of a small group of individuals with expert-confirmed epilepsy and their relationship with the clinical features and course of illness in BD.

However, the findings also need to be considered in the light of several limitations. Firstly, a limitation applicable to all studies reported throughout this thesis is the cross-sectional nature of the study methodology. Whilst such designs are useful to investigate associations between risk factors and an outcome of interest and are particularly suitable for estimating the prevalence of a behaviour or disease in a population, they do not allow determination of causality. Therefore, in order to gain a better understanding of the temporal relationship between BD and migraine, and BD and epilepsy, longitudinal prospective studies are required. Moreover, due to the cross-sectional study design, it is possible that a non-response bias exists, whereby individuals choosing to take part in the study differ on important variables from those who do not. Thus, individuals recruited into BDRN may not be representative of the bipolar population. In addition, completion of the self-report questionnaires to initially assess migraine and epilepsy within the BD sample may also be subject to non-response bias, such that those with the condition may have been more likely to complete the questionnaire. However, given that both of these questionnaires were part of a larger questionnaire pack, it is unlikely that individuals completed this questionnaire based on their affected status. This is further supported by an examination of questionnaire pack completion rates, which revealed that 96% of those who completed the migraine questionnaire, and 94% of those who completed the epilepsy questionnaire, also completed all other questionnaires included within the pack. Moreover, no individuals completed the migraine or epilepsy questionnaires only.

A second limitation of this thesis involves the retrospective assessment methods used. Whilst such methods permit evaluation of the lifetime course of the bipolar illness, as well as assessment of the lifetime history of migraine and epilepsy, once again, it is difficult to establish the temporal precedence of these comorbid conditions and BD. Moreover, retrospective studies are prone to recall bias and given that the mean age of BDRN subjects at interview is approximately

45 years and onset of BD typically occurs during late adolescence, such bias may be particularly relevant here. Recall bias may also have limited the subject's ability to clearly recall details regarding their headache, and seizure history, potentially leading to an under or overestimate of these disorders.

A third limitation of the current thesis concerns the overrepresentation of females within the bipolar sample (approximately 70%). Such gender bias is often observed in research participation, and given that a major research interest of BDRN is to examine the experience of affective illness in relation to childbirth, this may also help to explain the high proportion of females observed within this particular sample. Whilst rarely found to be significantly different, the incidence of epilepsy is reported to be higher among males than in females (Banerjee and Hauser, 2008), and so may have resulted in an underestimate of epilepsy within the current sample. In contrast, there is a known female preponderance of migraine, with a sex ratio for lifetime migraine being two to threefold greater among women (Low et al., 2007). A higher rate of migraine among women was observed in the current thesis, with 21.7% of women and 12.9% of men meeting criteria for migraine. It is therefore possible that the overrepresentation of females within the current thesis led to an overestimate of migraine. There was also a significant gender difference between bipolar subjects with and without a history of migraine (82.3% vs. 69%, respectively) however this was accounted for within multivariate analysis.

Fourthly, as all subjects were recruited as part of ongoing molecular genetic studies, they were required to be of UK/ Eire white ethnicity in order to reduce genetic heterogeneity between subjects. It is important to acknowledge the implications of such an inclusion criterion on the generalizability of findings, which may not extend to other ethnic groups.

Finally, a limitation relevant to all studies reported in this thesis is the lack of detailed information regarding psychiatric medication. Medication use will inevitably modify the bipolar illness and so it would have been useful to control for different treatment regimens between BD individuals with and without migraine (Chapter 4), and epilepsy (Chapter 6). Moreover, it has already been

discussed within this thesis that the pharmacological agents used to treat BD, migraine and epilepsy overlap. For example, antiepileptic medications are known to be effective mood stabilizers and are often used in the primary treatment of BD (Kaufman, 2011; Moreno et al., 2004). Similarly, some of the pharmacological agents used within BD (most notably valproate) are known to be successful in treating migraine (Silberstein, 1996). Therefore, it is possible that the use of these medications for psychiatric purposes may have acted to modify migraine symptomatology or seizure activity, potentially influencing the prevalence rates and presentation of these disorders within the bipolar sample.

7.4 Suggestions for future work

The findings of this thesis suggest that comorbid migraine and epilepsy may be used to delineate clinical subgroups among individuals with bipolar disorder (BD). Moreover, BD, migraine, and epilepsy share several characteristics, for example, all three conditions; follow an episodic course, are chronic disorders, are heritable, and respond to antiepileptic medication. These lines of evidence all point to a common underlying pathophysiology for which potential shared environmental and/or biological risk factors may produce an underlying brain state precipitating these conditions. However, further research is needed to unravel the complex relationship between BD and the neurological comorbidities of migraine and epilepsy in order to better understand and characterise their relationship, both clinically and aetiologically. Below I will summarise particular research areas that have been identified within this thesis as potential important avenues for future research.

In Chapter 3, I reported that 21.3% of individuals with BD met criteria for probable migraine, a figure that was actually found to exceed the proportion of individuals meeting full IHS criteria for migraine (19.4%). Given the overlap in their epidemiological and symptom profile (Patel et al., 2004), it is likely that probable migraine involves the same pathophysiological process as strictly-defined migraine. Currently, no studies have examined either the clinical or

aetiological relationship of probable migraine with BD. If the findings associated with comorbidity of strict migraine with BD were to be replicated with probable migraine, this would support the proposal of adopting a broader definition of migraine when examining the comorbid relationship between migraine and affective disorders, which would act to dramatically increase sample sizes of future studies. Moreover, if the findings were not found to replicate, this would help to identify important differences between probable and strictly-defined migraine, which may provide further insight into the biological underpinnings of these disorders.

Chapter 4 found that the comorbid expression of the relationship between BD and migraine was dependent on migraine subtype, with the observed differences in the clinical presentation of BD associated with migraine comorbidity being largely explained by the association with migraine with aura (MA). Moreover, when examining the association between migraine and bipolar diagnostic subtypes, Chapter 3 reported a significant association between migraine and bipolar II disorder and that this association was stronger for those with MA. An association between MA and psychiatric disorders has previously been shown (Breslau et al., 1991; Oedegaard et al., 2005a; Samaan et al., 2009), however this is the first study to differentiate between the migraine subtypes of migraine with (MA) and without aura (MoA) when investigating the impact of migraine on the clinical course of BD. Therefore, it is important to replicate these findings in additional large, well-characterised samples.

Differentiating between migraine subtypes may also be beneficial for future studies examining the genetic susceptibility to BD and migraine. There is much debate over whether MA and MoA form part of the same disease spectrum or whether they represent distinct subtypes (Ligthart et al., 2006; Nyholt et al., 2004; Russell et al., 2002, 1996). The finding that MA has a higher genetic component than MoA (Russell and Olesen, 1995) suggests potentially distinct aetiologies. Given findings of the current thesis demonstrating that the association with MA may be explaining the distinct symptom profile associated with migraine comorbidity in BD, this suggests it would be beneficial for future studies to examine MA and MoA separately when searching for potential shared

genetic variation between BD and migraine. In addition, the three studies to date that have looked to identify susceptibility regions for the migraine-BD phenotype have only used self-reported doctor diagnosis definitions of migraine (Oedegaard et al. 2010a; Oedegaard et al. 2010b; Jacobsen et al. 2015). It is therefore, essential for future studies adopt recognized, standardized criteria (such as that of the International Headache Society) in their assessment of migraine.

Moreover, Chapter 5 argued that a potential explanation for the current thesis not finding evidence of genetic variation associated with the migraine-BD phenotype may be due to the small number of cases and controls involved. Chapter 5 also argued that it was possible that susceptibility to the migraine-BD phenotype may be explained by rare variants which were unable to be detected by the GWAS approach undertaken. Findings from a recent meta-analysis of migraine GWAS revealing larger effect sizes for implicated loci in individuals with MoA compared to MA suggest that MA may be mediated more by rare variants with larger effect. Taken together these findings suggest that it would be useful for future studies to use more powerful approaches to detect both common and rare variation when searching for shared variation, such as next generation sequencing.

Moreover, future research looking to explore potential shared aetiological underpinnings between migraine and BD, may benefit from focusing on the rare subtype of MA, familial hemiplegic migraine (FHM). FHM is genetically heterogeneous, and polymorphisms in at least three genes have so far been implicated; *CACNA1A* (Ophoff et al., 1996), *ATP1A2* (DeFusco et al., 2003), and *SCN1A* (Dichgans et al., 2005). Mutations in these three FHM genes are reported to explain between 50-70% of published families with FHM, thus the existence of other genes involved in the pathogenesis of FHM is likely (Thomsen et al., 2007). All three FHM genes either encode ion channels or are involved in ion transportation, therefore highlighting the importance of ion channels in the molecular mechanism of migraine. Given that two of the strongest associations to come out of genome-wide association studies of BD have been for two genes involved in ion transportation (ANK3 and CACNA1C), this suggests that

disturbances in ion channel function are relevant for both migraine and BD. This proposed similarity in the underlying mechanisms of FHM and BD, may, therefore, suggest a greater likelihood of genetic overlap between the two disorders. Within the current thesis, 45 individuals within the MA group met criteria for hemiplegic migraine (HM) (3.1% of total sample). This is much higher than that reported within a Danish population-based epidemiological survey, which estimated the prevalence of HM to be 0.01%, with the familial and sporadic forms being equally prevalent (Thomsen et al., 2002). A possible avenue for future research would be to conduct next generation sequencing on these individuals in an attempt to identify potential shared genes that may be explaining the high rate of HM observed in the bipolar sample.

To date, very few studies have examined the rate of epilepsy within individuals with BD, with those that have often assessing epilepsy among a larger number of other medical conditions in order to assess the medical burden experienced within BD (Forty et al., 2014; Moreira et al., 2011; Weber et al., 2011). The wealth of aetiological-based research suggesting a link between BD and epilepsy, and initial findings suggesting that epilepsy may be overrepresented in individuals with BD, suggest that establishing epilepsy prevalence within BD should be a priority for future research. Chapter 6 of this thesis employed the use of a single screening question to identify the rate of self-reported epilepsy within the bipolar sample. This screening question has been previously shown to have a sensitivity of 76%, and so it is possible that the rate of self-reported epilepsy identified within the current thesis of 8% is an underestimate. Whilst this may be appropriate for a study of comorbidity, looking to identify individuals with epilepsy for further analysis, estimates of prevalence would require the use of a screen with maximum sensitivity to avoid underestimation. Such studies would require all positive screens to be followed up within a second stage of screening, due to the high number of false positives that often accompany highly sensitive screening tools. Due to time constraints, the current thesis could not follow-up all individuals who screened positively for epilepsy within the first assessment stage and was therefore unable to comment on the prevalence of confirmed epilepsy cases following further review. Rather, the 1.8% of individuals

confirmed to have epilepsy following detailed telephone interview and expert review could only be considered a conservative estimate. Chapter 6 was the first study of its kind to assess bipolar illness characteristics associated with comorbid epilepsy. Given its exploratory nature and modest sample size, corrections were not made for multiple testing. Therefore, future research using larger samples is needed to confirm the bipolar clinical correlates associated with BD and epilepsy.

The mechanisms underlying the comorbid relationship between BD and comorbid migraine, and epilepsy are poorly understood. Therefore, future prospective research is required in order to better understand their relationship and to determine whether migraine and/or epilepsy are risk factors for BD, whether BD is a risk factor for the development of migraine and/or epilepsy, or both. Moreover, a focus of future research on treatment response and prognosis of BD with comorbid migraine, and epilepsy, may help to elucidate the underlying mechanisms of shared pathophysiology between these disorders.

7.5 Final conclusions

This thesis has identified that the neurological disorders of migraine and epilepsy are common in individuals with bipolar disorder (BD), and that their presence may be associated with a distinct course of the bipolar illness. Such findings highlight the need for effective identification of these conditions within BD and have implications for the management and treatment of individuals with BD. Findings of this thesis suggest that individuals with bipolar II disorder may be particularly susceptible to migraine and that the identification of aura symptoms within those with comorbid migraine and BD may identify those who may be at particular risk for adverse psychiatric outcome. In addition, this thesis revealed that suicide risk may be a particular concern for bipolar individuals with comorbid migraine, and epilepsy, further emphasizing the need for an awareness of comorbidity and its complications in the management of BD as a

means of improving patient outcomes. Further research unravelling the complex relationship between BD with migraine and epilepsy is needed to help elucidate the nature, impact and mechanism of the co-occurrence of these disorders.

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Appendices

Appendix A – Self-report migraine questionnaire disseminated to the Bipolar Disorder Research Network (BDRN) sample (Chapters 3, 4 and 5).

HEADACHE QUESTIONNAIRE

1. a) Have you ever had recurrent headaches? ☐ No ☐ Yes

1. b) At their most frequent, how often do/did your headaches occur?
☐ Daily ☐ Every 1-3 months ☐ Less than once a year
☐ Weekly ☐ Every 3-6 months ☐ Unsure
☐ Monthly ☐ Yearly ☐ Not applicable (as no recurrent headaches)

Other
[Please specify]

2. Have you ever had moderate to severe headaches accompanied by nausea and/or vomiting? ☐ No [never] ☐ Yes [1-4] ☐ Yes [5+times]

3. Have you ever had moderate to severe headaches accompanied by hypersensitivity to sound or light? ☐ No [never] ☐ Yes [1-4] ☐ Yes [5+times]

If your answers to questions 1-3 are all "No" this completes the questionnaires - thank you very much for your time.

4. How old were you when you first started to experience these headaches? (Age in years) [If unsure leave blank] ☐☐

5. Typically, what type of headaches do/did you get?

	No	Yes	Unsure
Pulsating	☐	☐	☐
Band-like	☐	☐	☐
One-sided	☐	☐	☐

Other
[Please specify]

6. Typically, are/were your headaches...
☐ Mild [able to continue with daily activities]
☐ Moderate [some limitation in daily activities]
☐ Severe [unable to function]

7. What does/did make them worse? [You can pick more than one]
☐ Walking [or similar physical activities]
☐ Certain foods [please specify which foods below]
☐ Nothing

Other
[Please specify]

8. What do/did you do to relieve the headaches? [You can pick more than one]

- ☐ Rest
- ☐ Being in a dark room
- ☐ Sleep
- ☐ Taking pain killers
- ☐ Taking migraine tablets

9. Typically, how long do/did the headaches last?

- ☐ 0-1 hour
- ☐ 2-3 hours
- ☐ 4-72 hours
- ☐ more than 72 hours

10. Have you ever had any of the symptoms listed below accompanied by or followed by (within 60 minutes) a headache?

a) Visual disturbances [e.g. flickering lights, spots or lines, blurred vision or loss of vision] ☐ No ☐ Yes once ☐ Yes [2+ times]

If Yes:

	No	Yes	Unsure
Does/did this symptom come on gradually over a period of 5 minutes or more?	☐	☐	☐
Does/did this symptom last for between 5 and 60 minutes?	☐	☐	☐
Are/were these symptoms only on one side of your visual field? [e.g. more on the right side than the left or vice versa]	☐	☐	☐

b) Sensory symptoms [e.g. pins & needles or numbness] ☐ No ☐ Yes once ☐ Yes [2+ times]

If Yes:

	No	Yes	Unsure
Does/did this symptom come on gradually over a period of 5 minutes or more?	☐	☐	☐
Does/did this symptom last for between 5 and 60 minutes?	☐	☐	☐
Are/were these symptoms only on one side of your body?	☐	☐	☐

c) Speech disturbance [e.g. loss of speech] ☐ No ☐ Yes once ☐ Yes [2+ times]

If Yes:

	No	Yes	Unsure
Does/did this symptom come on gradually over a period of 5 minutes or more?	☐	☐	☐
Does/did this symptom last for between 5 and 60 minutes?	☐	☐	☐

If answers to 10a, b and c are all "No", please go to question 14.

If answers to 10a, b or c are "Yes", please go to question 11 and then complete the full questionnaire.

11. How old were you when you first experienced the symptoms described in 10 a, b or c (visual, sensory, speech) before or during a headache? (Age in years)

[If unsure leave blank] ☐☐

12. Do/did the symptoms described in 10 a, b or c (visual, sensory, speech) ever occur one after the other (in succession) over a period of 5 minutes of more? ☐ No ☐ Yes ☐ Unsure

13. Have you ever experienced motor weakness [muscle weakness, feeling paralysed] accompanied by or followed by (within 60 minutes) a headache? ☐ No ☐ Yes once ☐ Yes [2+ times]

If Yes:

	No	Yes	Unsure
Does/did this symptom come on gradually over a period of 5 minutes or more?	☐	☐	☐
Does/did this symptom last for between 5 and 60 minutes?	☐	☐	☐
Does/did this only affect one side of your body?	☐	☐	☐

14. Have you ever been given a medical explanation/ diagnosis for your recurrent headaches? [including effects of medication]
☐ No
☐ Yes

Other
[Please specify]

15. Have your headaches ever been investigated? [e.g. have you been referred to a specialist, or had a brain scan, brain wave tracing (EEG)]
☐ No
☐ Yes

Other
[Please specify]

16. Has a doctor or health professional ever told you that you have any of the following? (you may choose more than one)

☐ Classic Migraine
☐ Common Migraine
☐ Migraine with Aura
☐ Migraine without Aura
☐ Familial Hemiplegic Migraine
☐ Sporadic Hemiplegic Migraine
☐ Hemiplegic Migraine (unsure which type)
☐ Unsure

Any other type
of migraine?

Family History of Headache/Migraine

17. a) Do you have any biological first or second degree relatives (see below) who have experienced Migraine Headaches?

☐ No ☐ Yes ☐ Unsure

First degree relatives include parents, brothers/sisters, children.
Second degree relatives include grandparents, grandchildren, aunts/uncles, nephews/nieces.

Please only include relatives who are related to you by blood. For example, please do not include adopted family members or step-family members.

If "No" this completes the questionnaires - thank you very much for your time.

If "Yes", please go to 17b and complete the rest of the questionnaire.

17. b) Have any of these family members experienced aura symptoms (the symptoms referred to in questions 10a, b and c in this questionnaire) before or during their headaches?

☐ No ☐ Yes ☐ Unsure

17. c) Have any of these family members experienced motor weakness [muscle paralysis] before or during their headaches?

☐ No ☐ Yes ☐ Unsure

17. d) Have any of these family members ever been told by a doctor or a health professional that they have any of the following? (you may choose more than one)

☐ Classic Migraine
☐ Common Migraine
☐ Migraine with Aura
☐ Migraine without Aura
☐ Familial Hemiplegic Migraine
☐ Sporadic Hemiplegic Migraine
☐ Hemiplegic Migraine (unsure which type)
☐ Unsure

Any other type of migraine?

THIS COMPLETES THE QUESTIONNAIRES - THANK YOU VERY MUCH FOR YOUR TIME

Appendix B – Migraine telephone interview employed within the current thesis within a sub-sample of bipolar subjects (Chapter 3).

MIGRAINE HEADACHES

1. Have you had at least one headache in your lifetime OTHER THAN those caused by a head injury, a hangover, (pregnancy), or an illness such as a cold or the flu?

- ☐ Yes *(GO TO Q2)*
- ☐ No *(GO TO Q1A)*
- ☐ Don't know

1A. Let me make sure I understand. Any headache you have ever had was directly caused by an illness, a cold, the flu, a head injury, pregnancy, or a hangover. Is this correct?

- ☐ Yes *(GO TO Q22)*
- ☐ No
- ☐ Don't Know

Many people have more than one 'kind' of headache. For example, headaches could be considered different kinds if the intensity of pain, where it is located, the symptoms, or the length, varies significantly from one headache to another.

For the next set of questions, I want you to concentrate only on your **most severe type of headache**. By this I mean out of all the different types of headache you might have had, the one that most interferes/interfered with your ability to work, study, do the housework, or enjoy life.

2. How old were you the first time you had one of these headaches?

(Probe for best estimate and if unsure probe for age range; code in years; DK = 99)

☐☐

- ☐ 10 years or younger
- ☐ 11-20 years
- ☐ 21-30 years
- ☐ 31-40 years
- ☐ 41-50 years
- ☐ 51-60 years
- ☐ 70 years or older

Comments (i.e. was this before or after completing the migraine questionnaire in 2011?):

3. Have you had at least 5 of these headaches in your lifetime?

- ☐ Yes
- ☐ No *(GO TO Q5)*
- ☐ Don't know

Comments:

4. Have at least 5 of these headaches lasted 4 hours or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

5. When was the last time you had this type of headache? ☐☐☐☐

(Probe for best estimate; DK= -9; Record answer in only one of below formats but code in days)

☐☐ Days ago ☐☐ Weeks ago ☐☐ Months ago ☐☐ Years ago

6. One a scale of 1 to 10, with 1 being very mild pain and 10 being pain as bad as it can be, how would you rate the pain that you have with your most severe type of headache? ☐☐

(Probe for best estimate; DK = 99)

7. How often is your most severe type of headache made worse by activities like climbing stairs or walking? Would you say...

- ☐ Never
- ☐ Rarely
- ☐ Less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

8. With your most severe type of headache, how often do or did you have pain only on one side of the head? Would you say...

- ☐ Never
- ☐ Rarely
- ☐ Less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

9. With your most severe type of headache, how often do or did you experience pounding or pulsating pain? Would you say...

- ☐ Never
- ☐ Rarely
- ☐ less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

10. With your most severe type of headache, how often have you felt nauseous or been sick to your stomach or felt like vomitting? Would you say...

- ☐ Never
- ☐ Rarely
- ☐ Less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

11. With your most severe type of headache, how often are or were you especially bothered by or unusually sensitive to light? Would you say?

- ☐ Never
- ☐ Rarely
- ☐ Less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

12. With your most severe type of headache, how often are or were you especially bothered by or unusually sensitive to sound or noise? Would you say...

- ☐ Never
- ☐ Rarely
- ☐ Less than 1/2 the time
- ☐ 1/2 the time or more
- ☐ Don't know

13. Have you ever seen things like spots, stars, lines, flashing lights, zigzag lines or 'heat waves', either during your most severe type of headache, or the headache follows these visual disturbances within 60 minutes?

- ☐ Yes
- ☐ No *(GO TO Q14)*
- ☐ Don't know *(GO TO Q14)*

13A. How many headaches with these visual changes have you had in your lifetime? Would you say...

- ☐ One
- ☐ Two or more
- ☐ Don't know

13B. Does/did this symptom come on gradually over a period of 5 minutes or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

13C. Does/did this symptom last for between 5 and 60 minutes?

- ☐ Yes
- ☐ No
- ☐ Don't know

13D. Are/were these symptoms only on one side of your visual field?

- ☐ Yes
- ☐ No
- ☐ Don't know

14. Have you ever experienced sensory symptoms (such as pins and needles or numbness) either during your most severe type of headache or the headache follows these visual disturbances within 60 minutes?

- ☐ Yes
- ☐ No *(GO TO Q15)*
- ☐ Don't know *(GO TO Q15)*

14A. How many headaches with these sensory symptoms have you had in your lifetime? Would you say...

- ☐ One
- ☐ Two or more
- ☐ Don't know

14B. Does/did this symptoms come on gradually over a period of 5 minutes or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

14C. Does/did this symptoms last for between 5 and 60 minutes?

- ☐ Yes
- ☐ No
- ☐ Don't know

14D. Are/were these symptoms only on one side of your body?

- ☐ Yes
- ☐ No
- ☐ Don't know

15. Have you ever experienced any speech disturbance (e.g. loss of speech), either during your most severe type of headache or the headache follows these symptoms within 60 minutes?

- ☐ Yes
- ☐ No *(GO TO Q16)*
- ☐ Don't know *(GO TO Q16)*

15A. How many headaches with these speech disturbances have you had in your lifetime? Would you say...

- ☐ One
- ☐ Two or more
- ☐ Don't know

15B. Does/did this symptom come on gradually over a period of 5 minutes or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

15C. Does/did this symptoms last for between 5 and 60 minutes?

- ☐ Yes
- ☐ No
- ☐ Don't know

16. Have you ever experienced motor weakness (muscle weakness, feeling paralysed) accompanied by your most severe headache or the headache follows these symptoms within 60 minutes?

- ☐ Yes
- ☐ No *(GO TO Q17)*
- ☐ Don't know *(GO TO Q17)*

16A. How many headaches with motor weakness have you had in your lifetime? Would you say...

- ☐ One
- ☐ Two or more
- ☐ Don't know

16B. Does/did this symptom come on gradually over a period of 5 minutes or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

16C. Does/did this symptom last for between 5 and 60 minutes?

- ☐ Yes
- ☐ No
- ☐ Don't know

ONLY ASK THE FOLLOWING QUESTION IF ANSWERED 'YES' TO TWO OF Q13-16

17. Do/did the symptoms described above (visual, sensory, speech, motor) ever occur one after the other, in succession, over a period of 5 minutes or more?

- ☐ Yes
- ☐ No
- ☐ Don't know

18. Have you ever been given a medical explanation for your most severe headaches (including effects of medication)?

- ☐ Yes
- ☐ No
- ☐ Don't know

Comments (i.e. what/when/by who?)

19. Have your headaches ever been investigated, for example, have you been referred to a specialist, had a brain scan, EEG (brain wave tracing)?

- ☐ Yes
- ☐ No
- ☐ Don't know

Comments (i.e. what/when/where/who/result?)

20. Have you ever received any treatment for your most severe type of headaches?

- ☐ Yes
- ☐ No
- ☐ Don't know

Details (what/when/prescribed/over-the-counter?)

21. At their most frequent, how often do/did your most severe type of headaches occur?

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Every1-3 months
- ☐ Every 3-6 months
- ☐ Yearly
- ☐ Less than once a year
- ☐ Don't know

Family History

The next set of questions relate to family history and will ask about biological first and second degree relatives.

First degree relatives include parents, brothers/sisters, children.
Second degree relatives include grandparents, grandchildren, aunts/uncles, nephews/nieces/half brothers and sisters.

22. Do you have any biological first or second degree relatives who have experienced migraine headaches?

- ☐ Yes
- ☐ No *(Go to Q25)*
- ☐ Don't know *(Go to Q25)*

Details:

PROMPT QUESTIONS:

When did they start experiencing migraines? (i.e. prior to or following completion of 2011 questionnaire)? **Diagnosis**? By **who**?

Has this relative also been diagnosed with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder? **What** treatment?

23. Do you have any first or second degree relatives who have experienced aura symptoms (the visual, sensory or speech disturbances described earlier), either before or during their headaches?

☐ Yes

☐ No *(Go to Q25)*

☐ Don't know *(Go to Q25)*

Details:

PROMPT QUESTIONS:

When did they start experiencing these aura symptoms? (i.e. prior to or following completion of 2011 questionnaire)? **Diagnosis** of migraine with aura? By **who**?

Has this relative also been diagnosed with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder? **What** treatment?

24. Do you have any first or second degree relatives who have experienced motor weakness (paralysis) before or during their headaches?

- ☐ Yes
- ☐ No *(Go to Q25)*
- ☐ Don't know *(Go to Q25)*

Details:

PROMPT QUESTIONS:

When did they first experience these motor symptoms? (i.e. prior to or following completion of 2011 questionnaire)? **Diagnosis** of hemiplegic migraine? By **who**?

Has this relative also been diagnosed with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder? **What** treatment?

25. Do you have any first or second degree relatives who have experienced seizures or epilepsy?

- ☐ Yes
- ☐ No
- ☐ Don't know

Details:

PROMPT QUESTIONS:

When did they start experiencing epilepsy/seizures?
Have they been **diagnosed**? **What** with? By **who**?

Has this relative also been diagnosed with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder? **What** treatment?

Medical records:
When individuals consent to participate in the Bipolar Disorder Reseach Network, we ask if they give their permission for their medical records to be looked at in strict confidence by responsible people from the Mood Disorder Research Team.

Do you consent for your medical records to be looked at by the Mood Disorder Research Team?

☐ Yes

☐ No

Details of GP/psychiatric care team:

Wrap up:
So that brings us to the end of our questions, is there anything else you would like to add?

This completes the interview - Thank you very much for your time

Interviewers impressions:

Q1. Respondents understanding of questions

- ☐ Excellent
- ☐ Good
- ☐ Adequate
- ☐ Poor

Q2. Comment on rapport established throughout interview:

Q3. Other impressions:

Appendix C – Self-report epilepsy questionnaire disseminated to the Bipolar Disorder Research Network (BDRN) sample (Chapter 6).

EPILEPSY QUESTIONNAIRE

This questionnaire asks about your history and your family history of epilepsy and seizures.

1. Did anyone ever tell you that you had a seizure or a convulsion caused by a high fever when you were a child? (*please mark one box*):

☐ No ☐ Yes ☐ Possible ☐ Don't know

2. Other than the seizure(s) you may have had because of a high fever, described in Q1, have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy? (*please mark one box, and add any comments if applicable*):

☐ No ☐ Yes ☐ Possible ☐ Don't know

Comments:

3. Other than the seizure(s) you may have had because of a high fever described in Q1, have you EVER had, or has anyone ever told you that you had, any of the following? (*please mark one box for each*):

	No	Yes	Possible	Don't know
a) A seizure, convulsion, fit or spell under any circumstances?	☐	☐	☐	☐
b) Uncontrolled movements of part or all of your body such as twitching, jerking, shaking or going limp?	☐	☐	☐	☐
c) An unexplained change in your mental state or level of awareness; or an episode of 'spacing out' that you could not control?	☐	☐	☐	☐
d) Did anyone ever tell you that when you were a small child, you would daydream or stare into space more than other children?	☐	☐	☐	☐
e) Have you ever noticed any unusual body movements or feelings when exposed to strobe lights, video games, flickering lights, or sun glare?	☐	☐	☐	☐
f) Shortly after waking up, either in the morning or after a nap, have you ever noticed uncontrollable jerking or clumsiness, such as dropping things or things suddenly 'flying' from your hands?	☐	☐	☐	☐
g) Have you ever had any other type of repeated unusual spells?	☐	☐	☐	☐

If yes, please describe:

4. Have you ever had, or has anyone ever told you that you have: non-epileptic attacks; pseudoseizures; functional or dissociative or psychogenic attacks?
***(please mark one box, and add any comments if applicable*)**:

☐ No ☐ Yes ☐ Possible ☐ Don't know

Comments:

5. How old were you when you experienced your first seizure? (Age in years)
[leave blank if unknown] ☐☐

☐ Don't know ☐ Not applicable

6. Have you ever been prescribed medication for your seizures/seizure disorder/epilepsy?
(please mark one box):

☐ No ☐ Yes ☐ Don't know ☐ Not applicable

If yes, please tick if you have ever been prescribed any of the following medications for your seizures/ epilepsy. ***(Both trade and generic names are provided. Please tick all that apply):***

☐ Carbamazepine (Tegretol)	☐ Sodium Valporate (Epilim)	☐ Lamotrigine (Lamictal)
☐ Levetiracetam (Keppra)	☐ Phenytoin (Epanutin)	☐ Topiramate (Topramax)
☐ Zonisamide (Zonegran)	☐ Clobazam (Frisium)	☐ Oxcarbazepine (Trileptal)
☐ Phenobarbital	☐ Eslicarbazapine acetate (Zebinix)	☐ Other (please specify below)

Note: Above are some of the common medications prescribed for seizures/ epilepsy, however not all possible medications are listed. If you have been prescribed a medication which is not listed above, please specify below:

Other (*please specify*):

The following questions are about your family history of seizures/epilepsy.

First degree relatives include parents, brothers/sisters, children.
Second degree relatives include grandparents, grandchildren, aunts/uncles, nephews/nieces.

Please only include relatives who are related to you by blood (biological relatives). For example, please do not include adopted family members or step-family members.

7. Do you have any biological first or second degree relatives (see above for definition) who have experienced seizures/seizure disorder/epilepsy?
(*please mark one box, and add any comments if applicable*):

☐ No ☐ Yes ☐ Don't know

If yes, please give details:

8. Do you have any biological first or second degree relatives (see above for definition) who have experienced febrile seizures (a seizure or convulsion caused by a high fever when they were a child?
(*please mark one box, and add any comments if applicable*):

☐ No ☐ Yes ☐ Don't know

If yes, please give details:

9. Do you have any biological first or second degree relatives (see above for definition) who have experienced migraine headaches?
(*please mark one box, and add any comments if applicable*):

☐ No ☐ Yes ☐ Don't know

If yes, please give details:

You have now finished Questionnaire 5.
Please move on to Questionnaire 6 over the page.
Thank you.

Appendix D - Epilepsy telephone interview employed within the current thesis within a sub-sample of bipolar subjects (Chapter 6).

EPILEPSY INTERVIEW

Notes for interviewer:

Section A: Description of seizure(s)/event(s)

A) If subject answered **Unsure** to Q2 from the questionnaire, but reported other events or symptoms 3A-G; say the following and start interview from Q3.

A1. From the questionnaire we sent you, asking about seizures and epilepsy, you said that; you are unsure whether you have a seizure disorder or epilepsy, but you have experienced seizure-related symptoms/events.

Specifically, you stated that:

1.
2.
3.
4.
5.
6.

Is this correct? (Ask whether they have experienced any other repeated unusual spells)

If subject answered **'unsure'** to Q2 but reported **no symptoms**, ask the following:

A2. From the questionnaire we sent you, asking about seizures and epilepsy, you said that you are unsure whether you have a seizure disorder or epilepsy.

Have you ever experienced any type of repeated unusual spells?

1.
2.
3.
4.
5.
6.

B) If subject reported they **have** or **possibly** have a **seizure disorder or epilepsy** from the questionnaire, say the following and begin interview at Q1.

From the questionnaire we sent you asking about seizures and epilepsy, you said that:

- ☐ You have/have had a seizure disorder or epilepsy
- ☐ It is possible that you have/have had a seizure disorder or epilepsy

Specifically you stated that:

Is that correct?

I would now like to ask you a few questions, to get a detailed description of the seizures/events you have experienced.

Many people have more than one 'type' of seizure. What we mean by 'different type' is that you feel different during the event, or if what happens before, during or after the event is different from your other types.

Q1. With this in mind, how many 'different types' of seizures would you say you've had? | | |

If only one type, skip to Q3 *(page 7)*.

Q2. To make it easier to describe each one, could you give me a name to use for each type of seizure?

Please give me the names in order, from the type you have had most frequently, to the type you have had least frequently. For each type, I'll ask you to briefly list the major symptoms you have.

1.
2.
3.
4.
5.
6.

Repeat Q3 -12 for each of the above seizures/events.

Event/seizure number 1

Q3A. What month and year was the last time you had one of these seizures/events? ☐☐ / ☐☐☐☐

Q3B. How old were you then? *(Enter in months if younger than 2 years)* ☐☐ ☐ Months ☐ Years

It's important for us to know the sequence of events that happens during these seizures/events. Thinking back to your most recent event of this:

Q4A. What would you say is the very first thing that happened when you had this event?

Q4B. What is the next thing that happened?

Q4C. How did you feel, what happened, or what were you told you did during the rest of this event?

Q4D. How did you feel, what happened, or what were you told you did afterwards?

(Ask the following only if subject reports being dizzy or light-headed. Otherwise to go Q5).

Q4E. What do you mean by dizzy/light-headed?

Q5. How long did the event last? Would you say...

☐ Less than 15 seconds
☐ 15 seconds to 5 minutes
☐ More than 5 minutes
☐ Don't know

Q6. During the event, which of the following best describes your awareness of the surroundings...?

- ☐ Fully aware
- ☐ Somewhat aware, but less than usual
- ☐ Fully unaware
- ☐ Don't know

Q7. During this event, were you able to communicate as you normally do?

- ☐ Yes
- ☐ No
- ☐ Don't know

Q8A. Were you tired or confused afterwards?

- ☐ Yes
- ☐ No *(Go to Q9)*
- ☐ Don't know *(Go to Q9)*

Q8B. For how long were you tired or confused? Would you say...

- ☐ Less than 10 seconds
- ☐ 10 seconds or more
- ☐ Don't know

Q9. About how many times in your life would you say you experienced events like the one you just described? Would you say...

- ☐ One *(Go to Q12)*
- ☐ 2 or 3
- ☐ More than 3 but less than 20
- ☐ More than 20 but less than 100
- ☐ More than 100
- ☐ Don't know

Q10. At the time in your life when you had this type of event most frequently, how often did you have them? Would you say...

- ☐ Less than once a month
- ☐ 1 to 4 times a month
- ☐ More than 4 times a month, but less than once a day
- ☐ Once a day or more
- ☐ Don't know

Q11. How old were you at that time? Would you say...

- ☐ <1 year old
- ☐ 1-5 years old
- ☐ 6-10 years old
- ☐ 11-19 years old
- ☐ 20 years old or older
- ☐ Don't know

Q12. How old were you the first time you had one of these events? ☐☐ ☐ Months ☐ Years

(Enter in months if younger than 2 years)

Repeat section for seizure/event number 2.

Note: within original interview, the above section is repeated for all stated seizures/events.

Move on to family history questions

The following questions are about your family history of seizures/epilepsy.

First degree relatives include parents, brothers/sisters, children.
Second degree relatives include grandparents, grandchildren, aunts/uncles, nephews/nieces/half brothers and sisters.

Q13. Do you have any biological first or second degree relatives who have experienced seizures/epilepsy?

- ☐ Yes
- ☐ No *(Go to Q14)*
- ☐ Don't know *(Go to Q14)*

Details:

PROMPT QUESTIONS:

Have they been **diagnosed? What** with?
When? By **who?** Have they received **treatment** for their seizures/epilepsy?

Has this relative also been **diagnosed** with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder?

Q14. Do you have any biological first or second degree relatives who have experienced febrile seizures (seizure or convulsion caused by a high fever when they were a child)?

- ☐ Yes
- ☐ No *(Go to Q15)*
- ☐ Don't know *(Go to Q15)*

Details:

PROMPT QUESTIONS:

When did they experience these? Did they see a **doctor**? Did they receive **treatment** for their febrile seizures?

Has this relative also been **diagnosed** with a mood disorder?
- **What** were they diagnosed with?
- **Who** were they diagnosed by?
- **When** were they diagnosed?
- Have they received **treatment** for their mood disorder?

Q15. Do you have any biological first or second degree relatives who have experienced migraine headaches?

- ☐ Yes
- ☐ No *(Go to Section B)*
- ☐ Don't know *(Go to Section B)*

Details:

PROMPT QUESTIONS:

Have they been **diagnosed? What** with?
When? By **who?** Have they received **treatment** for their migraines?

Has this relative also been **diagnosed** with a mood disorder?
What were they diagnosed with?
Who were they diagnosed by?
When were they diagnosed?
Have they received **treatment** for their mood disorder?

Section B: Seizure Triggers

Have any of your seizures/events been triggered by any of the following?

Q1. Standing up?

☐ Yes ☐ No ☐ Don't know

Could you tell me more about that?

Q2. Poor sleep?

☐ Yes ☐ No ☐ Don't know

Could you tell me more about that?

Q3. Stress?

☐ Yes ☐ No ☐ Don't know

Could you tell me more about that?

Q4. Flashing or blinking lights?

☐ Yes ☐ No ☐ Don't know

Could you tell me more about that?

Q5. Any other triggers?

☐ Yes ☐ No ☐ Don't know

Could you tell me more about that?

Section C: Investigation and Medication

Q1A. Have you ever been to your GP because of the seizures or turns you have had?

- ☐ Yes
- ☐ No *(Go to Q6)*
- ☐ Don't know *(Go to Q2)*

Q1B. How old were you when you first saw a GP because of your seizures or events? ☐☐ ☐ Months ☐ Years

Q1C. How many times in the last 12 months have you visited this doctor about your seizures or events? ☐☐

Q2A. Have you ever seen a specialist because of the seizures or turns you have had?

- ☐ Yes
- ☐ No *(Go to Q3)*
- ☐ Don't know *(Go to Q3)*

Details of specialist:

Q2B. How old were you when you first saw a specialist because of your seizures or events? ☐☐ ☐ Months ☐ Years

Q2C. How many times in the last 12 months have you visited this specialist about your seizures or events? ☐☐

Q3. Have you ever had your seizures investigated, for example, with an MRI scan, CAT scan, or EEG?

- ☐ Yes
- ☐ No
- ☐ Don't know

Details (i.e. when/where/result?)

Q4. Has a doctor or health professional ever given you a diagnosis of epilepsy or a seizure disorder?

- ☐ Yes
- ☐ No
- ☐ Don't know

Comments:

Q5. Has a doctor or specialist ever suggested a potential cause for your seizures or events?
(i.e. alcohol, stress, head injury, infection)

- ☐ Yes
- ☐ No
- ☐ Don't know

Details:

Q6. Have you ever taken medication for your seizures/epilepsy?

- ☐ Yes
- ☐ No
- ☐ Don't know

If yes, which medications have you taken for your seizures/epilepsy?

Q7. Is there anything else you would like to add?

Section D: Alcohol

Alcohol questions should only be administered to subjects with an onset of epilepsy > 12 years. If onset <12 years, skip alcohol section.

The next questions are about drinking alcohol. We are asking you about alcohol use because we know alcohol can affect the likelihood of having seizures and we want to better understand the relationship between alcohol and seizures in individuals. As with all questions we ask, your answers will be strictly confidential.

Q1. How often do you drink alcohol? Would you say...

- ☐ 3-4 times per month
- ☐ 2-3 times per week
- ☐ More than 4 times per week but not every day
- ☐ Every day
- ☐ Don't know

Q2. How many units of alcohol do you drink in a typical week? ☐☐☐

NB. 1 unit of alcohol is equal to one glass of wine, a single measure of spirits or half a pint of beer/larger.

If unsure about number of units;

What do you drink in a typical week?

Q3A. Thinking of the time in your life when you drank the most, how many units of alcohol did you have in a typical week? ☐☐☐

NB. 1 unit of alcohol is equal to one glass of wine, a single measure of spirits, or half a pint of beer/larger.

If unsure about number of units;

What do you drink on a typical week?

Q3B. Around how old were you at the time when you drank the most? ☐☐

Q4. Has there ever been a time in your life when you drank three or more drinks everyday for a month or longer?

- ☐ Yes
- ☐ No
- ☐ Don't know

Q5A. Have any of your seizures/events occured within 24 hours of drinking 3 or more drinks of alcohol?

- ☐ Yes
- ☐ No
- ☐ Don't know

Q5B. Have <u>all</u> of your seizures/events occured within 24 hours of drinking alcohol?

- ☐ Yes
- ☐ No
- ☐ Don't know

Q6. Have you ever been told by a doctor that you had a seizure as a result of withdrawal from alcohol?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Not asked

Q7A. Do you think your seizures/events are related to drinking?

- ☐ Yes
- ☐ No *(Go to "Medical records")*
- ☐ Don't know *(Go to "Medical records")*

Q7B. In what ways are they related to drinking?

Wrap up:
So that brings us to the end of our questions, is there anything else you would like to add?

Medical records:
When individuals consent to participate in the Bipolar Disorder Reseach Network, we ask if they give their permission for their medical records to be looked at in strict confidence by responsible people from the Mood Disorder Research Team.

Do you consent for your medical records to be looked at by the Mood Disorder Research Team?

☐ Yes

☐ No

Details of GP/psychiatric care team:

Interviewers impressions:

Q1. Respondents understanding of questions

☐ Excellent

☐ Good

☐ Adequate

☐ Poor

Q2. Comment on rapport established throughout interview:

Q3. Other impressions:

Appendix E – Summary of significant predictors of migraine with aura (MA) compared with bipolar subjects with no migraine entering only variables that surpassed Bonferroni correction for multiple comparisons into the logistic model as predictor variables.

	Wald X^2	df	P value	OR (95% CI)
Female	7.259	1	.007	2.582 (1.295-5.149)
Bipolar II disorder diagnosis	4.458	1	.035	1.817 (1.044-3.164)
History of suicide attempt	6.630	1	.010	1.974 (1.176-3.312)

BDII=bipolar II disorder; df=degrees of freedom; OR=odds ratio; 95% CI=95% confidence intervals.

Appendix F - Description of genes in regions implicated by the top 10 independent SNPs from genome-wide association analysis.

PRSS57 (Protease, Serine, 57)

PRSS57 is involved in serine-type endopeptidase activity. Proteases are enzymes that break the peptide bond that joins amino acids together in proteins. Serine proteases are proteolytic enzymes that break the peptide bond that joins amino acids together in proteins. In mammals, serine proteases are involved in a number of biological processes, such as; digestion, blood clotting, reproduction and the complement system.

IQCG (IQ Motif containing G)

IQCG is one of several IQ motif–containing genes of unknown function. IQ motifs are present in several hundred proteins, most notably myosins, but also in a variety of nonmyosin proteins such as neuronal growth proteins, voltage-gated channels, phosphatases, spindle-associated proteins, and sperm surface proteins (Bahler & Rhoads, 2002). Harris, Schimenti, Munroe, and Schimenti (2014) recently reported a male-specific infertility mutant in which the genetic lesion was traced to IQCG. These mice exhibited spermiogenesis defects. IQ motif-containing genes typically regulate calmodulin (CaM) (a multifunctional intermediate calcium-binding messenger protein expressed in all eukaryotic cells). CaM activation can stimulate actin cytoskeleton changes. Therefore, it is possible that the flagellum formation defects in mutants reflect an involvement of IQCG in spermatid morphogenesis and suggest a potential role for localized calcium signaling in sperm flagellum morphogenesis.

LINC00683 (Long Intergenic Non-Protein Coding RNA 683)

LINC00683 is a non-annotated RNA gene, affiliated with the non-coding RNA class.

SP3 (Sp3 Transcription Factor)

SP3 is a protein coding gene, belonging to a family of Sp1 related genes that encode transcription factors that regulate transcription. This protein contains a zinc finger DNA-binding domain and several transactivation domains, and functions as a bifunctional transcription factor, both activating and repressing transcription (Suske, 1999).

EML4 (Echinoderm Microtubule Associated Protein Like 4)

EML4 is a Protein Coding gene and is a microtubule-associated WD-repeat protein of the echinoderm microtubule-associated protein family Heidebrecht, H.J. et al. (2000) *Genomics* 68, 348-350. Expression of EML4 is necessary for correct intracellular microtubule network formation (Pollmann et al. (2006) *Exp. Cell Res.* 312, 3241-3251.). Abnormal fusion of parts of this gene with portions of the anaplastic lymphoma receptor tyrosine kinase gene, which generates EML4-ALK fusion transcripts, is one of the primary mutations associated with non-small cell lung cancer. Diseases associated with EML4 include congenital pulmonary airway malformation and inflammatory myofibroblastic tumor.

TLE1 (Transducin-like enhancer protein 1)

TLE1 is one of 4 Transducin-Like Enhancer of split (TLE) genes that encode human transcriptional repressors homologous to the Drosophila corepressor, Groucho (transcriptional factor that plays a critical role in Drosophila embryotic development) (Stifani et al. (1991) *Nat Genet*. 2, 119-27). The TLE family proteins are required for many developmental processes, including lateral inhibition, segmentation, sex determination, dorsal/ventral pattern formation, terminal pattern formation and eye development (Chen & Courey (2000) *Gene*. 249 (1–2): 1–16). TLE1 has been implicated in the pathogenesis of cancer (Chuang et al. (2013 Pathol Int. 63 (12), 573-80); Brunquell et al. (2012) Mol Cancer Res. 10 (11), 1482-95).

TMEM245 (Transmembrane Protein 245)

TMEM245 is a non-annotated, protein coding gene.